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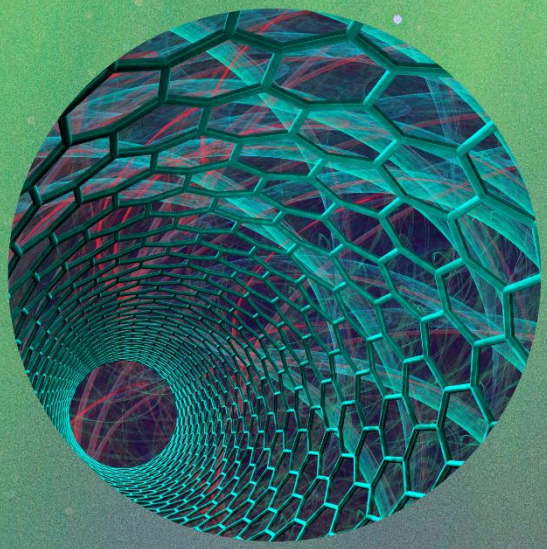
RESEARCH AND REVIEWS IN NANOTECHNOLOGY

VOLUME II



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Research and Reviews in Nanotechnology Volume II

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PREFACE

Nanotechnology, the study and manipulation of matter at the nanoscale, has emerged as a cornerstone of modern scientific inquiry. At this scale, materials exhibit unique properties and behaviors, offering unprecedented opportunities for advancement in diverse domains ranging from medicine and electronics to energy and environmental sustainability.

This book serves as a compendium of cutting-edge research, insightful reviews, and thought-provoking perspectives from experts and scholars at the forefront of nanotechnology. Through its pages, readers will encounter a diverse array of topics, from fundamental principles of nanoscale phenomena to the latest breakthroughs in nanomaterials synthesis, characterization, and applications.

The interdisciplinary nature of nanotechnology underscores its significance as a catalyst for interdisciplinary collaboration and cross-pollination of ideas. As such, this volume reflects the collaborative efforts of researchers from various disciplines, including physics, chemistry, materials science, engineering, biology, and medicine, among others. It is through this interdisciplinary lens that we gain deeper insights into the multifaceted nature of nanotechnology and its profound implications for science, technology, and society.

As editors, we are honored to present this compilation of contributions, which we believe will inspire, inform, and stimulate further inquiry into the fascinating realm of nanotechnology. We extend our gratitude to the authors for their scholarly contributions and to the readers for their interest and engagement in this exciting field.

May this volume serve as both a testament to the remarkable progress achieved thus far in nanotechnology and a harbinger of the boundless possibilities that lie ahead.

Editors

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SEMICONDUCTOR ALLOYS OF GROUP II-VI: TECHNOLOGICALLY IMPORTANT WIDE BANDGAP MATERIALS FOR OPTO-ELECTRONIC DEVICES

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Abstract:

The II-VI semiconductor alloys and compounds have opened up new avenues in designing optoelectronic devices like hetero-structure bipolar transistors, diode lasers, light emitting diodes, detectors, mixers and modulators, bright light emitters, nonlinear optics applications namely in integrated optics and optical computing systems. These materials exhibit emission/absorption wavelengths in the green/blue part of the visible spectrum and in the UV region. A semiconductor alloys is a combination of two or more semiconducting compounds which provide tenability in the bandgap and other structural and electronic parameters. In this chapter a brief introduction about materials aspects of ternary and quaternary semiconductor alloys of group II-VI used in various electronic and optoelectronic devices is presented. The properties of semiconductor alloys formed by mixing the II-VI materials i.e. BeO, MgO, ZnO, CdO, BeS, MgS, ZnS, CdS, BeSe, MgSe, ZnSe, CdSe, BeTe, MgTe, ZnTe, and CdTe etc are presented and discussed here.

Keywords: II-VI Semiconductors, Semiconductors Alloys, Hetero-structures, Opto-electronic devices

Introduction:

The semiconducting materials have indispensible place in our daily life. These materials are being used extensively and form the basis of modern electronic devices such as diodes, transistors, integrated circuits, and opto-electronic devices like laser diodes, photo-diodes, photo-detectors, ultra violet lasers, infra red sensors and optical fibers etc. The development of new semiconducting materials and device technology requires practical knowledge of materials engineering together with the clear understanding of fundamental physics underlying its characteristic behavior [1-4]. The semiconductors materials can have nano, thin films, organic and crystalline forms. Our focus in this chapter will be on the bulk semiconducting materials.

Semiconductor alloys are useful technologically important materials precious in the sense that the forbidden gap can be tailored and optimized to fabricate devices operating in a window of given wavelength. Particularly the III-V and II-VI semiconductor alloys have opened up new

vistas to propose design of solid state semiconducting devices. Wide band gap semiconducting materials are specific as the band gap can be optimized to operate in a window of given wavelength. Band gap of the most of the II-VI semiconductor compounds and alloys lie in this range. The broad range of bandgaps together with high optical absorption and emission coefficients make the II-VI materials highly suitable for thin film optical devices [5]. A typical thin film solar cell constructed by CdTe/CdS layers is shown in figure 1 [6] in which the thin layer of CdS is used to reduce absorption and enhance the output current.

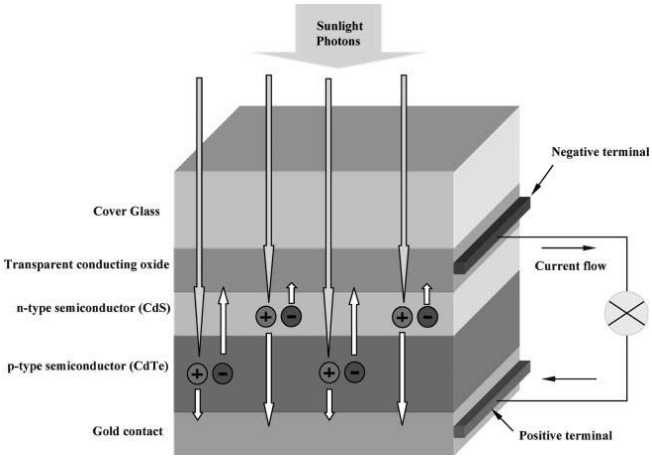

Figure 1: A schematic layout of a conventional p–n junction thin-film solar cell using CdTe. The picture is taken form Ref. [6]

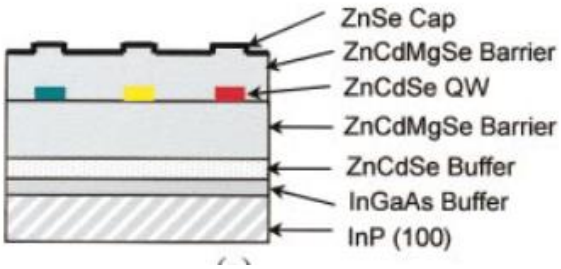

Figure 2: A schematic diagram of the integrated three-color quantum well structure grown on InP. The picture is taken form Ref. [8]

The development in the advanced crystal growth techniques like molecular beam epitaxy (MBE) and organometallic chemical vapor deposition (OMCVD) makes it possible to control the doping or mixing in the semiconductor materials with enhanced accuracy and efficiency [1]. The II-VI materials generally have lattice constant values near some II-V materials. So the growth of II-VI semiconductor on the base of GaAs, GaN, InP and AlN etc. have attracted a lot of experimental as well as theoretical studies in recent years. The blue–green laser diodes constructed by ZnSe, ZnSSe, MgZnSSe and MgZnSSe grown on GaAs or InP substrates have been investigated extensively due to its enhanced lifetime and high emissivity [7]. The

ZnCdSe/ZnCdMgSe grown on single InP substrate exhibit emissions in the red, green, and yellow regions thus covering almost all the visible part [8].

II-VI semiconductor compounds as base materials for alloys:

The materials formed by elements of II group (e.g. Be, Mg, Ca, Zn, Cd and Hg) with the VI group (O, S, Se and Te) elements are referred as II-VI compound semiconductors BeO, MgO, ZnO, CdO, BeS, MgS, ZnS, CdS, BeSe, MgSe, ZnSe, CdSe, BeTe, MgTe, ZnTe, and CdTe etc. are some of the II-VI compound semiconductors [9,10]. These compounds generally crystallize in cubic zinc-blende (zb), cubic rocksalt or hexagonal wurtzite (wz) type structures. The coordination numbers of the atoms in cubic zinc-blende and hexagonal wurtzite structures is 4 while in the cubic rocksalt it is 6. The zinc-blende type structure is more common than rest two as in this structure the sp^3 hybridization take place which leads to a strong bonding between the II and VI group atoms. All the three types of structures are shown in the figure 3.

The II–VI compounds have ionic type bonding due to higher electronegativity of group IV element resulting in the larger values of bandgaps of these compounds [5]. From the conductivity point of view it has been observed that compounds like ZnO, CdS, CdSe and ZnS have n-type conductivity, while ZnTe and ZnSe have n-type conductivity [5].

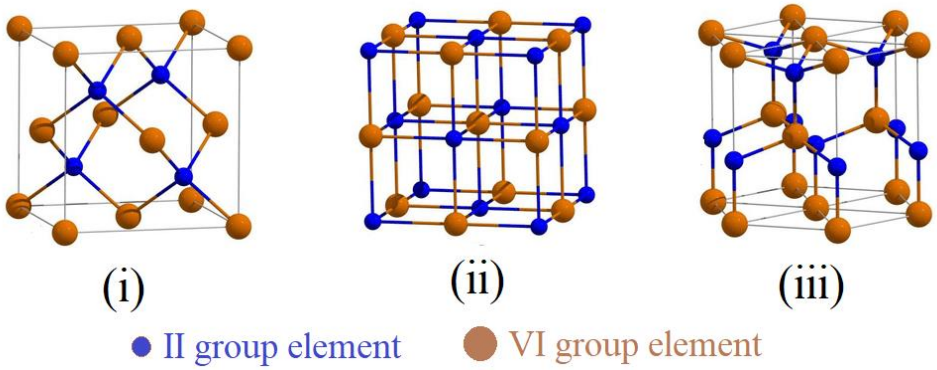

Figure 3: The (i) cubic zinc-blende, (ii) cubic rock-salt and (iii) hexagonal wurtzite type structures of some II-VI materials.

The ternary and quaternary semiconductors may be formed from these compounds. The II-VI group semiconductors generally show large bandgap ($1.4 \leq Eg \leq 6$ eV). So these are known as wide bandgap materials. Consequently these have shorter emission/absorption wavelength in optical devices. These semiconductors exhibit emission/absorption wavelengths in the blue-green and the ultra-violet (UV) region of the electromagnetic spectra acquiring important place as optical devices namely light emitting diodes, laser diodes, photodiodes, photoconductive sensors, electro-modulation devices and optical–optical modulation devices [11-14]. The main advantage is availability of compounds with different energy gaps at a given lattice constant; a necessary condition for the fabrication of hetero-junctions. The II-VI semiconductors doped with transition

metal as solid-state laser material cover extended wavelength in the infrared spectral region. These are also useful in fabricating the Tera-Hz photoconductive emitters [11-14]. The use of II-VI materials is also opening new avenues and challenges in material preparation. The bandgaps and lattice constants of some II-VI compounds crystallizing in zb structure are shown in Figure 4.

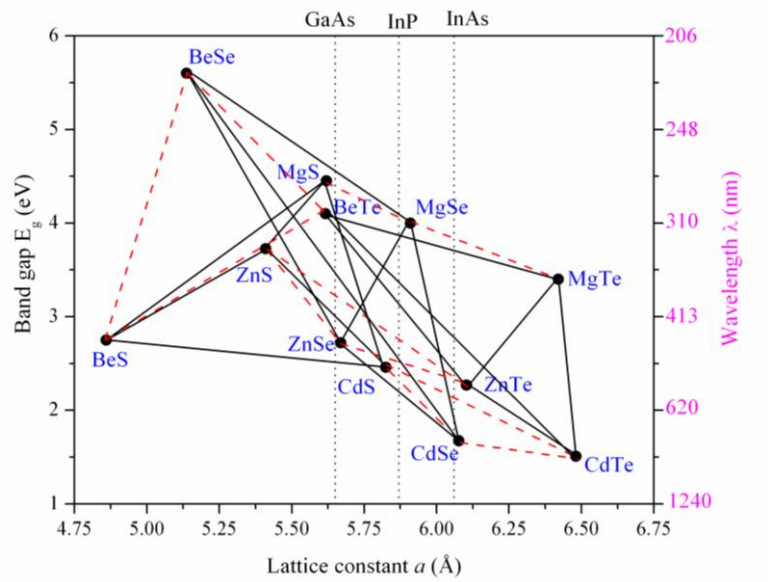

Figure 4: Bandgap and lattice constant for some II-VI compounds. The dotted vertical lines show the lattice matching condition with a few III-V compounds.

Figure shows that wide gap II-VI materials cover a considerable part of the light spectrum, from near infrared to the ultraviolet region. Figure 1 depicts that the solid lines joining two compounds show variation in lattice constant of a cationic alloy (II-II-VI type). The dashed lines joining the compounds show possibility of anionic alloys (II-VI-VI type). Lattice constants are found to follow the Vegard's linear law according to which the lattice constant of an ternary alloy ZnS_xSe_{1-x} can be given as –

$$a = xa_{ZnS} + (1-x)a_{ZnSe} \qquad (1)$$

The vertical dotted lines show the lattice constants of GaAs, InP and InAs. Intersection of these lines gives the lattice match of III-V compound with II-VI alloys. For instance, ZnS_xTe_{1-x} and $Be_xZn_{1-x}Te$ systems can have lattice matching with three III-V compounds i.e. GaAs, InP and InAs.

II-VI semiconductor ternary and quaternary alloys:

1. Formation of a ternary alloy:

An alloy is prepared from the physical mixture of two or more substances. The alloy crystal is called a solid solution or a mixed crystal. The II-VI compounds offer to form anionic or cationic type of ternary and quaternary alloys. Usually cationic ternary alloys are denoted as

$A_xB_{1-x}C$ containing three types of elements A, B and C; here A and B are cations and C is an anion. The *zb* structures of a symbolic cationic ($A_xB_{1-x}C$) alloy for x=0.0,0.25,0.50,0.75,1.0 is shown in Figure 5.

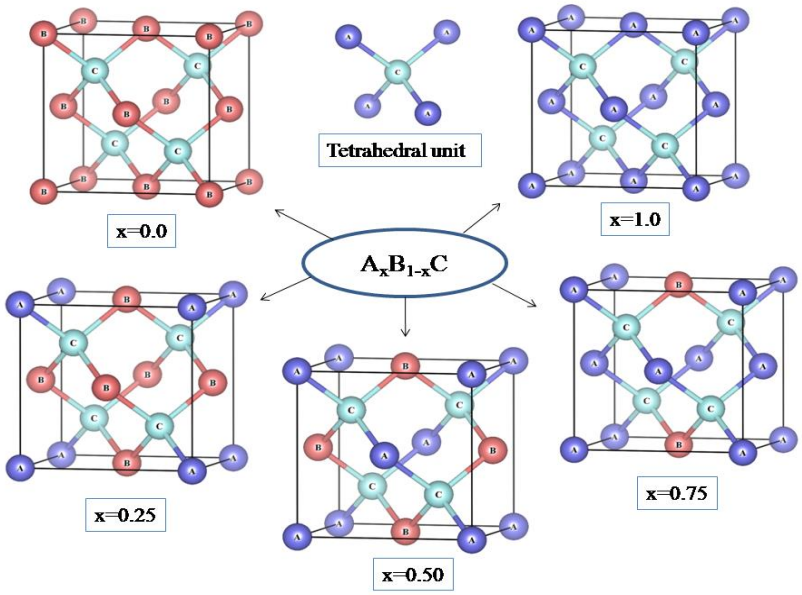

Figure 5: The zinc-blende structures of cationic $A_xB_{1-x}C$ alloys for various values of *x*

The solid solution of a cationic alloy $A_xB_{1-x}C$ is defined as mixing of two compounds AC and AB according to their fraction in the solution and can be expressed as –

$$xAC + (1-x)BC \rightarrow A_xB_{1-x}C\,. \qquad (2)$$

The composition dependence of any quantity Q (like bandgap, lattice constant, bandgap or thermal conductivity) for a cationic alloy $A_xB_{1-x}C$ can be given as –

$$Q_{A_xB_{1-x}C} = xQ_{AC} + (1-x)Q_{BC}, \qquad (3)$$

where Q_{AC} and Q_{BC} are the magnitudes of a particular quantity for compounds AC and BC respectively. If there is any non-linearity in Q with respect to composition *x*, then the bowing is said to be non-zero. The bowing (*b*) parameter in Q is defined as –

$$Q_{A_xB_{1-x}C} = xQ_{AC} + (1-x)Q_{BC} - bx(1-x)\,. \qquad (4)$$

Similarly an anionic alloy is represented as AB_xC_{1-x}; here A is a cation and B and C are anions. All the equations written above can also be rewritten for the anionic alloy AB_xC_{1-x} also.

Thus this is obvious that the energy bandgap may or may not vary linearly. Above equations offer a strategy of band engineering. One can tune bandgap and other properties according to the above equations and design materials of interest. Remarkably, when nature of bandgap of compounds AC and BC is different, materials designed may have specific opto-electronic applications.

The II-VI ternary and quaternary alloys are grown on III-V substrates to achieve better operation stability and enhanced life time in opto-electronic devices operating in blue-green to UV region [15-19].The ternary alloys prepared from II and VI group elements can be categorized into two types i.e. II-II-VI (cationic) and II-VI-VI (anionic). The quaternary alloys can be categorized into three types i.e. II-II-VI-VI, II-II-II-VI and II-VI-VI-VI. The possibility of preparing these alloys may be understood from the phase diagrams [20]. These alloys are grown generally on a lattice matching substrate. Here, a brief information about some II-VI ternary alloys is presented.

2. II_x-II_{1-x}-VI ternary cationic alloys:

This category includes II-II-O, II-II-S, II-II-Se and II-II-Te alloys. Except II-II-O, other ternary alloys are shown by solid lines in Figure 4. The examples of II-II-O alloys are $Be_xZn_{1-x}O$ and $Zn_xCd_{1-x}O$ and $Mg_xZn_{1-x}O$. Due to large difference in the bandgap of BeO (~10 eV) and ZnO (~ 3.17 eV) this system may cover the large range of bandgap. $Be_xZn_{1-x}O$ is grown in *wz* structure [9, 21]. $Zn_xCd_{1-x}O$ is an interesting system as ZnO has direct bandgap of 3.17 eV while CdO has indirect bandgap of 0.84 eV. Thus this alloy can cover the green to UV region of optical spectrum. The Cd rich phase ($0.0 \leq x < 0.2$) of the alloy is rocksalt while Zn rich phase ($0.2 \leq x < 1.0$) is wurtzite [9, 22]. For $Mg_xZn_{1-x}O$ the mixed phase of wurtzite and cubic rocksalt structures is observed around x=0.4 [9].

The $Mg_xZn_{1-x}S$, $Zn_xCd_{1-x}S$ and $Cd_xHg_{1-x}S$ are among II-II-S alloys which are experimentally reported. The $Mg_xZn_{1-x}S$ is grown both in the *zb* and *wz* type structures [9]. The $Zn_xCd_{1-x}S$ is grown in both *zb* and *wz* type structures, while $Cd_xHg_{1-x}S$ shows composition dependent structure. The Hg rich phase of $Cd_xHg_{1-x}S$ ($x \leq 0.4$) crystallizes in the *zb* structure while Cd rich phase ($x \geq 0.6$) has the *wz* structure [9,23].

The $Mg_xZn_{1-x}Se$, $Be_xZn_{1-x}Se$, $Be_xCd_{1-x}Se$, $Mg_xCd_{1-x}Se$, $Zn_xCd_{1-x}Se$ and $Cd_xHg_{1-x}Se$ group represent the II-II-Se type alloys. Among these alloys the $Mg_xZn_{1-x}Se$, $Be_xZn_{1-x}Se$, $Be_xCd_{1-x}Se$, $Zn_xCd_{1-x}Se$ and $Cd_xHg_{1-x}Se$ alloys crystallize in the *zb* structure [9] while $Mg_xCd_{1-x}Se$ is grown as bulk in *wz* structure [9, 24] while its layers are grown on InAs substrate in *zb* structure [25].
$Mg_xZn_{1-x}Te$, $Be_xZn_{1-x}Te$, $Mg_xCd_{1-x}Te$, $Zn_xCd_{1-x}Te$, $Zn_xHg_{1-x}Te$ and $Cd_xHg_{1-x}Te$ are the examples of II-II-Te alloys. Among these alloys, $Be_xZn_{1-x}Te$ alloy is an important material for the blue-green laser diodes [17]. The $Mg_xZn_{1-x}Te$ crystallizes in the zinc-blende structure when $x > 0.53$ and in wurtzite structure when $x < 0.53$ [26]. Similarly the $Mg_xCd_{1-x}Te$ alloy is zinc-blende when it is Cd rich ($x \leq 0.60$) and wurtzite when it is Mg rich ($x \geq 0.75$) [27].

3. II-VI_x-VI_{1-x} ternary anionic alloys:

Some of the possible anionic ternary alloys of II-VI-VI type are shown by dashed connecting lines in Figure 4. Among Zn-VI-VI type alloys the ZnO_xS_{1-x}, ZnO_xSe_{1-x}, ZnS_xSe_{1-x},

ZnS_xTe_{1-x}, and $ZnSeTe_{1-x}$ are studied experimentally. The thin films of ZnO_xS_{1-x} are grown in the wz structure [28] while rest of the three alloys i.e. ZnO_xSe_{1-x}, ZnS_xSe_{1-x}, ZnS_xTe_{1-x} have been fabricated in the zb structure [9]. The ZnO_xS_{1-x} and ZnS_xTe_{1-x} show large size mismatch thus resulting in the larger value of bowing parameter in the bandgap [9].

Among Be-VI-VI type alloys, only $BeSe_xTe_{1-x}$ is studied experimentally. $BeSe_{0.49}Te_{0.51}$ has been grown on Si substrate [29]. We could not trace any other experimental report in literature of Be-VI-VI type alloy.

The CdS_xSe_{1-x}, CdS_xTe_{1-x} and $CdSe_xTe_{1-x}$ are the member of Cd-VI-VI group, these are useful in IR detectors and photo-cells. CdS_xSe_{1-x} in *wz* structure form direct bandgap alloys in the entire range of composition [30]. On the other hand due to the difference in the structures of CdS, CdTe and CdSe the remaining alloys have the composition dependent structure. CdS_xTe_{1-x} has *zb* structure in the lower concentration region of S while it crystallizes in *wz* structure at high concentration of S. Similarly $CdSe_xTe_{1-x}$ has *zb* structure for $x \leq 0.60$ and *wz* structure for $x \geq 0.60$ [31].

4. Quaternary II-VI alloys:

The quaternary alloys can be of three types II-II-VI-VI, II-II-II-VI or II-VI-VI-VI. These are represented as $A_xB_{1-x}C_yD_{1-y}$, $A_xB_yC_{1-x-y}D$ and $AB_xC_yD_{1-x-y}$ alloy. First one is made by mixing four II-VI compounds i.e. AC, AD, BC and BD where A,B are from II group and C,D are from VI group. A cationic quaternary alloy $A_xB_yC_{1-x-y}D$ is formed by three II-VI compounds AD, BD and CD where A,B and C belong to the II group and D belongs to the VI group. Any measurable quantity Q for $A_xB_{1-x}C_yD_{1-y}$ type alloy can be estimated as :

$$Q_{A_xB_{1-x}C_yD_{1-y}} = xyQ_{AC} + x(1-y)Q_{AD} + y(1-x)Q_{BC} + (1-x)(1-y)Q_{BD} \qquad (8)$$

The smilar expressions can also be given for $A_xB_yC_{1-x-y}D$ and $AB_xC_yD_{1-x-y}$ alloys. Among the quaternary alloys of $A_xB_{1-x}C_yD_{1-y}$ category, $Zn_{0.50}Cd_{0.50}S_{0.80}Se_{0.20}$ and $Zn_{0.90}Cd_{0.10}S_{0.07}Se_{0.93}$ are grown on lattice matched GaAs [32]. In the category of cationic quaternary alloys of $A_xB_yC_{1-x-y}D$ type, $Be_xMg_{1-x}Zn_{1-x-y}Se$ is grown on GaAs substrate whereas $Mg_xZn_yCd_{1-x-y}Se$ and $Be_xZn_yCd_{1-x-y}Se$ are grown on InP; and $Cd_xZn_yHg_{1-x-y}Te$ is grown on CdZnTe substrate.

Summary:

The II-VI semiconductor compounds and alloys are useful in fabricating various opto-electronic devices due to advantage of high life time and high emissivity. The spectral range of these devices is very broad covering almost complete visible spectra. The key parameter which decides all these applications is the forbidden energy bandgap and its nature. The II-VI semiconductor ternary and quaternary alloys are experimentally grown in mainly zinc-blende

type and wurtzite type structures on a lattice matched substrate like InP or GaN etc. Further the structure also depends upon the composition of compounds in the solid solution. Thus these alloys offer tunable structures and other properties like bandgap, mechanical strength, absorption coefficient etc by varying just the composition of a particular compound.

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NANOTECHNOLOGY IN WATER TREATMENT

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Abstract:

Over the past ten years, the research on nanomaterials has grown in significance to mitigate water pollution. Nanoparticles are very profitable as sorbents due to two essential characteristics (high surface and Tailorable Properties). Compared to macro particles, they have substantially greater surface areas on a mass basis. Their chemical affinity for target chemicals can also be increased by augmenting them with other reactor groups. Nowadays, cations, naturally occurring organic materials, biological pollutants, organic pollutants, nitrates, and arsenic are frequently removed from surface and groundwater using nanofiltration technology. In order to remove both organic and inorganic pollutants from contaminated water, nanosorbents are frequently utilized as separation media in water purification processes. Titanium dioxide (TiO_2) nanoparticles have shown promise as water filtration photocatalysts over the previous decade. As a result, a number of researchers began using techniques such chemical precipitation, sol-gel, vapour deposition, solvo thermal, solid state reaction, etc., to create various nanostructured mixed oxides that are useful for treating groundwater. Iron-cerium, iron-manganese, iron-zirconium, iron-titanium, iron-chromium, cerium-manganese, and other mixed oxide nano-agglomerates have been synthesized, extensively studied using advanced equipment such as SEM, TEM, FT-IR, AFM, and have been effectively used for water treatment. Adsorption is one of the best technologies now in use because of its high efficiency, affordability, and ease of handling. When choosing and designing materials for water filtration, considerations such as toxicity and the material's environmental fate are crucial.

Keywords: Nanomaterials, Adsorption, Sorbents, Filtration, Innovative methods

Introduction:

Water is mentioned as a life-sustaining element that is essential to the environment, the economy, and the health of the entire world. The urgent problem of providing clean water in the face of extended droughts, population expansion, deteriorating water quality, contamination of surface and groundwater, flooding, and competing needs is addressed. The essay emphasizes the necessity of strategic planning and management of water resources and acknowledges water as a

vital resource for humankind as well as a valuable national asset. It attributes the problem of worldwide water shortage to population expansion and overuse of water resources, which contaminates already-existing freshwater supplies. It is observed that the amount of wastewater generated is increasing, underscoring the necessity of prompt treatment and control to stop more pollution. A contributing cause to the increased individual water consumption is noted as urbanization. In order to avoid shortages in the future, the passage emphasizes how important it is to manage the current water supply. The importance of groundwater for a variety of water demands is emphasized, highlighting worries about access to safe drinking water that are shared by people worldwide.

According to UNEP research, it states that over 2 billion people rely on aquifers for drinking water and that 40% of the world's food output is dependent on irrigated agriculture using groundwater. Since groundwater makes up over 95% of freshwater on Earth, its significance for human existence and economic growth cannot be overstated. However, adequate groundwater treatment is required due to the substantial threat posed by the declining amount and quality of groundwater, especially in rural regions. The passage highlights the strain that unrestrained consumption is placing on the world's groundwater resources and calls for a change in terminology from "groundwater development" to "groundwater management" for sustainable use.

Nanoscience is the defined as the study of materials and processes at the atomic, molecular, and macromolecular scales, where characteristics are very different from those at larger scales. Designing, analyzing, creating, and implementing systems, devices, and structures by manipulating size and shape at the nanoscale is the scope of nanotechnology. The use of nanostructured materials as adsorbents or catalysts to remove harmful compounds from wastewater has received a lot of interest lately. Examples of these materials are single and multi-metal or doped metal oxides. When compared to bulk materials, these materials have special qualities such as improved magnetic and catalytic capabilities and a high surface-to-volume ratio. To produce oxides, a variety of synthetic techniques are used, including sol-gel and chemical precipitation. More advancements are being made in the field of nano-enabled water treatment technologies, specifically nanofiltration, which are currently in use.

Role of nanomaterials in water treatment

Nanoscience is the study of materials and processes at the molecular, atomic, and macromolecular scales; these scales differ greatly from larger ones in terms of properties. Nanotechnology is the study, analysis, design, and implementation of systems, devices, and structures through manipulation of size and shape at the nanoscale. Recently, there has been a lot

of interest in the use of nanostructured materials as catalysts or adsorbents to remove toxic chemicals from wastewater. Doped metal oxides, both single and multi-metal, are examples of these materials. These materials offer unique properties, such as a high surface-to-volume ratio and enhanced magnetic and catalytic capabilities, when compared to bulk materials. Numerous synthetic processes, such as sol-gel and chemical precipitation, are employed to generate oxides.

While there is hope that nanotechnology will play a big part in efficiently, affordably, and sustainably supplying developing nations with clean water, worries about the possible negative consequences of nanoparticles still persist. It is known that there is a double-edged aspect to nanotechnology: while the catalytic activity of nanoparticles is useful for the breakdown of pollutants, it can also present hazardous hazards when ingested by cells. The chapter makes the case that, in spite of these difficulties, nanotechnology has the potential to significantly reduce costs and outperform existing methods for the long-term removal of contaminants from water. Potential uses for nanoparticles include separation media, sorbents, catalysts for the photochemical breakdown of pollutants, and parts of nanofiltration membranes.

Nanomaterials play a crucial role in water treatment due to their unique properties and versatile applications. Some key aspects of their role in water treatment include:

- Adsorption and Catalysis
- Nanostructured Membranes
- Sorbents for Heavy Metals
- Photocatalysis
- Nano-enabled Technologies
- Efficiency and Cost-Effectiveness.

In worldwide, the unique characteristics of nanomaterials, like their high surface area and reactivity, allow for the effective removal of pollutants, making them indispensable tools for tackling problems with water quality. Innovative and sustainable methods to guarantee access to clean and safe water have a bright future as we continue to investigate and utilize the possibilities of nanomaterials.

Mechanism of removing pollutants by nanomaterials

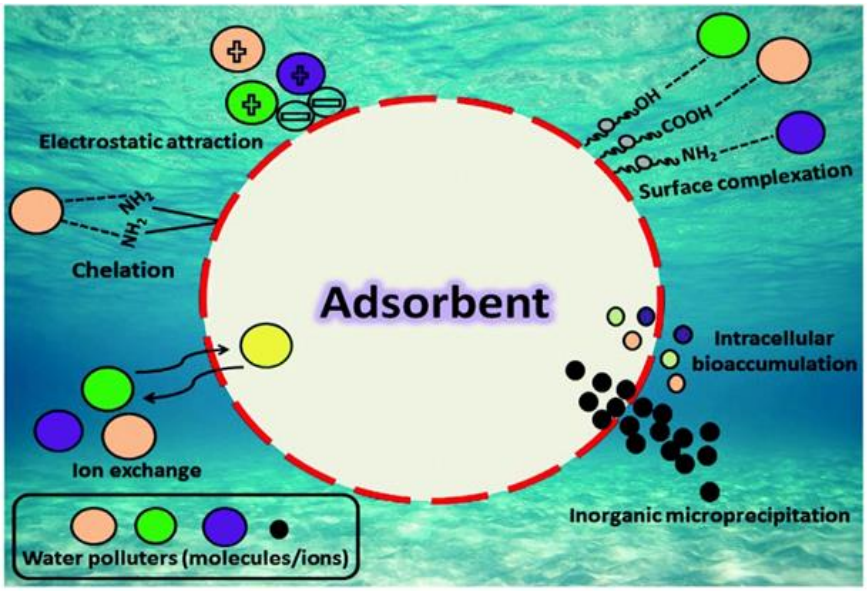
Nanomaterials employ their inherent physical, chemical, and structural properties in a synergistic manner for efficient pollutant remediation. With their large surface area, nanomaterials can catalytically degrade or absorb contaminants, while their compact size enables enhanced penetration and mobility for effective treatment in diverse environmental settings. Interactions at the molecular level underscore the flexibility of nanomaterials in addressing a broad spectrum of pollutants in air and water, emphasizing their potential to advance sustainable

and efficient pollution control solutions. Some of the methods to remove the pollutants from the wastewater based on the efficiency of the treated water; they are,

1. Nanosorbents
2. Nanofiltration
3. Nanoscale Zerovalent Iron Treatment

1) Nanosorbents

Nanomaterials serve as cutting-edge and versatile sorbents, offering innovative solutions to water and environmental pollution. Their exceptional properties, notably larger surface areas per mass and the ability to customize chemical reactivity with various functional groups, make nanoparticles highly effective in adsorbing and eliminating diverse contaminants. This versatility is demonstrated in nanocrystals like akaganeite and engineered compounds (cerium oxide) supported on carbon nanotubes (CeO2-CNTs). The adaptability and enhanced adsorption capabilities of these nano sorbents, coupled with their application in advanced processes like photo-oxidation using nanocrystalline TiO2, have their promising role in developing efficient and sustainable solutions for water treatment challenges.



Mechanism of sorbents in water treatment

The mechanism of sorbents involves the adsorption or attachment of contaminants to the surface of the material. Sorbents, which can be various substances like activated carbon, silica gel, or nanomaterials, possess a high surface area and specific binding sites that attract and hold onto target molecules. The process is driven by physical and chemical interactions, such as van der Waals forces, electrostatic attractions, and chemical bonding.

Factors affecting action of nanosorbents

1. **Surface area:** The high surface area per mass unit of nanosorbents increases their ability to adsorb substances. There are more sites accessible for interaction with pollutants the bigger the surface area
2. **Particle size:** Because it affects both their mobility and penetration, nanoparticle size is very important. Smaller nanoparticles can interact and absorb pollutants more successfully since they frequently show higher reactivity and accessibility.
3. **Chemical composition**: The affinity of nanosorbents for particular pollutants is determined by their chemical composition. Selectivity and reactivity towards target pollutants can be improved by customizing surface changes and functionalization with different groups.
4. **Porosity**: A nanosorbent's capacity to capture and retain pollutants is influenced by its porosity. In addition to offering more binding sites, highly porous materials can also boost adsorption capacity.
5. **pH:** The charge on the pollutants and the nanosorbent can both be affected by the pH of the fluid. pH variations may modify the electrostatic interactions and impact the total effectiveness of adsorption.
6. **Temperature:** Adsorption processes frequently depend on ambient temperature. Temperature variations can have an effect on a particle's kinetic energy, which can change the rate and degree of adsorption.
7. **Concentration of pollutants:** The adsorption ability of nanosorbents may be impacted by the initial concentration of pollutants in the solution. Binding sites may saturate faster at higher doses.
8. **Existence of other substances:** The selectivity of the solution may be affected by the competition between other substances, such as ions or organic matter, for binding sites on the nanosorbent surface.

Some of the nanosorbent materials

1. Carbon-based nanomaterials:

- **Carbon Nanotubes (CNTs):** These are cylindrical structures made of carbon atoms. They have high surface areas and excellent adsorption capabilities, making them useful in water purification and pollutant removal.
- **Graphene:** A single layer of carbon atoms arranged in a hexagonal lattice. Graphene-based nanosorbents are known for their high adsorption capacity, particularly for heavy metals and organic pollutants.

2. Metal and metal oxide nanoparticles

- **Metal nanoparticles:** Nanoscale particles of metals like silver, gold, and iron have shown adsorption capabilities for various contaminants. Silver nanoparticles, for example, are used for their antibacterial properties.
- **Metal oxide nanoparticles:** Materials like titanium dioxide (TiO2), iron oxide (Fe2O3), and zinc oxide (ZnO) exhibit excellent adsorption properties. They are employed in wastewater treatment and environmental remediation.

3. Polymeric nanosorbents:

- **Polymeric Nanoparticles:** Nanoscale particles made of polymers can be designed to have specific functional groups for targeted adsorption. They are used in drug delivery systems and environmental applications.
- **Nanogels:** Crosslinked polymer networks in the nanoscale, these gels can encapsulate and adsorb various substances. They are used in drug delivery and controlled release applications.

4. Clay-based nanosorbents: Materials like montmorillonite and kaolinite at the nanoscale have large surface areas and are used for adsorption of heavy metals, dyes, and other contaminants.

5. Biological nanosorbents:

- **Nanocellulose:** Derived from plant-based cellulose, nanocellulose has a high surface area and is used for adsorption of pollutants. It is environmentally friendly and biocompatible.
- **Protein-based nanosorbents:** Proteins and peptides can be engineered at the nanoscale for specific adsorption applications. They are used in drug delivery and biosensing.

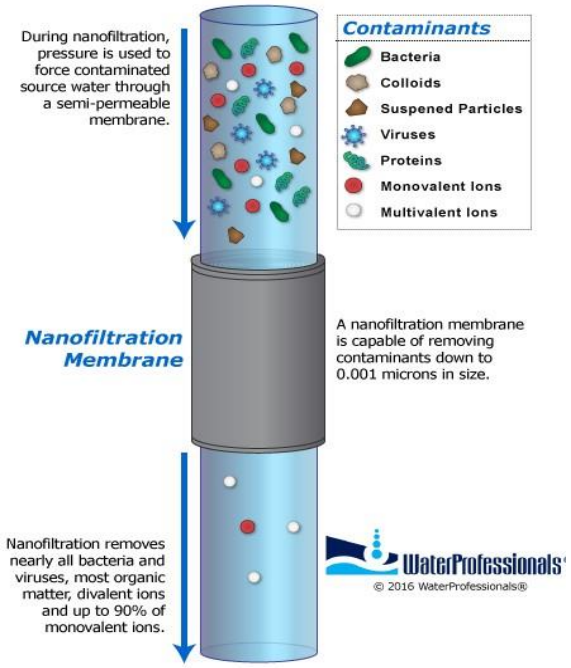
6. Composite nanosorbents (Hybrid): Combinations of different nanosorbent materials, such as metal nanoparticles embedded in a polymer matrix, can provide synergistic effects and enhanced adsorption capabilities.

These nanosorbent materials had advantages like high surface area, tunable surface chemistry, and specific adsorption properties, making them valuable in addressing various challenges in pollution control and, water treatment.

2) Nanofiltration

Nanofiltration (NF) is the membrane technique which is becoming more and more popular for purifying water, especially for drinking water and wastewater treatment. Their membranes efficiently separate materials in the 0.001-0.1 micrometer size range while operating at low

pressure. These membranes, which have pore diameters ranging from 0.2 to 4 nm, have characteristics in between those of reverse osmosis and ultrafiltration membranes.



Mechanism of nanofiltration

Important uses for nano-filtration membrane

- **Softening of groundwater:** By eliminating ions like calcium (Ca) and sodium (Na), NF membranes are used to lower the hardness of the water.
- **Removal of contaminants from surface water:** NF membranes are used to remove turbidity, microorganisms, and inorganic ions from surface water.
- **Treatment of wastewater:** NF membranes can remove dissolved organic materials and both organic and inorganic contaminants from wastewater.
- **Pretreatment in seawater desalination:** NF membranes are used in the pretreatment stage of seawater desalination to successfully handle problems with water quality.

Factors affecting the nanofiltration process

Between reverse osmosis (RO) and ultrafiltration (UF) in terms of membrane pore size during water treatment is nanofiltration, a membrane-based separation technique. The effectiveness and efficiency of nanofiltration procedures can be impacted by a number of factors. They are,

1. Properties of membranes:

- **Pore Size:** The range of pore sizes in nanofiltration membranes is usually 1–10 nanometers. The pore size distribution of the membrane determines its rejection and selectivity characteristics.

- **Material**: Chemical resistance, stability, and separation effectiveness can all be impacted by membrane material. Polyamide, polyethersulfone, and thin-film composite materials are common materials used in membranes.

2. The parameters of operation:

- **Pressure:** Compared to reverse osmosis, nanofiltration usually works at lower pressures. Permeate flow and solute rejection are impacted by the applied pressure.
- **Temperature:** The temperature affects the separation efficiency, membrane permeability, and feed solution viscosity. It's critical to take the process's temperature into account.

3. Features of the feed solution:

- **Concentration:** The osmotic pressure, which in turn affects the necessary operating pressure and separation efficiency, is influenced by the concentration of solutes in the feed solution.
- **pH:** The stability of the membrane and the charge of the solute particles can both be impacted by the pH of the solution, which can change the rejection rates.

4. Solute properties:

- **Size and molecular weight**: Nanofiltration is selective based on size and molecular weight. Large molecules may be rejected, while smaller ones may pass through the membrane.
- **Charge**: The charge of solute particles and the membrane surface charge can influence electrostatic interactions, affecting rejection rates.

5. Pre-treatment:

- **Fouling:** Pretreatment is crucial to prevent fouling caused by suspended solids, microorganisms, or scaling. Common pretreatment methods include microfiltration and ultrafiltration to remove larger particles.

6. Crossflow velocity: The velocity of the feed solution parallel to the membrane surface, which helps to reduce the fouling by continuously sweeping away rejected particles.

7. Module design and membrane configuration: The design and configuration of the nanofiltration module influence the overall efficiency and ease of maintenance.

8. Environmental conditions: The environmental conditions in the operating area can impact the overall performance of the nanofiltration process.

3) Nanoscale zerovalent iron treatment

Nanoscale zerovalent iron (nZVI) refers to tiny particles of zerovalent iron with sizes typically ranging from 1 to 100 nanometers. These nanoparticles exhibit strong reducing properties, making them useful for environmental applications such as groundwater and

wastewater remediation. nZVI can chemically reduce and immobilize contaminants, including heavy metals and chlorinated compounds. Challenges include particle agglomeration and understanding transport in different environments. Synthesis methods include wet chemistry and green synthesis. Ongoing research focuses on optimizing applications, addressing safety concerns, and developing environmentally friendly production methods. nZVI shows promise for addressing environmental challenges, but continued research is essential for responsible use.

Some of the uses in water treatment

Nanoscale zerovalent iron (nZVI) finds application in various environmental and industrial contexts due to its unique properties. Some major uses of nZVI include:

1. **Groundwater remediation:** nZVI is used for the in-situ remediation of groundwater contaminated with chlorinated solvents, such as trichloroethylene (TCE) and perchloroethylene (PCE). It can facilitate the reduction and immobilization of these contaminants.
2. **Wastewater treatment:** nZVI is applied in wastewater treatment processes to remove pollutants, including heavy metals and organic compounds. It can assist in the precipitation, adsorption, and reduction of contaminants, leading to improved water quality.
3. **Environmental decontamination**: nZVI is employed in the decontamination of soil and sediments contaminated with various pollutants. Its strong reducing properties enable the transformation or immobilization of contaminants, reducing their environmental impact.
4. **Catalysis:** nZVI nanoparticles are used as catalysts in various chemical reactions. Their high surface area and reactivity make them suitable for catalyzing certain reactions in organic synthesis and industrial processes.

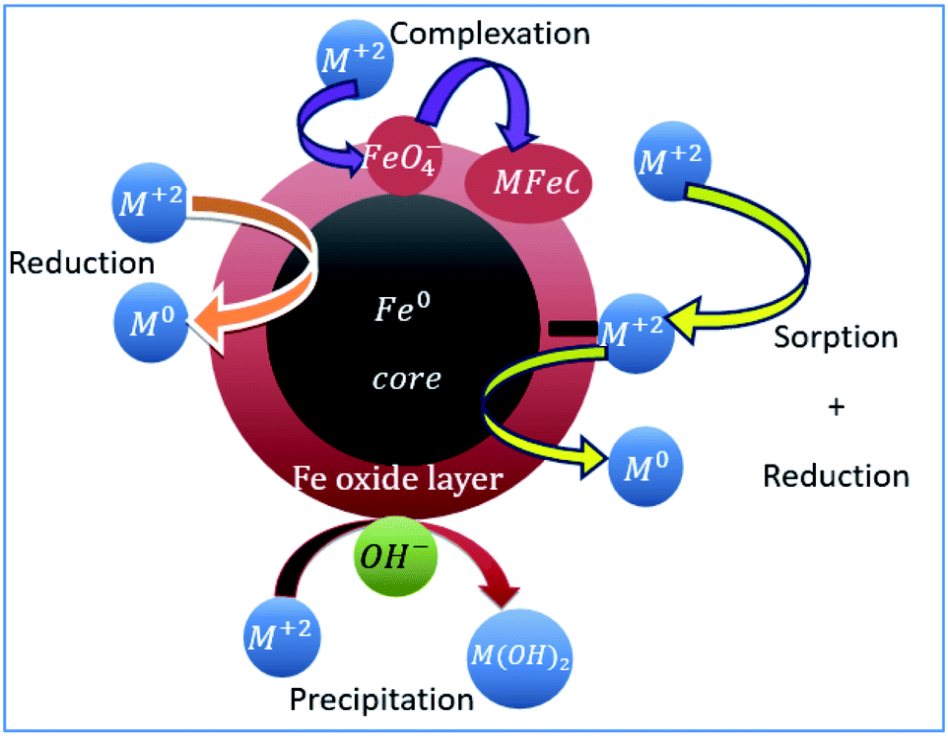
Mechanism

In particular, the characteristics and uses of nanoscale zerovalent iron (nZVI) in environmental remediatio specifically, its ability to extract heavy metals from aqueous solutions—is observed.

Rapid oxidation creates an oxide shell around a metallic iron core to make nanoscale zerovalent iron (nZVI). Its ability to reduce contaminants is attributed to its reductive power. When nZVI is dissolved in water, it forms an iron (hydr)oxide outer layer that can be adsorbed. The method of removing heavy metals consists of two stages: first reduction and then adsorption onto the core-shell structure. Surface charge is influenced by pH, which has an impact on complex formation. Co-precipitation and reduction are impacted by co-existing ions. Surface complexation, physisorption, precipitation, and reduction are examples of adsorption mechanisms. Metals close to Fe^0's redox potential are removed through sorption or precipitation,

whereas nZVI acts as an electron donor for these metals. In short, the combination of reduction, adsorption, and precipitation mechanisms that are regulated by pH and co-existing ions allow for the efficient removal of heavy metals thanks to the characteristics of nZVI.

The general outline will be as stated below:



Mechanism of nanoscale zerovalent iron treatment

Factors affecting the Nanoscale zerovalent iron process

1. **Particle size**: Smaller particle sizes generally result in larger surface areas, which can enhance reactivity and effectiveness in contaminant degradation.
2. **Surface coating**: Coatings can improve stability, dispersibility, and reactivity of nZVI, potentially enhancing its performance in different environments.
3. **Concentration**: The concentration of nZVI used and the dosage applied can influence its efficiency in contaminant removal or remediation.
4. **pH**: pH levels can affect the surface charge of nZVI particles, impacting their stability and reactivity towards contaminants.
5. **Amount of dissolved oxygen:** Oxygen can oxidize nZVI, reducing its reactivity and effectiveness over time.
6. **Temperature:** Reaction rates and the effectiveness of nZVI can vary with temperature, with higher temperatures generally increasing reaction rates
7. **Type of contaminants:** Different contaminants may interact differently with nZVI, affecting its effectiveness in contaminant removal or degradation.

8. **Presence of other ions:** Co-existing ions in the environment can compete for reactive sites on nZVI, potentially reducing its effectiveness.
9. **Agitation process**: Agitation process can improve the contact between nZVI particles and contaminants, enhancing reaction rates and overall performance.
10. **Redox potential**: The redox potential of the environment can influence the reactivity of nZVI and its ability to reduce contaminants.

New innovations in water treatment

Innovative advanced water technologies are desperately needed, especially to guarantee clean drinking water, get rid of micropollutants, and boost industrial production processes using water treatment systems that can be adjusted on the fly. Nanoengineered materials have the ability to provide unique water technologies that are easily customized to meet the needs of individual customers. Examples of these materials include nanoadsorbents, nanometals, nanomembranes, and photocatalysts. The majority of them may be easily integrated into traditional modules and are compatible with current treatment technologies. When compared to traditional water technologies, one of the most significant benefits of nanomaterials is their capacity to combine different features, creating multifunctional systems such nanocomposite membranes that allow for the removal of impurities as well as particle retention.

Furthermore, because of their special qualities like a high response rate where the nanomaterials allow for improved process efficiencies. Nonetheless, there are still a number of disadvantages to be dealt with. Materials functionalized with integrated or deposited nanoparticles on their surface may be at risk of release and emission of the nanoparticles into the environment, where they may collect over an extended period of time. There is a great deal of room for innovation because there are currently no online monitoring systems that deliver trustworthy real-time measurement data on the number and quality of nanoparticles that are only present in trace amounts in water. Many national and international legislation and regulations are being prepared to reduce the health risk. The fact that nanoengineered water technologies are currently not competitive with traditional treatment methods and are rarely transferable to mass processes is another technical restriction of these technologies. However, in the upcoming decades, nanoengineered materials hold enormous promise for water improvements, particularly for heavily degradable pollutants, point-of-use devices, and decentralized treatment systems.

Conclusion:

In conclusion, there is a great deal of promise for nanotechnology to transform the water treatment industry. Because of their special qualities, nanomaterials have been successfully used in a variety of creative applications, including as adsorbents, membranes, and catalytic systems,

to remove a wide range of contaminants from water. The development of intelligent water treatment systems with real-time monitoring capabilities is made possible by this technology. For practical deployment on a broader scale, however, issues like risk assessment, environmental impact, financial concerns, scalability, and long-term stability need to be resolved. Despite these obstacles, nanotechnology presents viable and long-lasting ways to reduce water pollution; nevertheless, further study and cooperative efforts are needed before these solutions can be fully realized on a worldwide scale.

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IS A FUSED RING A MORE EFFICIENT Π–SPACER THAN AN UNFUSED SPACER FOR DYE-SENSITIZED SOLAR CELLS? A CRITICAL REVIEW

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Abstract:

In addressing the growing need for energy, this chapter explores the utilization of renewable sources, particularly solar energy, as primary sources like oil, natural gas, and coal continue to deplete and pollute the atmosphere. It delves into the emergence of dye-sensitized solar cells (DSSC) and the discovery of organic dyes. Highlighting the importance of fused π–spacer in DSSCs, comparison results indicate that the efficiency is more significantly influenced by fused spacer groups compared to unfused rings.

Keywords: Dye Sensitized solar cells; Scarce metal dyes; Donor-π-Acceptor dyes; Thiophene spacer; Fused ring spacer.

Introduction:

1. Necessity of energy and Solar cell:

In recent years, the demand for alternative energy sources has grown significantly. This can be attributed to the rapid depletion of natural resources such as oil and coal, as well as the associated risks of nuclear power technology [1]. The increased demand for alternative energy sources in recent years has prompted the exploration of solar energy, which is captured by solar cells. Solar energy offers the advantages of being pollution-free and potentially cost-effective [2]. However, conventional silicon-based solar cells, despite achieving impressive efficiency levels (~25%), face limitations for large-scale power generation due to their high cost and fabrication challenges with large panels [3].

2. Dye-Sensitized Solar Cells (DSSC) and its advantages:

As a result, there is growing interest in cheaper alternatives such as organic dye-sensitized solar cells (DSSC) that utilize ruthenium sensitizers, offering promising prospects as an alternative solution [4]. Dye-sensitized solar cells (DSSCs) have garnered significant attention for their intriguing ability to convert photovoltaic energy at a lower cost compared to conventional silicon-based semiconductor photovoltaic devices. This attention stems from the seminal work reported in 1991 by O'Regan and Gratzel [5]. Photosensitizers play a crucial and

decisive role within the components of a DSSC, as they significantly influence the overall performance of the solar cells. Furthermore, they are responsible for light absorption, efficient electron injection into the mesoporous TiO_2 layer, and preventing the recombination of injected electrons with the oxidized redox mediators (Figure 1 and 2). Therefore, the development of photosensitizers has been one of the important research topics in DSSCs and various dyes explored such as ruthenium complexes, porphyrin dyes, and organic dyes [6]. In recent times, metal-free organic sensitizers have garnered significant interest for practical applications, due to their (i) chemically ingenious and facile synthetic strategies for molecular engineering; (ii) tunable spectral properties enabling broad and efficient visible-light absorption; and (iii) cost-effectiveness in manufacturing [7].

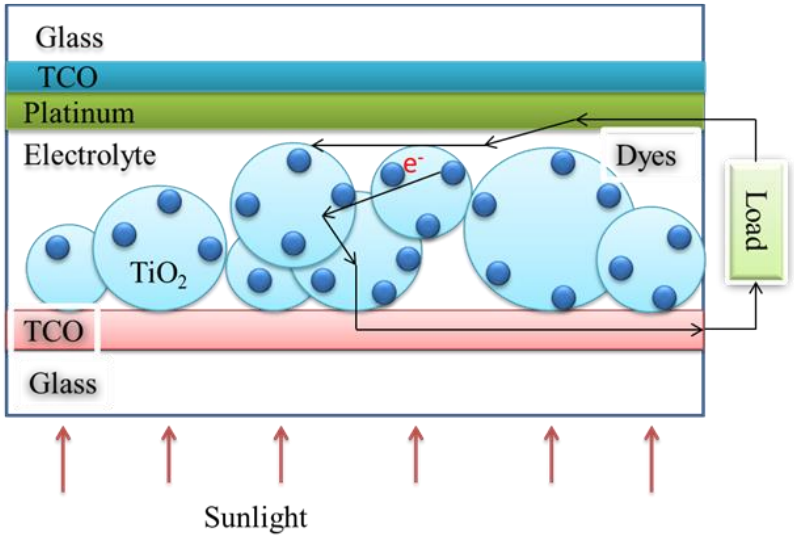


Figure 1: Schematic view of DSSCs.

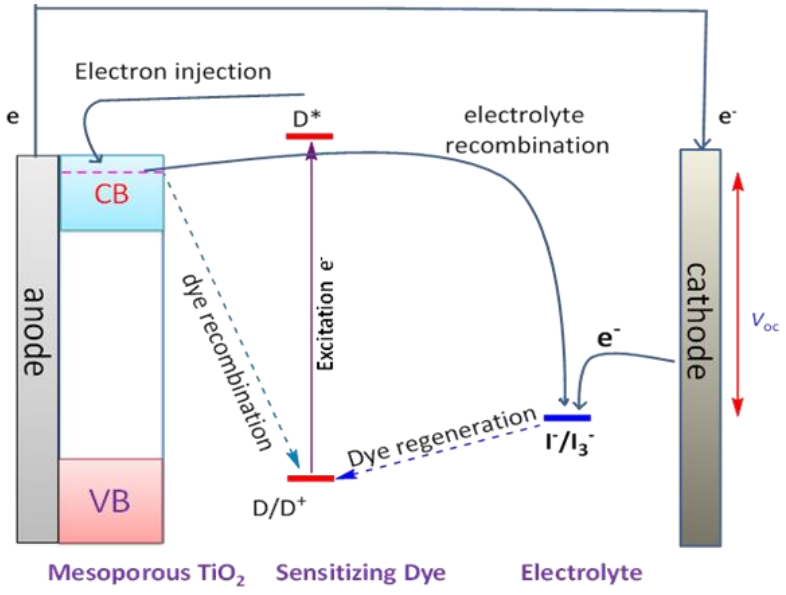


Figure 2: Schematic energy level diagram of a type DSSCs.

The parameters that determine the power conversion efficiency of a DSSC include the short-circuit photocurrent (J_{sc}), open-circuit photovoltage (V_{oc}), fill factor (FF), and incident solar power on the cell (P_{inc}). The short-circuit photocurrent is influenced by the dye's light-harvesting power, injection characteristics, and back electron transfer processes. The open-circuit photovoltage is determined as the difference between the Fermi level of the semiconductor (with a given value) and the Fermi level of the redox couple (with a given value) [8].

$$\eta = \mathrm{FF}\ \frac{V_{\mathrm{OC}}\ J_{\mathrm{SC}}}{P_{inc}} \qquad (1)$$

The majority of organic dyes that have been reported utilize the donor–pi–acceptor (D–π–A) structural motif, with aryl amine and 2–cyanoacrylic acid being the most commonly employed donors and acceptors, respectively [9]. A wide range of organic scaffolds has been utilized in dye-sensitized solar cells (DSSCs) based on the D–π–A approach, with reported device efficiencies exceeding 10% in many cases [10-20]. The advantage of the D–π–A or push-pull structure architecture is evident in its effective intra-molecular charge transfer (ICT) properties, facilitating the transfer of electrons from the donor (D) to the acceptor (A) through the π-conjugated bridge. Furthermore, upon electron injection into the TiO_2 conduction band, the hole formed on the π–spacer migrates to the donor portion of the sensitizer, thereby minimizing electron recombination from the TiO_2 conduction band with the excited dye [21]. The acceptor side appears to be the only part that has been optimized, with cyanoacrylic acid being the predominant anchoring group. This choice is primarily driven by its potent electron–withdrawing properties and the presence of an acidic group that facilitates the binding of the dye to TiO_2. There is currently no definitive consensus on the donor choice. Nevertheless, triphenylamine-derivatives have consistently exhibited favourable photovoltaic properties in numerous research reports.

3. Electron donor–π bridge–electron acceptor DSSCS:

Typically, organic dyes follow a D−π−A (electron donor–π bridge–electron acceptor) framework, where electron transfer occurs from the donor (D) to the acceptor (A) segments via the π–conjugated linker when photoexcited. This structure is commonly observed in pure organic dyes. The properties of D−π−A dyes can be modulated through various approaches, including: (i) the reduction of the molecular energy gap (ΔE) to achieve a more substantial overlap between the electronic absorption spectrum of the dye and the standard solar emission spectrum, thereby increasing photocurrent efficiency, and (ii) the tuning of steric and/or electronic structures of the dye to modulate the physicochemical characteristics of the titania/dye/electrolyte interface, resulting in a reasonable open-circuit photovoltage [22]. Apart from providing exceptional

thermal and electrochemical stability, the π-bridge also plays a crucial role in fine-tuning the primary optoelectronic characteristics of the dyes. It accomplishes this by adjusting the energy levels of frontier molecular orbitals and expanding the optical absorption range into the red or even near-infrared region [23].

4. Importances of pi spacer:

Among the π-linkers thiophene derivatives have shown their effectiveness as π-linkers in organic dyes for dye-sensitized solar cells (DSSCs). Furthermore, the presence of π-linkers, such as furan, and benzene, significantly contributes to the improvement of spectral response in sensitizers. This enhancement is attributed to the unique properties of these π-linkers, including resonance energy, thermal stability, and more. It is observed that the inclusion of thiophene has been found to be beneficial in expanding the spectral response of chromophores when compared to reference dyes lacking π-linkers [24].

Fused thiophene derivative containing organic dyes:

The electronic absorption spectrum of a dye can be augmented through the rigidification of conjugated linkers achieved by covalently immobilizing adjacent 5-or 6-member aromatic rings. This approach not only mitigates the rotational disorder of molecules but also enhances the delocalization capacity of π-electrons, resulting in a reduced energy difference (ΔE). Wang *et al.* conducted an investigation on the effects of various π-linkers, namely di(3-hexylthiophene), dihexyldithienosilole, dihexylcyclopentadithiophene, and N-hexyldithienopyrrole, in a triphenylamine-cyanoacrylic acid dye system. In comparison to a dye containing the di(3-hexylthiophene) linker, its three counterparts with rigidified dithiophene moieties exhibit red-shifts of the maximum visible absorption wavelength. The TD-DFT calculations effectively augment the observed red-shifts from **C239** to **C240**, **C218**, and **C241**. **C218** dye (Figure 3), exhibited an impressive efficiency of 9.4% with a short-circuit current density (J_{sc}) of 13.01 mA cm^{-2} and a fill factor (FF) of 0.76 [22].

Robertson investigated the influence of different π-spacers, namely thiophene, 3,4-ethylenedioxythiophene (EDOT), and cyclopentadithiophene (CPDT), in quinoxaline-based organic dyes (designated as **AQ201**, **AQ202**, and **AQ203**, respectively) (Figure 3) [25]. The calculated lowest HOMO-LUMO energy gap of **AQ203** is in good agreement with the observed maximum absorption peaks. Furthermore, the **AQ202**-based cell exhibited the highest PCE of 8.37% when utilizing a cobalt-based electrolyte. This enhanced performance is attributed to a broader absorption spectrum and a greater driving force for dye regeneration. To explore the incorporation of another fused thiophene ring, Lin *et al.* conducted an investigation into the influence of different π-conjugated linkers on the photophysical properties, electrochemical

properties, and photovoltaic performances. They introduced rigidified electron-rich heteroaromatics, namely cyclopentadithiophene (**CPDT**), dithieno[3,2-b:2′,3′-d]silole (**DTS**), and dithieno[3,2-b:2′,3′-d]pyrrole (**DTP**), into the π-conjugated bridge to enhance the electronic communication between the donor and the acceptor moieties.

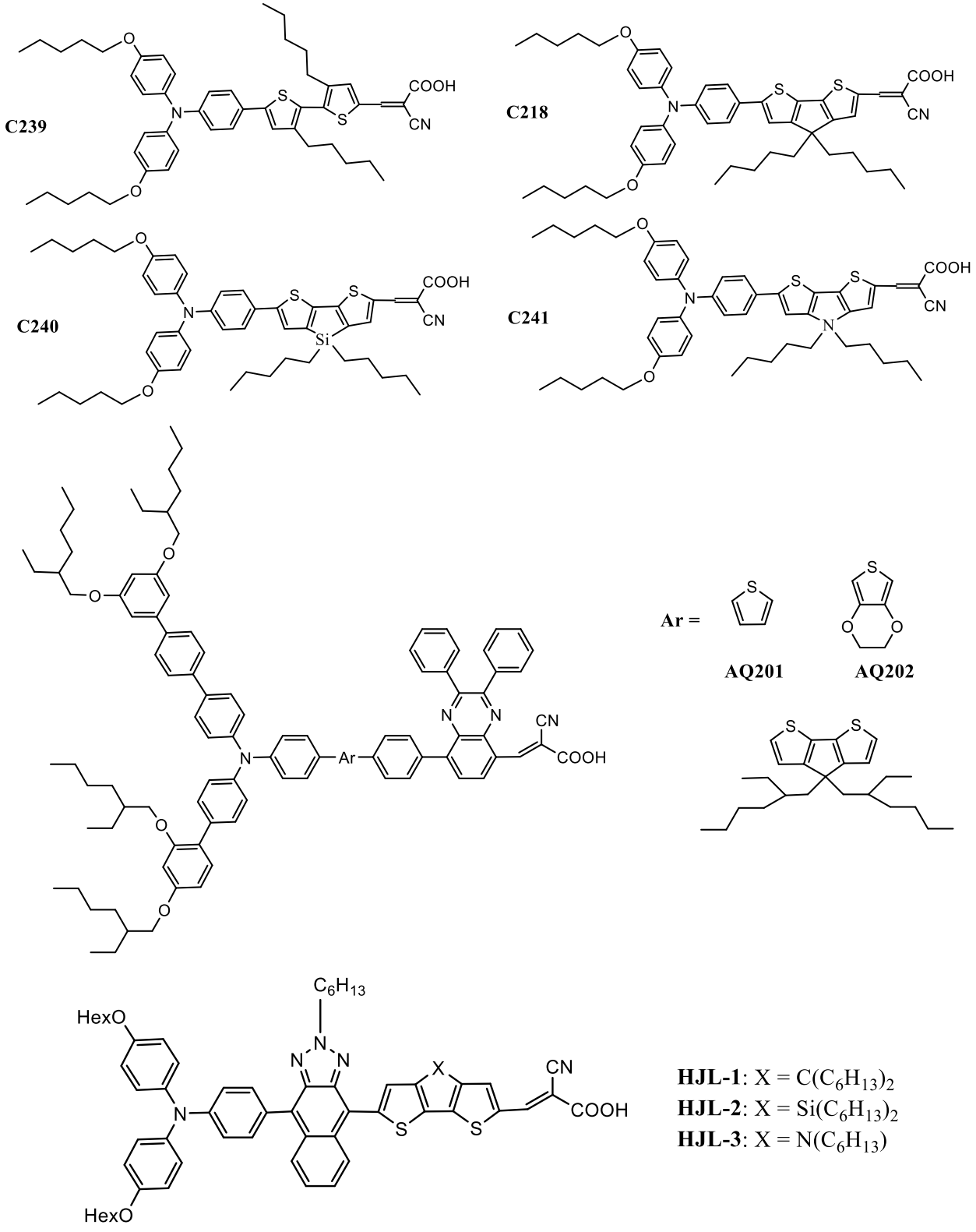
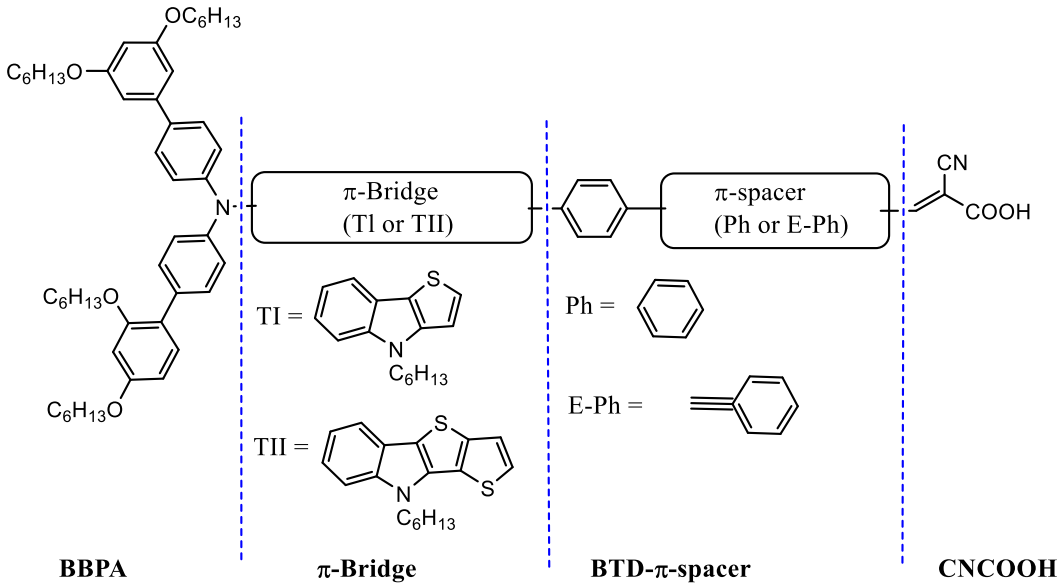


Figure 3: Geometries of different D-π-A structures.

They demonstrated that the incorporation of these dithienoheterocycles, **CPDT**, **DTS**, and **DTP**, in the π-conjugation frameworks resulted in a red-shift of the spectral response compared to the thiophene-bridged **NTz-1**. **HJL-3**, among the three dyes investigated, exhibited the highest Incident Photon-to-Current Efficiency (IPCE). This was attributed to its higher adsorption capacity on the TiO_2 substrate, reduced dark current, and efficient electron injection from the excited sensitizers [26].

In another study, Kim *et al.* developed **SGT–138**, **SGT–150**, and **SGT–151** to investigate the effects of the π-bridging unit and acceptor unit extensions in **SGT**–organic dyes. Interestingly, extending **TI** to **TII** resulted in a bathochromic shift of the aromatic π–π* band to a greater extent compared to the extension of **BTCA** to **BTECA** (Figure 4). Conversely, the acceptor extension caused a more pronounced red-shift than the π–bridge extension in the ICT band. Additionally, the extension of **TI** to **TII** primarily increased the HOMO energy level of the dye, while the extension of **BTCA** to **BTECA** predominantly decreased the LUMO energy level of the dye. Ultimately, the DSSCs utilizing the newly developed **SGT**-dyes along with an HC-A1 co-adsorbent demonstrated favorable power conversion efficiencies. Specifically, **SGT–137, SGT–138, SGT–150, and SGT–151** achieved high efficiencies of 11.23%, 11.30%, 11.05%, and 10.80%, respectively [27].



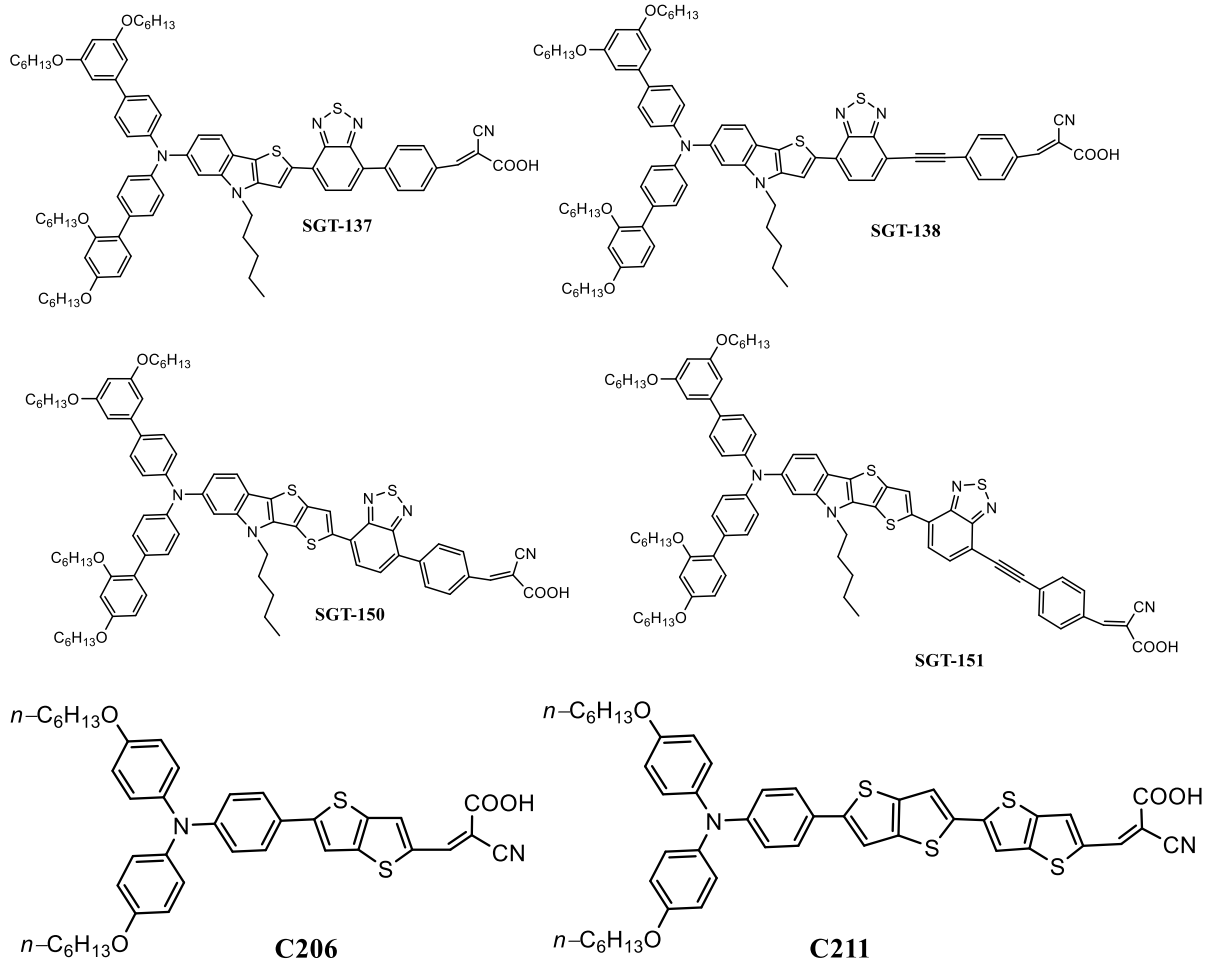


Figure 4: Geometries of different D-π-A structures

Peng Wang and colleagues conducted an investigation to explore the impact of thienothiophene (**C206**) and bisthienothiophene (**C211**) spacer groups in enhancing the light-harvesting capacity and gaining insights into the optoelectronic properties of these two chromophores (Figure 4). Computational studies revealed that the addition of one more thienothiophene unit not only slightly elevated the HOMO level but also reduced the LUMO level, leading to a narrowed HOMO-LUMO gap primarily influenced by the LUMO level. Dye **C211** demonstrated an overall conversion efficiency of 8.02%, surpassing **C206** (PCE=7.5%), thus highlighting the significance of the additional thienothiophene spacer group [28].

Dihexyl- and dihexyloxybenzene-substituted dithieno[2,3-d:2′,3′-d′]thieno[3,2-b:3′,2′-b′]dipyrrole (DTDP) were employed as effective π-conjugated linkers in Dye-Sensitized Solar Cells (DSSCs) (Figure 5). Xue and co-workers conducted a comparative study on the electronic properties of both dyes in comparison to a reference dye incorporating the hexyl-substituted dithieno[3,2-b:2',3'-d]pyrrole (**DTP**) linker. Their findings revealed that both dyes with multifused thiophenes exhibited red-shifts by 35–37 nm and an enhanced maximum molar visible absorption coefficient. Moreover, the presence of double peripheral side chains on the

DTDP-bridge contributed provided steric hindrance, which facilitated to prevent the dye aggregation. When a dye-sensitized solar cell employed the **X77** photosensitizer and the Co-bpy electrolyte, it exhibited a power conversion efficiency of 6.6% [29]. Marks *et al.* conducted a study on a series of organic chromophores containing fused thiophenes, specifically **TPA-TTAR-A (1), TPA-T-TTAR-A (2), TPA-TTAR-T-A (3)**, and **TPA-T-TTAR-T-A (4)**, which were employed as sensitizers in dye-sensitized solar cells (DSSCs). It is widely recognized that the inclusion of a thiophene moiety in these molecules enhances the conjugation length, extends the absorption wavelength, and results in a gradual increase in the energy level of the highest occupied molecular orbital (HOMO). Among the dyes investigated in this study, dye **3** exhibited a notable power conversion efficiency (PCE) of 10.1%, accompanied by a *V*oc of 0.833 V, J_{sc} of 16.5 mA/cm^2, and FF of 70.0%. Importantly, this PCE stands as one of the highest reported to date for metal-free organic DSSC sensitizers utilizing an I^-/I_3^- redox shuttle [16].

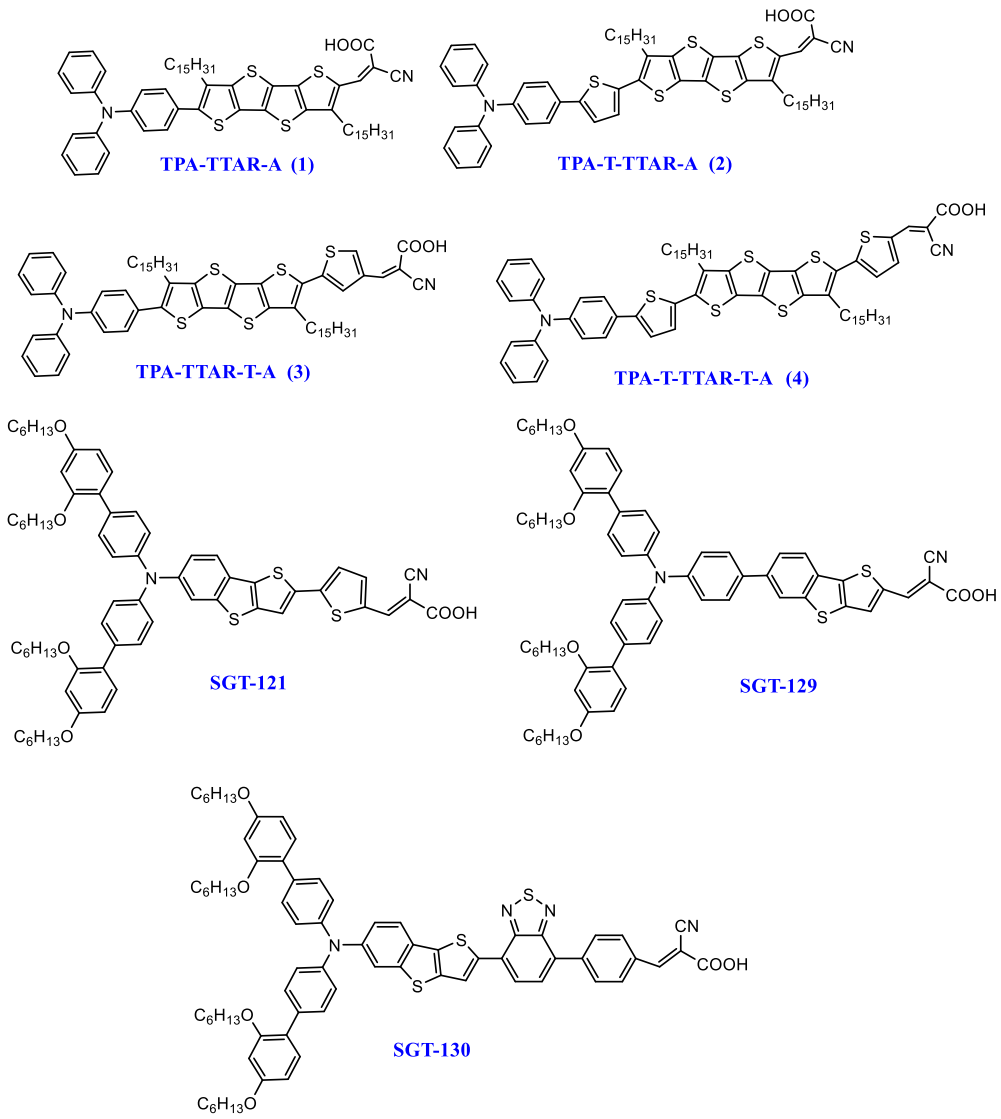


Figure 5: Geometries of different D-π-A structures

Kim *et al.* reported three novel types of metal-free organic sensitizers based on thieno[3,2-b][1]benzothiophene (**TBT**), designated as **SGT–121**, **SGT–129**, and **SGT–130** (Figure 5) [10]. This thieno[3,2-b][1]benzothiophene (**TBT**) possesses an asymmetric structure, where the thienothiophene unit is incorporated adjacent to the benzene moiety **SGT–130.**

Computational studies:

Zhang *et al.* conducted quantum chemical calculations to investigate a class of D–π–A dyes featuring rigid fused π–bridges consisting of electron–rich and electron–deficient segments [30]. In their pioneering research, Su and coworkers investigated a series of metal-free organic dyes containing diverse π-spacer groups and compared their findings with previously reported synthesized dyes. In their comparative analysis with dye **1**, they observed that the π-conjugation degree of dye **4** could be enhanced by substituting thiophene with thienothiophene (Figure 6). Furthermore, this modification resulted in similar driving forces, improved light harvesting efficiency, and a red-shifted absorption, leading to a larger J_{sc} potential. Furthermore, in comparison to the reference dye **1**, the incorporation of a thienothiophene spacer in dye **4** resulted in an enhanced V_{oc} (open-circuit voltage). This observation suggests that dye **4** holds promise as a more efficient diarylamine-fluorene-based organic dye for use in DSSCs.

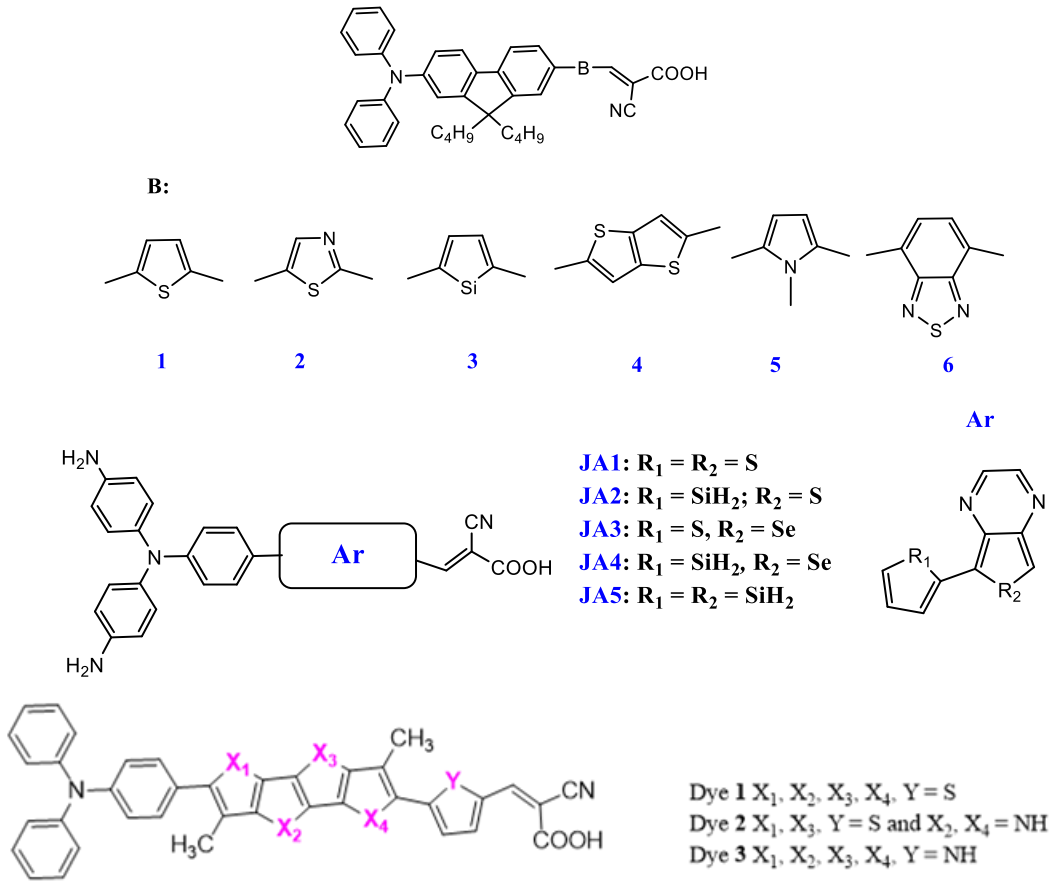


Figure 6: Geometries of different D-π-A structures.

Jiang *et al.* have presented a series of D–π–A dyes (**JA2**–**JA5**) utilizing five-membered heterocyclic silole-spacer and selenophene-spacer moieties (Figure 6). In comparison to the conventional thiophene-based dye **JA1**, the designed dyes **JA2**, **JA4**, and **JA5** exhibited significantly broadened and red-shifted UV–Vis absorption spectra in the visible region. The computational results indicate that incorporating a silole/selenophene-based spacer into the D–π–A configuration, especially in the case of **JA2** and **JA4** dyes, leads to improved performance in Dye-Sensitized Solar Cells (DSSCs). This is attributed to their enhanced photocurrent response compared to the other designed sensitizers [31].

Our contribution:

Through my contributions to the field and other research, it has been affirmed that computational studies make the prediction of promising DSSCs much easier. Such studies prove beneficial in guiding experimentalists to achieve the ideal design for dyes applicable to both n- and p-type semiconductors. In the designed dye molecules, fused-pyrrole rings were utilized as spacer units, aiming to narrow the HOMO–LUMO energy gap [32]. This choice is based on the lower resonance energy observed in the fused-pyrrole spacer groups compared to thiophene spacer groups. Playing a significant role, the higher conjugative effect of fused-pyrrole rings influences various factors in determining the short-circuit current density (J_{sc}), including the driving force of electrons ($\Delta G_{injection}$) and the singlet excited state lifetime (τ). Additionally, these conjugative effects extend to impact the open-circuit photovoltage (V_{oc}), relying on dipole moments (μ_{normal}) and the number of electrons transferred from the dye to the TiO_2 surface (Δq). Upon comparing specific calculated values, it becomes apparent that dye **3** demonstrates a superior λ_{max} (539 nm) and $\Delta G_{injection}$ (1.82 eV) compared to dye **1**, where λ_{max} is 497 nm, and $\Delta G_{injection}$ is 1.28 eV (Figure 6). Moreover, the singlet excited state lifetime of dye **3** (2.2 ns) surpasses that of dye **1** (1.7 ns). Consequently, the calculated results strongly suggest that dye **3** is likely to exhibit a higher J_{sc} value than dye **1**, given its elevated $\Delta G_{injection}$, τ, and λ_{max} values.

Conclusion:

The primary objective of this study is to conduct a comprehensive review of the importance of fused π–spacer in DSSCs. The goal is to enhance the feasibility of developing low-cost, flexible, environmentally sustainable, and easily synthesized Dye-Sensitized Solar Cells (DSSCs). Despite nuclear fission being initially considered a promising alternative, it poses significant environmental challenges and issues related to waste disposal. Consequently, the second alternative emerges as a more viable and sustainable option. The aforesaid literatures suggest that the dyes having fused ring pi spacer have superior performance than the single ring pi spacer.

Acknowledgements:

I extend my gratitude to Mahishadal Raj College and all my colleagues for their unwavering support throughout my research endeavors. Special thanks to Dr. Bishwajit Ganguly, my PhD supervisor, for invaluable guidance. Heartfelt appreciation goes to my loving wife, a constant pillar of support, and to my parents for their enduring encouragement. I would also like to express my thanks to the diligent reviewer and editors whose constructive comments significantly contributed to refining this chapter. Finally, my acknowledgment extends to the Almighty for His guidance and blessings.

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RECENT ADVANCEMENTS IN NANOTECHNOLOGY AND THEIR PREDICTED APPLICATIONS IN PHARMACY

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Abstract:

As baby boomers retire, the already large sector of healthcare would grow much more. Given the growth of the consumer base and rising demand, the pharmaceutical industry would create new technologies to suit patient expectations. As medications become increasingly complicated and harmful, new distribution systems are needed to get them to the right regions of the body. As a result, well-known pharmaceutical companies are applying innovative approaches and technology. Pharmaceutical nanotechnology is one of the most comprehensive technologies. Pharmaceutical nanotechnology is one of the most comprehensive technologies. Pharmaceutical nanotechnology gives up new avenues, techniques, and perspectives that are predicted to have a profound influence on many areas of disease diagnosis and treatment. Pharmaceutical Nanotechnology offers the ability to enhance materials and medical technology while also contributing to technological growth in sectors where more experienced and traditional technologies may be reaching their limits. Finally, recent advancements, the commercialization of many pharmaceutical nanotools, and increased interest from academia, governments, and organizations all suggest nano-based drug delivery systems have immense potential and range soon.

Keywords: Nanostructures, Future of nanotechnology, Nanoshell, Cancer treatment.

Introduction:

Nanotechnology is the investigation of extremely small structures. Pharmaceutical nanotechnology is concerned with the formation and development of small structures, such as atoms, molecules, or compounds, ranging in size from 0.1 to 100 nm, into structures that can then be developed into special devices with desired properties.

Nanoparticle drug delivery systems are engineered technologies that use nanoparticles for the targeted delivery and controlled release of therapeutic agents. The modern form of a drug delivery system should minimize side-effects and reduce both dosage and dosage frequency.

Typical accessible structures are frequently sub-micrometer in size, lie within the optical resolution envelope, and can only be seen faintly under a microscope. Because the typical organisational size is now in the nanoscale range, recent advances have concentrated on the size range below these dimensions, and the procedures and methods are known as "nanotechnology". Drugs typically travel throughout the body until they reach the area where the disease is prevalent. These nanotechnology-based drugs can deliver medicine to a specific location, increasing efficacy while decreasing the likelihood of side effects. Nanotechnology may be essential for target-specific drug treatment and early illness detection, which are top research priorities.

Various Types of nanosystems in pharmaceuticals

Nanotechnology is classified as two types.

1. Nanodevices 2. Nanostructures.

Naotechnology is classification briefly shown in Figure.1.

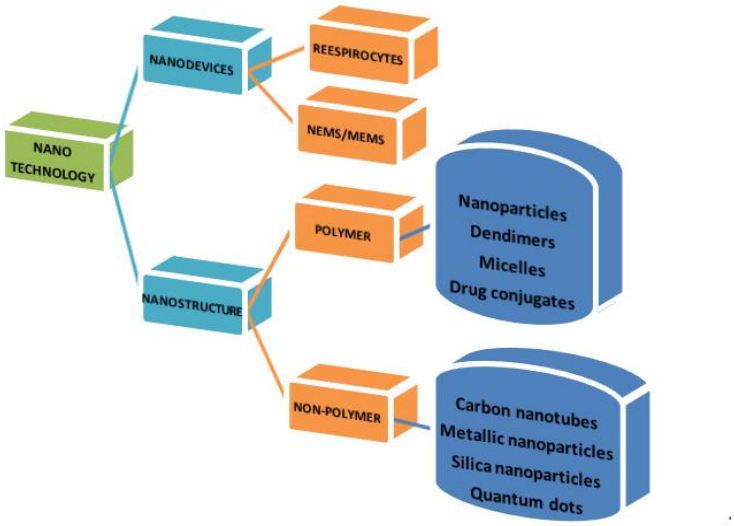

Figure 1: Various types of Nano systems in pharmaceuticals

1. Nanodevices

Nanodevices are nanoparticles engineered to interact with cells and tissues and perform specific functions. Imaging tools are the most well-known nanodevices. Miniature camera pills can be taken orally. Examples include high electron mobility transistors, heterojunction bipolar transistors, resonant tunnelling diodes, and quantum well optoelectronic devices such as lasers and detectors. Nanodevices have numerous applications, including electronics, medicine, energy, and environmental science. Continued research and development in these fields holds enormous promise for future advances and innovations.

2. Nanostructures

A nanostructure is a structure with dimensions ranging from microscopic to molecular. When discussing nanostructures, it is critical to distinguish between the number of nanoscale dimensions in an object's volume. Nanoparticles are colloidal particles ranging in size from 1 to 100 nm, which can be used to encapsulate, adsorbed, or dispersed drugs. Liposomes, micelles, nanoporous materials, nanofibers, and other nanoparticulate drug delivery systems have all been studied previously. Nanostructures are categorised into two types. A. Non-polymeric nanostructures; B. Polymeric nanostructures.

A. Non-polymeric nanostructures

These are some various types explain briefly on the below. Pictorial representation shown in figure 2.

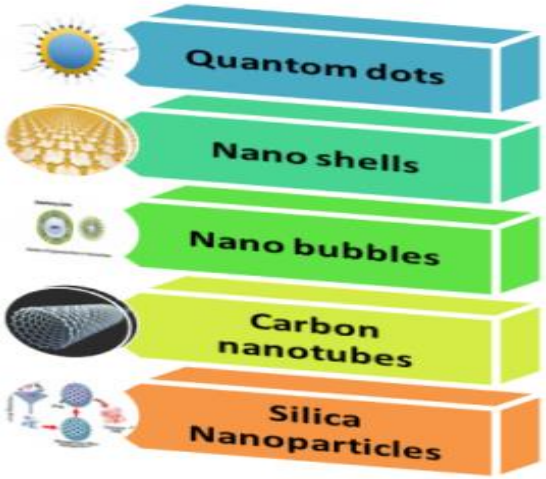

Figure 2: Non-polymeric nanostructures

a. Carbon nanotubes

Carbon nanotubes were first discovered in 1991. They're tubular carbon-based structures. These tubes are made up of cylinders of graphite sheets that are sealed at one or both ends with bucky balls and range in length from 1 to 100 nanometers. Single-walled nanotubes (SWNTs) and multiwalled nanotubes (MWNTs) are two recently popular designs. C60-fullerenes are also present in typical configurations. They come in a variety of graphite cylinder configurations and are characterised by their cage-like and hollow structure. They are ideal for drug encapsulation due to their surface features and size, as well as their important physical properties. The DNA helix has half the diameter of SWNTs. MWNTs, on the other hand, have diameters ranging from a few to tens of nanometers, depending on the number of walls in their structure. Fullerenes and carbon nanotubes are most commonly produced via chemical vapour deposition, combustion procedures, and electric arc discharge. The strength and stability of these structures are used to

characterise them as reliable drug transporters. Nanotubes enter cells via endocytosis, which is insertion across the cell membrane. Fullerene structures were capable of tissue targeting as well as intracellular mitochondria targeting. Furthermore, they were discovered to have both antioxidant and antimicrobial properties.

b. Quantum dots

Quantum dots (QDs) are small semiconducting structures ranging in size from 2 to 10 nm. They are nanocrystals made up of an inorganic semi-conductor core (CdSe) and an organic shell coated with zinc sulphide to improve optical properties, and they glow when exposed to light. A cap increases the solubility of QDs in aqueous buffers. The particle's radius ranges between 2 and 10 nm. Long-term tracking of intracellular processes, in vitro bio-imaging, and real-time monitoring have all been linked to a number of benefits. Some of the diagnostic and therapeutic applications of QDs include cell labelling, biomolecule detection and biological performance, DNA hybridization, immunoassays, and the development of non-viral vectors for gene therapy, cancer carriers, and transport vehicles for biological and non-biological agents.

c. Nanoshells

Nanoshells are modified drug targeting models that consist of a silica core and a metal outer layer. These nanoshells have received a lot of attention in recent times. The properties of these particles can be altered by varying the ratio of core to shell. It is now possible to create nanostructures with specific physical properties, such as size and morphology. Because not all materials can be formulated in the desired morphologies, nanoshells are used to create new systems with a range of morphologies. To achieve the desired morphology, particles of specific shapes could be coated with a thin shell. These shells are cost-effective because precious materials can be added to low-cost cores. Immunological techniques can be used to target nanoshells; for example, gold nanoshells were occupied with antibody moieties on their outer gold surface to increase their targeting power towards cancer cells. Nanoshells serve a variety of functions, including chemical stabilisation of colloids, improved luminescence properties, and drug delivery.

d. Nanobubbles

Nanobubbles are bubble-shaped particles that form at the nanoscale at the interface between lipophilic surfaces in liquids. When heated to body temperature, they mix and form microbubbles that remain stable at room temperature. They form in supersaturated solutions as a result of gas nucleation at the hydrophobic surface, which causes air gas trapping. There are four types of nanoparticles: plasmonic, bulk, oscillating, and interfacial nanobubbles. Drugs for

cancer treatment were successfully loaded into these particles, allowing them to target tumour tissues and increase tumour cell uptake under ultrasound exposure.

e. Liposomes

Liposomes are artificial particles made of amphiphilic phospholipids that self-assemble. They are composed of spherical double-layered vesicles that surround an aqueous core domain that varies in size from 50 nm to several micrometres depending on the type. Liposomes' general biocompatibility and biodegradability make them appealing biologically. Liposomes are the most common nanosystems used as drug carriers in clinical trials. They can be used to reduce medication clearance while also lowering systemic effects and toxicity. Nanoscale modified liposomes have good pharmacokinetic properties for carrying DNA, RNA, proteins, and cancer treatments. Schematic pictorial representation shown in figure .3.

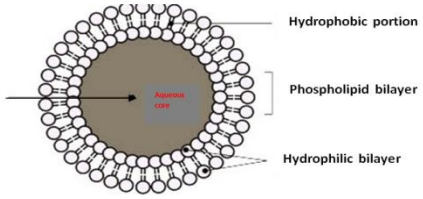

Figure 3: Liposome

Liposomes' limitations include a low loading capacity, rapid drug release, and the lack of adjustable drug release patterns. Because liposomes do not penetrate cells, drugs are released into the extracellular fluid as well. Surface modification can help to achieve stability and structural integrity against a hostile bio-environment after oral or parenteral administration. To counteract the drug's rapid release from liposomes, an ammonium sulphate gradient can be used to incorporate drugs into the water phase of liposomes. This will allow for consistent drug trapping and minimal drug loss in the circulation. Liposomes have also been paired with antibodies to deliver medication to specific targets.

f. Niosomes

Niosomes are molecular clusters formed in the aqueous phase by the self-assembly of non-ionic surfactants. Niosomes have a distinct architecture that enables them to serve as a novel delivery method for both lipophilic and lipophobic agents. Niosomes are made up of non-ionic surfactants, are non-toxic, and have high stability, making them a viable replacement for liposomes. In vivo, niosomes function similarly to liposomes, extending the circulation of the entrapped drug while altering organ distribution and metabolic stability. In addition to the preparation technique, the bilayer determines the characteristics of niosomes. It has been demonstrated that the entrapment volume during formulation decreases due to cholesterol

intercalation in the bilayers, resulting in a reduction in entrapment efficiency. The current conclusions for the use of niosomes in drug delivery are broadly focused on the entrapment of potent drugs, anticancer, and antiviral medications. Niosome shown in Figure.4.

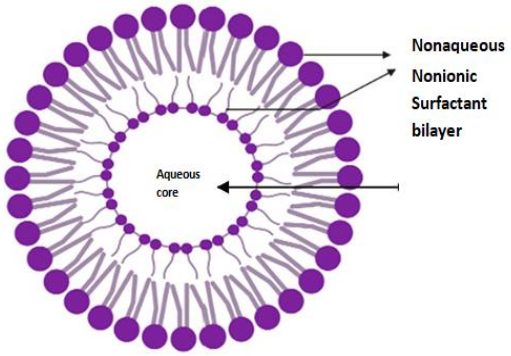

Figure 4: Niosome

B. Polymeric nanostructures

These are again classified briefly explain below and pictorial representation shown in Figure 5.

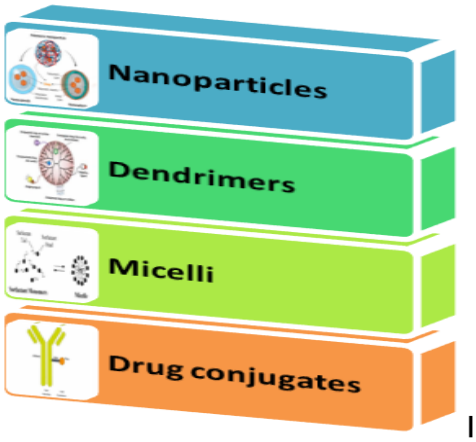

Figure 5: Polymeric nanostructure

a. Dendrimers

Dendrimers are a type of polymer distinguished by their multi-branched structure and controllable size and shape. The degree of branching determines the size of these dendrimers, which can be adjusted. Furthermore, spherical branching within dendrimers forms voids that can be used for drug entrapment and delivery. Dendrimers' free ends, on the other hand, can be changed to form conjugates with other molecules. These nanostructures have advanced surface functionalization and stability, making them ideal for drug delivery. Construction is divided into three major categories: core, branches, and surface. These networks aid in the delivery of bioactives such as medications, genes, and vaccines to specific tissues. Solubility, gene therapy,

dendrimer-based drug delivery, immunoassay, and an MRI contrast agent are only a few of the uses for dendrimers.

b. Polymeric micelles

Polymeric micelles are micelles composed of lipophilic and lipophobic monomer units arranged in a block copolymer. They are composed of a centre of lipophilic blocks that is supported by a corona of lipophilic polymer chains. Corona-forming PEG blocks are used, and the length of a lipophilic center-forming block is comparable to that of a hydrophilic one. A micellar system has several advantages over traditional drug delivery systems. Using micelle-forming surfactants to promote drug solubility increases the solubility of a weakly water-soluble medicine.

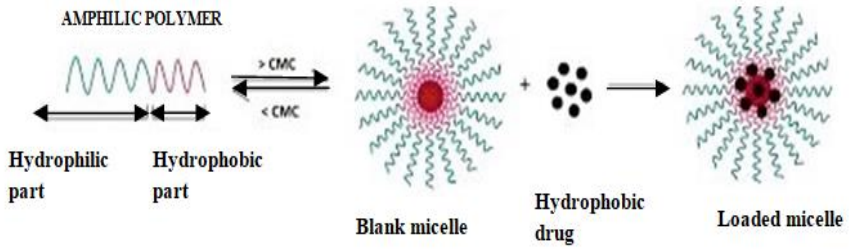

Figure 6: Polymeric micelle

They also increase medication permeability across physiological barriers, improving bioavailability. As a result, drug biodistribution has changed. They contribute to reducing the negative side effects of critical medications. Polymeric micelles remain in the blood for longer periods of time after intravenous delivery due to their smaller size and lipophilic shell, reducing their uptake by the reticulo-endothelial system. Micelles can also be made target-specific by chemically attaching a component to their surface. Because it is in micellar form, the medication is effectively protected from biological deterioration. Because it is micellar in nature, it will find its way to the desired organ or tissue.

c. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are mostly biodegradable and biocompatible, so researchers are interested in using biodegradable PNPs as a drug delivery system. PNPs are classified into vesicular systems (nanocapsules) and matrix systems (nanospheres). Researchers recently investigated advanced modifications of natural polymers, including synthetic polyesters. Chitosan is one of the best-known natural polymers. Many polymers, including artificial polymers, reduce toxic issues. Natural PNPs outperformed traditional delivery systems due to their superior efficiency and effectiveness. Nonetheless, they have some disadvantages, including poor reproducibility, degradation issues, and potential antigenicity. The manufacturing

technique determines how the encapsulated drug is released. PNPs have the potential to target intracellular and specific sites.

d. Nanocapsules

Nanocapsules and nanospheres differ in that the former are drug carriers with a core surrounded by a polymeric membrane, whereas the latter are structures with the drug dispersed throughout the polymeric matrix. PNPs can be thought of as a matrix in which the drug is evenly distributed. The medication can be dissolved, trapped, or encapsulated across or within the polymeric matrix. PNPs are an excellent alternative for cancer therapy and other applications because of their ability to customise medication delivery.

e. Solid lipid nanoparticles

Solid lipid NPs (SLN) were developed as a controlled alternative to emulsions, liposomes, and PNPs for colloidal drug delivery. SLNs are made from solid lipids and stabilised with surfactant(s). SLN has several advantages over other particle carriers for drug delivery, including improved tolerability, biodegradability, high bioavailability via the ocular route, and a targeted effect on the brain. SLN research has exploded in recent years, particularly with the high-pressure homogenisation technique. SLN has been produced and studied for a wide range of applications. Because of their small size, SLN can be injected intravenously and used to target drugs at specific sites.

Application of pharmaceutical nanotechnology

If poor adhesion and absorption are present throughout the body, a dose sufficient to be effective against the sick area is likely to have noticeably negative consequences. The medications currently in use rely on a minor difference in adhesion or absorption specificity. Pharmaceutical nanotechnology has also been focusing on the following applications:

1. Efficient delivery of drugs

Using nanoparticles to deliver medications has a number of benefits, including improved therapeutic efficacy and pharmacological properties. Nanoparticles improve poorly water-soluble drug solubility, change pharmacokinetics, lengthen drug half-life by lowering immunogenicity, increase drug precision for the target cell or tissue (thus reducing side effects), improve bioavailability, reduce drug metabolism, allow for a more controlled release of therapeutic compounds, and facilitate the simultaneous delivery of two or more medications for combination treatment.

2. Engineering tissue

Nanotechnology has the potential to assist in tissue regeneration and repair. To artificially boost cell proliferation, "tissue engineering" uses growth hormones and nanomaterial scaffolding. Tissue engineering has the potential to replace modern conventional treatments such

as organ transplants and implanted devices. Nano- and microtechnologies can be integrated with biomaterials to produce tissue-engineered scaffolding that can support and regulate cell behaviour.

3. Chemical diagnostics

This new problem could be solved by combining nanoparticles with other nanotechnology-based materials, as well as developing technologies that allow for diagnostics at the level of individual molecules and cells. QD particles serve as contrast agents in bioimaging, providing significantly higher resolution than existing fluorescent dyes. Cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide are the most commonly used quantum dots.

4. In curing cancer

Colloidal drug delivery methods, including liposomes, micelles, and nanoparticles, have received substantial investigation for use in the treatment of cancer. Drug-delivery systems are more effective because of their small size, decreased drug toxicity, time-controlled drug release, changed pharmacokinetics, and altered biological dispersion of the medicine.

5. Implants and artificial organs

Another area where nanotechnology advancements could be used effectively is the creation of artificial cells, tissues, and organs. Artificial cells, particularly those that perform metabolic functions, are being studied extensively in order to replace damaged or dysfunctional cells and organs.

6. Pharmaceutical drug discovery

Nanotechnology aids in the identification and validation of targets by identifying the protein at the interface or one was. Nanotechnology will improve medicine distribution by miniaturising, mechanising, imitating, and increasing test reliability. Single-walled carbon nanotubes are effective in detecting pathogen surface proteins. Quantum dots are used to track the movement of individual glycine receptors in the neuronal membranes of living cells for periods of milliseconds to hours.

Benefits of utilizing nanoparticles as a drug delivery system

The benefits of employing nanoparticles as drug vehicles are because of two key characteristics: their tiny size and the use of biodegradable materials in the majority of cases. The effectiveness of most medication delivery methods is found to be largely reliant on particle size. Drug nanoparticles exhibit increased solubility and superior bioavailability which is a result of their small particle size and large surface area. Additionally, their ability to cross the blood brain barrier, entering pulmonary system, endothelium of tumors and absorption through tight junctions of skin endothelial cells, give them added value. The nano-range size of these particles,

in general, allows for effective absorption by various cell types as well as selective drug accumulation in the target locations. Nanoparticles also have the benefit of being more adequate for intravenous administration than conventional microparticles. The smallest body capillaries have a diameter of 5–6 m. To make sure that particles do not cause embolism, the size of particles dispersed in the circulation should be substantially less than 5 m. Using both natural and synthetic biodegradable polymers for nanoparticle preparation give them the advantages of targeted drug delivery, improve bioavailability and achieve sustained release behavior of medications from a single dose at the target site over a prolonged period of time; by adaptation of the system, endogenous enzymes can be prevented from destroying the drug. Furthermore, typical oral or injectable medicines now accessible for use are not necessarily provided in the most suitable formulation. As a result, goods containing proteins or nucleic acids will require more creative carrier systems (nanoparticles) to improve their efficacy and avoid any instability

Advanced development of nanoparticles in medicine

1. Nanoparticles in the treatment of chronic kidney diseases

Nanoparticles are used in urology and nephrology to treat kidney diseases. Ferumoxytol has been combined with nanoparticles for the treatment of patients with chronic kidney disease or end-stage renal disease who do not produce enough erythropoietin. Because of the onset of numerous diseases in this area, PEGylated gold nanoparticles can also target the mesangium—contractile cells that make up the central stalk of the kidney's glomerulus. Rhein, an anthraquinone derivative used to treat diabetic nephropathy, has improved its distribution and therapeutic efficacy thanks to nanoparticle technology. Rhein nanoparticles were made with triblock amphiphilic. Rhein nanoparticles were produced using triblock amphiphilic polymers, specifically polyethylene glycol-co-polycaprolactone-co-polyethylenimine. The nanoparticles were approximately 75 nm in size, which is ideal for kidney-targeted drug delivery.

2. Nanoparticles for treatment of tuberculosis by chemotherapy

The changed release behaviour of the anti-TB medicine-loaded nanoparticles after oral administration was responsible for their increased efficacy. Three major medicines, rifampin, isoniazid, and pyrazinamide, were co-incorporated into PLG nanoparticles. The therapeutic concentrations of these medications in tissues lasted 10 days, but free drugs lasted only one day in plasma after injection.

3. Nanoparticles topical drug delivery for skin diseases

PNPs are the most common nanoparticles used to administer medications to the skin. PNPs derived from chitosan and alginate are used to treat acne, and they outperformed benzoyl peroxide alone in antibacterial efficacy against Propionibacterium acnes. Liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers all adhere to the skin's surface.

Liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC) adhere to the skin's surface, allowing for lipid exchange between the stratum corneum's outermost layers and the carrier, resulting in better medication penetration. Lipid-based carrier systems containing glucocorticoids and T-cell suppressing drugs like cyclosporin and tacrolimus were used to treat inflammatory skin diseases such as psoriasis and atopic eczema. Recent research has revealed that incorporating retinol into Compritol-based SLN causes the drug to be released more quickly than with conventional carriers.

4. Applications of nanoparticles in treating Alzheimer's disease

One of the most recent approaches to increasing CNS penetration for the diagnosis and treatment of neurodegenerative diseases such as Alzheimer's disease is the use of nanoparticles. PNPs are promising candidates among the various nanocarriers used because, in addition to being able to open the Blood Brain Barrier's tight junctions, they effectively conceal the membrane barrier confining the drug molecule's characterizations, prolonging drug release, and protecting drugs from enzyme hydrolysis.

5. Nanoparticles containing different anticancer agents

Nano-oncology is a new field of medicine that employs nanoparticles to treat cancer. Nanoparticles are an effective medication that improves cancer cell targeting and overcomes multidrug resistance in cancer tissues. Because of its biocompatibility and long-term drug release, PLGA is a popular polymer for creating nanoparticles. It has even been used to create drug-loaded nanoparticles for cancer therapy. PLGA has been successfully used to produce anticancer drugs such as doxorubicin, 5-fluorouracil, paclitaxel, and dexamethasone. In 1999, the FDA approved Nutropin Depot, a microsphere version of Somatropin-PLGA nanoparticle, as a once-only treatment. Nutropin Depot, a microsphere version of Somatropin-PLGA nanoparticle, was approved by the FDA in 1999 as a monthly alternative to daily HGH injections. Doxorubicin is an anticancer medication that is used to treat a wide range of cancers. This feature limits its therapeutic potential because it is a highly toxic substance that affects not only tumour tissue but also the heart and kidney. In contrast, creating doxorubicin in liposomes resulted in an FDA-approved nanomedical drug delivery system. The new liposomal formulation decreased doxorubicin transport to the heart and kidney while increasing doxorubicin accumulation.

6. Nanoparticles in vaccination against COVID-19

From 2020 onwards, all scientists and researchers are focusing their efforts on developing treatments to combat the global COVID-19 virus outbreak. In 2021, the importance of nanoparticle technology in the development of therapeutic formulations for the diagnosis, treatment, and promotion of long-term human immunity against COVID-19 was highlighted. The recorded genome structure of Corona viruses, as well as the sequence of the protein laying

the virus surface, served as the foundation for the creation of COVID-19 nanoparticle-based vaccines (CNPBV) and accelerated the time required for their development. Spikes exist.The presence of spike proteins on the outer surface of the COVID-19 virus, which have a high affinity for nano-formulations and a high affinity for host cell receptors, was used as a key feature in the development of CNPBV. The food and drug administration (FDA) approved a promising nanotechnology-based vaccine that demonstrated its significant value in prophylaxis against the COVID-19 virus, with a high percentage of 90% of the vaccinated population among various vaccines produced with moderate efficacy to fight and limit the spread of the COVID-19 pandemic around the world. Two of these vaccinations are provided by Pfizer-BioNTech (BNT162b2 vaccine) and Moderna (mRNA-1273 vaccine). Pfizer-BioNTech (BNT162b2 vaccine) and Moderna vaccine (mRNA-1273 vaccine) use mRNA to encode the COVID-19 virus's spike glycoprotein (S), which is then incorporated into lipid-based nanoparticles. The encapsulated modified mRNA then helps to transport the protein antigen (spike protein) to immune cells, stimulating T cell activity and inducing antibody immunological responses within the human body.

Conclusion:

Nanotechnology is now regarded as the fundamental technology of the twenty-first century. Nanostructured materials and nanotechnology techniques are now being used to create better composite materials, materials with increased catalytic activity, materials with increased hardness and abrasion resistance, and a variety of consumer goods (such as cosmetics and sun protection) that improve people's well-being. Pharmaceutical nanotechnology holds enormous promise for the development of intelligent tissue-engineered materials as well as the delivery of bioactives and diagnostics in space and time. It provides new opportunities, tools, and a broader range of applications through its nanoengineered tools, which are expected to have a significant impact on a variety of diseases, diagnosis, prognosis, and treatment. Pharmaceutical nanotechnology has the potential to improve materials, medical devices, and support the development of new technologies in areas where more established and conventional technologies may be reaching their limits. It gives businesses new hope in the face of financial losses caused by off-patent pharmaceuticals by offering new patented technologies. Modern nanotechnology will soon be available, significantly improving disease detection, diagnosis, treatment, and prevention. Nanorobots and intelligent medicine are two examples.

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RESEARCH PROGRESS ON SYNTHETIC POLYMER SOLID ELECTROLYTES FOR SODIUM-ION BATTERY APPLICATIONS

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Introduction:

With the rising demand for large-scale batteries in electrical energy storage, sodium-ion batteries have garnered significant attention due to the abundance and cost-effectiveness of sodium resources. The performance and safety of a sodium-ion battery are intricately linked to the electrolyte, which not only determines the electrochemical window and energy density but also governs the interfaces between electrodes and the electrolyte. This review systematically presents the need for Na-ion batteries the importance of Sodium Salts, different types of electrolytes, outlining their specific requirements and design strategies for various battery systems, while addressing the remaining challenges that require attention. The article aims to emphasize the critical importance of the electrolyte in the domain of sodium-ion batteries.

Why to switch from Li-ion to Na-ion batteries?

Rechargeable lithium batteries, known as Li-ion batteries or LIBs, have evolved into highly successful and advanced energy storage devices. These batteries consist of two lithium insertion electrodes and a lithium-ion conducting electrolyte, eliminating the need for lithium metal. Their success can be traced back to the first commercialization of the carbon-$LiCoO_2$ cell in 1991. Initially designed as a power source for portable electronic devices, these batteries had a limited energy capacity of under 100Wh per single battery pack. They predominantly used cobalt/nickel-based layered materials as positive electrodes to achieve high energy within small-sized batteries. Over time, advancements have led to the integration of LIBs as an alternative power source for combustion engines equipped with a fuel tank. In the automotive market, plug-in hybrid electric vehicles that use large-scale LIBs as power sources have emerged. This development can diminish the reliance on fossil fuels for future transportation systems.

While LIBs offer a promising solution to address the formidable challenges associated with achieving sustainable energy development in the rising electric vehicle and emerging energy storage markets, a re-evaluation of the viability of lithium, an elemental component in

LIBs, is necessary. Despite being present throughout the Earth's crust, lithium is not considered abundant, with its relative abundance limited to just 20 parts per million (ppm).

Sodium-based batteries (SIBs), like lithium-based ones, were the subjects of early research, dating back to the period between the 1970s and 1980s. Furthermore, the extensively researched and commercially employed high-temperature sodium–sulfur (NaS) batteries and sodium–nickel ($NaNiCl_2$) batteries raise safety concerns because of their demanding operating temperatures ranging from 270 to 350 degrees Celsius. In recent years, owing to limited resources and continuously rising lithium prices, rechargeable SIBs have emerged as a compelling alternative to LIBs for electrical energy storage (EES). This is primarily because sodium, which is abundant in the Earth's resources, offers a cost-effective alternative to lithium. Given the similar characteristics of sodium and lithium, the operational principles of SIBs closely resemble those of LIBs. In an organic– liquid SIB system, sodium insertion materials are electronically separated by a porous separator with an ion-conductive aprotic electrolyte between them. During the charge and discharge cycles, the SIB system functions like a rocking chair as Na+ ions oscillate between the two electrodes. When charging, Na+ migrates from the cathode, diffusing through the electrolyte into the anode, where it further reacts with the anode material. The discharge process operates in reverse.

In addition to their cost-effectiveness, aqueous sodium-ion batteries (ASIBs) have the following appealing features: high safety standards and environmental compatibility in large-scale applications. The mechanism for sodium storage in these batteries resembles that of non-aqueous systems, although the operational voltage range is narrower than that of organic electrolyte systems (~1.23 V). This limited voltage in ASIBs significantly influences the thermodynamic electrochemical capacity of the solvent used in the electrolyte, which is water. Solid-state SIBs offer a comprehensive solution to safety concerns by using non-flammable solid-state electrolytes. These electrolytes effectively eliminate issues related to leakage and flammability, which are common in liquid-based SIBs. Moreover, the wide electrochemical capacity of a solid-state electrolyte allows the use of a metallic sodium anode and a high-potential cathode, which leads to the design of high energy density batteries.

Suitable Sodium salts

Sodium salts constitute a crucial element within organic liquid electrolytes, significantly contributing to and influencing the overall performance of these electrolytes. When choosing a sodium salt, several key considerations must be addressed. Firstly, the salt needs to exhibit adequate solubility and dissociation within the solvent. It's crucial that the resulting cations from the dissociation can move freely without hindrance to ensure ample charge carrier availability.

Additionally, the sodium salt must maintain electrochemical stability within a defined window, avoiding oxidation or reduction. The interplay between the sodium salt and the solvent shapes the electrolyte's redox potential, where the salt's anion and the solvent interact electrostatically, impacting the oxidative stability of the electrolyte.

Moreover, the ideal sodium salt should possess robust chemical stability and safety, remaining inert towards the diaphragm, solvent, electrode, and collector fluid. A significant aspect involves the salt's ability to effectively encourage the formation of a solid electrolyte interphase (SEI) film at the electrode-electrolyte interface. This feature significantly enhances the electrochemical performance of the electrolyte, notably its cycling stability. The sodium salts commonly employed include sodium perchlorate ($NaClO_4$), sodium tetrafluoro borate ($NaBF_4$), sodium hexafluoro borate ($NaPF_6$), sodium trifluoromethane sulfonate ($NaCF_3SO_3$, also known as NaOTf), sodium bis(fluoro sulfonyl)imide ($Na(FSO_2)2N$, abbreviated as NaFSI), and sodium bis(trifluoromethane sulfonyl)imide ($Na(CF_3SO_2)2N$, abbreviated as NaTFSI) (Hu et al., 2020). Recently some of works were reported with Sodium Bromide (NaBr) and Sodium Iodide (NaI).

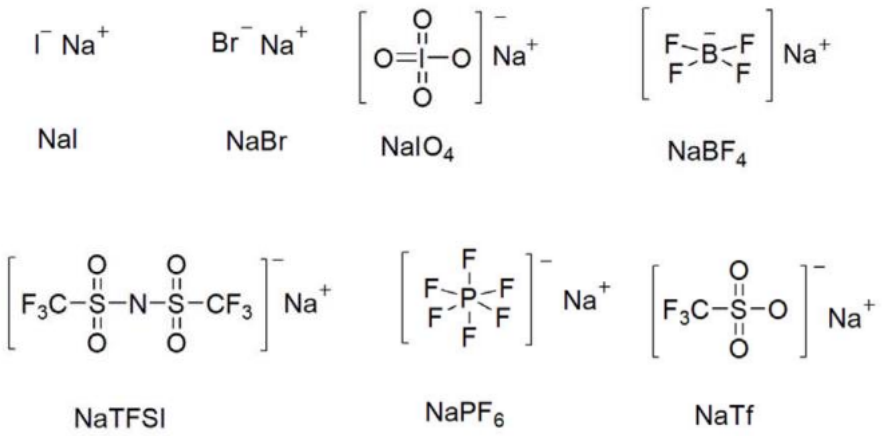

Figure 1: Chemical structures of Sodium salts used for sodium-ion batteries

Considering that each of the frequently utilized sodium salts presents its unique set of advantages and drawbacks, which are challenging to mitigate, researchers have explored hybrid systems that combine two or more sodium salts. The intention behind this exploration is to circumvent these disadvantages; however, the outcomes have not yielded notably significant results. Consequently, there is a pressing need for the development of new sodium salts.

Electrolytes in a battery and its importance

The electrolyte in a battery is a critical component that plays several vital roles, influencing the battery's performance, safety, and overall functionality.

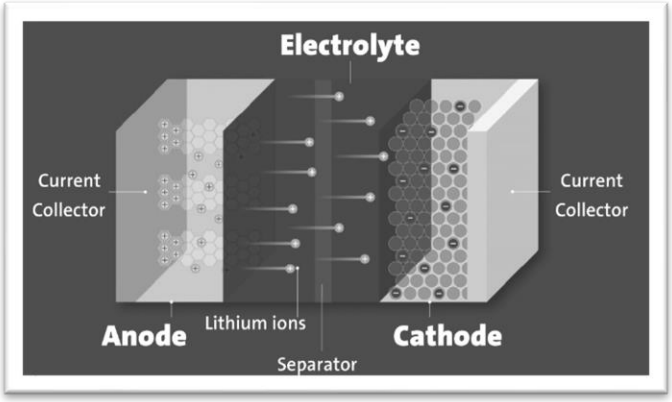

Figure 2: Structure of a battery Source: UL Research Institute

Some key aspects that highlight the importance of the electrolyte in a battery include:

- **Ion conduction:** Electrolytes facilitate the movement of ions between the positive and negative electrodes within a battery. In lithium-ion, sodium-ion, and other types of batteries, the electrolyte allows the transport of charged particles, enabling the flow of electrical current and the storage/release of energy.
- **Electrochemical window and energy density:** The choice of electrolyte significantly impacts the range within which the battery can operate safely and efficiently, known as the electrochemical window. Different electrolytes have various voltage ranges, affecting the battery's energy density and overall performance.
- **Interface control:** The electrolyte influences the electrode/electrolyte interface, which is crucial for the efficiency and stability of the battery. A well-designed electrolyte can create a stable interface, preventing unwanted reactions between the electrodes and the electrolyte solution.
- **Safety and stability:** The composition and properties of the electrolyte greatly affect the safety of a battery. For instance, in lithium-ion batteries, flammable electrolytes have raised safety concerns. Researchers are developing electrolytes that are less flammable and more stable to enhance battery safety.
- **Cycle life and performance:** The choice of electrolyte can influence the battery's cycle life and performance. Some electrolytes contribute to electrode degradation, leading to decreased battery capacity over time. Optimizing the electrolyte composition can help improve the longevity and performance of the battery.

Researchers and engineers continue to explore and develop Polymer-based Solid electrolyte materials to enhance the efficiency and safety of batteries.

Solid polymer electrolytes

Solid Polymer Electrolytes (SPE) is highly favored for applications in rechargeable batteries due to their numerous advantages, including the absence of electrolyte leakage, reduced

flammability, less corrosive interaction with electrodes, and their ability to serve as a separator between the electrodes. Polymer electrolytes are used in batteries as electrode applications due to their ability to accommodate electrode volume changes during charging and discharging. They facilitate flexible battery designs in various configurations and effectively prevent detrimental effects like electrolyte leakage by utilizing solid/gel polymer electrolytes. These polymer electrolytes offer additional advantages such as being lightweight and cost-effective, leveraging commonly used synthetic polymers like polyethylene oxide (PEO), polyacrylonitrile (PAN), polyvinyl alcohol (PVA), and poly-methyl-methacrylate (PMMA).

K. Vignarooban et. al illustrated the extensive research has traditionally focused on long-chain synthetic polymers in lithium systems. However, there has been a recent shift in attention towards sodium systems. This shift is evident from the substantial increase in recent research publications dedicated to sodium-ion conducting polymer electrolytes.

Most solid polymer electrolyte (SPE) systems typically operate at elevated temperatures to achieve the necessary ionic conductivity. For instance, a polyethylene oxide (PEO) SPE exhibiting high ionic conductivity in lithium-ion batteries (LIBs) was reported to require a minimum operating temperature of 60℃. However, unlike lithium metal batteries, sodium metal has a lower melting temperature of 98℃, which is in close proximity to the operational temperature range of SPEs. This circumstance imposes limitations on the practical applications of sodium metal batteries based on SPEs. This section focuses on the ionic conductivity and electrochemical performance of SPEs at moderate temperatures (≤ 60 ℃). We achieve this by summarizing recent studies on various polymer-based solid electrolytes designed for SIBs. The commonly investigated SPEs, namely polyethylene oxide (PEO), polyvinyl alcohol (PVA), polyacrylonitrile (PAN), and poly-(vinyl pyrrolidone) (PVP), have been extensively researched and predominantly utilized as polymer hosts for SPEs in SIBs.

Polyethylene oxide (PEO) and its derivatives are renowned as the earliest and extensively studied polymer hosts for solid polymer electrolytes (SPEs) in lithium-ion batteries (LIBs), owing to their remarkable solvation power, complexation capabilities, and ion dissociation capacity. In parallel with LIBs, PEO-based solid polymer electrolytes have been investigated and implemented in SIBs. As early as 1988, K. West *et al.* reported a PEO-based electrolyte utilizing NaClO4 as the salt in an all-solid-state sodium cell. The PEO/NaClO4 electrolyte exhibited its highest ionic conductivity, reaching 3.1×10^{-6} S/cm, with an EO/Na^+ molar ratio of 12:1 at 60 °C. In 1995, Chandra *et al.* prepared PEO–NaPF6 films with varying EO/Na^+ ratios using the solution casting technique, reporting a room-temperature ionic conductivity for the PEO–$NaPF_6$ electrolyte, with the highest conductivity reported at 5×10^{-6} S/cm for EO/Na^+ exceeding 0.065. Chandrasekaran *et al.* delved into the study of PEO–$NaClO_3$, a sodium-ion conducting polymer electrolyte, employing polyethylene glycol (PEG) as a plasticizer for Na/electrolyte/MnO_2

battery applications. The PEO–$NaClO_3$ electrolyte exhibited a high activation energy (0.539 eV) and low ionic conductivity (10^{-8} S/cm) at room temperature. Upon the incorporation of PEG, the ionic conductivity increased to 3.40×10^{-6} S/cm for PEO:PEG:$NaClO_3$ (30:60:10), accompanied by a decreased activation energy of 0.417 eV. The resulting Na/electrolyte/MnO_2 cell displayed an energy density close to 350 Wh kg^{-1}.

Similarly, in subsequent research, the conductivity increased and activation energy decreased with the addition of more sodium salt, $NaLaF_4$, in PEO. The comprehensive study conducted by Boschin *et al.* explored various anion types (e.g., NaFSI and NaTFSI) and molar ratios (O/Na). The NaTFSI(PEO)n SPE with n = 9 exhibited superior ionic conductivity (4.5×10^{-5} S/cm at 20 ℃ or 293 K) compared to NaFSI(PEO)n materials at temperatures below 40 ℃ (312 K). This difference was attributed to the internal flexibility and large volume of $TFSI^-$, inhibiting crystallization, while FSI^- was more prone to crystallize at room temperature. Furthermore, the stronger interaction between FSI^- with Na^+ compared to $TFSI^-$ was also responsible for the lower ionic conductivity of NaFSI-based SPEs.

Poly(vinyl alcohol) (PVA) has garnered attention from Bhargav *et al.* employed a solution-casting technique to prepare the PVA/NaBr electrolyte, using triple-distilled water as the solvent. The resulting product underwent thorough vacuum drying before use. The introduction of NaBr proved to enhance the ionic conductivity of the PVA polymer host, leading to the formation of PVA/NaBr complexes (weight ratio = 7:3). These complexes exhibited the highest ionic conductivity, measuring 1.362×10^{-5} S cm^{-1} at 40°C which has three orders of magnitude higher than that of pure PVA. Then, the activation energy demonstrated a notable decrease, reducing from 0.478 eV for pure PVA to 0.326 eV for PVA/NaBr (7:3) complexes. In the Na/(7:3 PVA/NaBr)/(I_2/C/electrolyte) cell configuration, superior electrochemical properties were observed in comparison to similar cell structures with other PVA based electrolytes. Based on these findings, Bhargav *et al.* suggested that PVA/NaBr electrolytes hold promising potential for application in all-solid SIBs.

Poly(vinyl pyrrolidone) (PVP), which has been investigated with various inorganic salts, including NaF, $NaClO_3$, and $NaClO_4$. Jaipal-Reddy *et al.* conducted a study on a PVP-based solid polymer electrolyte incorporating dispersed $NaClO_3$. The conductivity of PVP/$NaClO_3$ (7:3) was observed to be four orders of magnitude higher than that of pure PVP. The enhanced ionic conductivity in PVP/$NaClO_3$ electrolytes is attributed to a hopping mechanism involving local structural relaxation, coordination sites, and segmental mobility within the PVP chains. In a study by Chen et al., the same PVP host polymer was complexed with $NaClO_4$. The conductivity of PVP/$NaClO_4$ electrolytes increased with higher NaClO4 concentration and temperature in the range of 25–150°C (298–423 K). The increased amorphous nature of PVP in PVP/$NaClO_4$ electrolytes resulted in a lower activation energy compared to pure PVP (0.26 eV vs. 0.72 eV).

Moreover, the sodium-ion transference number of PVP/$NaClO_4$ was found to be 0.27, indicating significant concentration polarization caused by the inverse mobility of the counter-anion ($ClO4^-$). Kumar *et al.* explored the impact of NaF on the room-temperature ionic conductivity and activation energy of PEO/PVP blend electrolytes. The incorporation of NaF led to an improvement in ionic conductivity and a reduction in the activation energy of the PEO/PVP polymer electrolytes.

A cellulose-based hybrid polymer electrolyte for an all-solid SIB was an effective way to improve the mechanical properties. Gerbaldi *et al.* prepared a PEO-based polymer electrolyte blended with sodium carboxymethyl cellulose (Na-CMC) and found the optimal weight ratio (PEO: $NaClO_4$: Na-CMC = 82 : 9: 9). At the same time, Na-CMC as electrode binder optimized the interface between the electrode and electrolyte. Also, a PEO– Na-CMC electrolyte displayed a lower charge transfer resistance than a PEO electrolyte, implying a better compatibility and ideal ion diffusion between PEO–Na-CMC electrolyte and the electrodes. Half cells Na/SPE/TiO_2 and Na/SPE/$NaFePO_4$) using PEO–Na-CMC had good reversibility, a well-defined voltage plateau, and cycling stability.

Osman *et al.* conducted a comparative study on ion-conducting polymer electrolytes based on polyacrylonitrile (PAN), employing sodium triflate ($NaCF_3SO_3$) as salt, with dimethylformamide (DMF) as the solvent. The PAN + 24 wt% $NaCF_3SO_3$ exhibited superior performance with a higher ionic conductivity of 0.71 mS cm^{-1} and a lower activation energy of 0.23 eV. The observed higher ionic conductivity and lower activation energy in the $NaCF_3SO_3$-based electrolyte could be attributed to the increased Lewis acidity, leading to a weaker interaction between Na+ and the nitrogen atom of PAN compared to that of Li+.

Conclusion:

The significance of the electrolyte is unquestionable, extending beyond its influence on energy density and cycling life. It plays a crucial role in determining the manufacturing process, controlling costs, and impacting the safety of batteries. Consequently, the design of the electrolyte holds particular importance in the comprehensive development of the entire battery system. However, the development of electrolytes for sodium-ion batteries (SIBs) cannot solely depend on the knowledge gained from lithium-ion batteries (LIBs) due to the inherent differences between sodium and lithium. Nevertheless, given the shared characteristics between SIBs and LIBs, careful consideration in electrolyte design remains imperative.

Through extensive research, scholars have gradually recognized that the critical factor influencing the optimal performance and groundbreaking applications of sodium-ion batteries (SIBs) is the electrolyte. To be more precise, the electrolyte significantly shapes the electrochemical performance of cells, impacting crucial aspects such as first Coulombic

efficiency, rate capability, cycling life, energy density, as well as safety and operational conditions.

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SINGLE MOLECULAR SPECTROSCOPY USING SCANNING TUNNELING MICROSCOPY

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Introduction:

The combination of scanning tunneling microscopy (STM) and single molecular spectroscopy was a groundbreaking achievement in the field of nanoscale research in the early 90s. In this chapter, we delve into the complex methodology and carefully analyze each layer to fully comprehend the technique and its outcomes, making it a more effective tool. The phenomena of STM-based spectroscopy is a fascinating subject with intriguing complexities and enormous possibilities. We also cover a wide range of applications that have emerged at the intersection of STM and single-molecule spectroscopy, highlighting the various ways in which this combination has sparked research and technological development.

Principles of scanning tunneling microscopy and spectroscopy

Scanning Tunneling Microscopy (STM) is an advanced methodology that relies on the principle of quantum tunneling. This technique involves moving a sharp metal tip across a conductive surface while keeping a nanometer-scale separation. As the tip approaches the sample, electrons tunnel across the vacuum barrier, leading to a measurable tunneling current. This current is highly sensitive to the distance between the tip and the sample, allowing for atomic-scale resolution. Scientists can gain unprecedented insights into the electrical structure, energy levels, and charge transport characteristics of individual molecules by combining single molecule spectroscopy and STM. This is achieved by observing changes in the tunneling current as the tip interacts with the sample. The use of functionalized tips, which are often capped with molecules or molecular clusters, enables direct investigation of individual molecules.

Various techniques are employed in STM-based single molecule spectroscopy to collect precise information. Inelastic electron tunneling spectroscopy (IETS) is one such method that enables the study of vibrational modes within a molecule. This involves measuring the energy shift in electrons that participate in tunneling processes, resulting in a complex fingerprint of

molecular vibrations. It provides a unique perspective into the domain of chemical structures. Additionally, scientists use scanning tunneling spectroscopy (STS) to examine the electronic states and energy levels of small molecules. They map the electronic features by analyzing the electrical characteristics at different locations on a molecule. This helps them understand how various regions of the molecule's electrons and energy levels interact with each other, revealing the intricate electronic world that exists within each molecule.

Molecular structures and dynamics

Scientists use STM-based spectroscopy to capture the finest details of molecular structure and motion, which cannot be matched by any other approach. By using this method, researchers can observe individual atoms in a molecule, analyze how its shape changes when exposed to external forces, and study the minute details of chemical reactions at a very small scale. Recently, scientists have utilized STM to observe super-fast processes, such as electron transfers, molecule swapping, and other rapid changes, with a time resolution as low as a femtosecond, almost like watching a video of what happens inside molecules. STS applications are particularly useful for surface science and catalysis. Researchers use this technique to investigate the intricacies of surface chemistry, particularly how molecules adsorb, desorb, and interact on atomic and molecular levels. STS is valuable in comprehending the behavior of individual molecules on catalytic surfaces in the field of catalysis, where the efficiency of chemical processes is crucial. This knowledge is essential for developing more efficient catalysts and optimizing industrial processes.

Applications and futurs prospects

Scanning tunneling spectroscopy (STS) has a wide range of applications, but its most important one is the detailed analysis of electronic structures at the atomic level. By utilizing the quantum tunneling effect, STS allows researchers to track the energy levels and electronic states of individual atoms and molecules on surfaces. This skill has far-reaching ramifications for various scientific fields such as condensed matter physics, materials science, and semiconductor research. A precise understanding of electrical characteristics is required in these domains for the creation of novel materials and systems. STS is a critical tool for characterizing nanomaterials and nanostructures. It provides information about their electrical, vibrational, and structural properties. Researchers use STS to examine the electronic band structure of nanomaterials such as graphene and carbon nanotubes. This investigation reveals their particular electrical properties, which contribute to their extraordinary conductivity and strength. Furthermore, STS is extremely useful for studying the electronic behavior of nanostructured materials, which aids in the design and development of nanoelectronic devices. STS is an essential component in the

development of nanoelectronic devices. Researchers can create molecular-scale components, such as transistors and switches, with precision in mapping electronic states at the level of individual atoms and molecules. This application is at the cutting edge of nanotechnology, with the potential to produce ultra-compact, energy-efficient electrical devices with unrivaled performance. STS's capacity to manipulate and measure single atoms makes it an essential tool for studying quantum phenomena. Researchers use STS to investigate quantum states, quantum coherence, and quantum entanglement at the nanoscale. These studies add to our understanding of fundamental quantum principles and hold promise for the advancement of quantum technologies such as quantum computing and quantum communication.

Although single molecular spectroscopy using STM is highly effective, there are still certain issues that need to be addressed. The interaction between the tip and the sample is akin to a delicate dance, and we need to regulate it properly and understand how they function together. Another challenge we are working on is making the approach work on non-metal surfaces and insulating molecules, which do not conduct electricity well. The future of this science is very promising as we are acquiring better tools, finding new ways to make things function, and employing clever concepts to better understand things. This will increase the power and accuracy of single molecule spectroscopy using STM. There's also quantum-enhanced tunneling spectroscopy, which uses advanced quantum sensing theories to make us even more sensitive. It may enable us to investigate previously inaccessible areas, such as super-small portions of molecules.

Conclusion:

As we wrap up this discussion, we can see how proficient we are at comprehending even the smallest details by combining single molecular spectroscopy and scanning tunneling microscopy. We began by examining a single atom, and now we're delving deeper into the intricate details of how molecules move and utilize energy. This journey highlights our curiosity to learn about the most minute details of molecules and materials' electronic structure. The next phases of this study will likely revolutionize our understanding of things, paving the way for new technologies and discoveries in the world of nanoscience.

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ADENOID CYSTIC CARCINOMA: RECENT PROGRESS REVIEW AND RETROSPECTIVE CLINICAL UPDATE

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Abstract:

Adenoid cystic carcinoma, which makes up around 1% of all malignant tumours of the oral and maxillofacial region, is an epithelial tumour of the major and minor salivary glands that is rather uncommon. Despite having a broad age distribution, peak incidence mostly affects women between the fifth and the sixth decade of life. This tumour is known for its sluggish growth, perineural invasion, potential for local recurrence, and distant metastasis, among other characteristic clinical and pathological characteristics. According to histopathology, it is made up mainly of basaloid cells that have differentiated into myoepithelial/basal cells. There are three patterns that can be identified: cribriform, tubular, and solid. The prognosis for the solid type is lower than that of the cribriform type. The preferred course of treatment is wide-margin surgical excision; if lymph nodules become involved, postoperative irradiation is advised. In addition to their distinctive chromosomal translocation, adenoid cystic carcinomas can commonly acquire new mutations. The minimal prevalence of ACC and its sluggish increase pose challenges to clinical research. Agents that block the fibroblast growth factor receptor are being tested in a number of ongoing trials. signalling or alternative routes for signalling. On the basis of the freshly sequenced tumour genome, novel treatments are currently being developed. In order to maximise local disease management, surgery combined with postoperative radiation is widely regarded as the best course of action. In an attempt to identify individuals who are at a high risk of recurrence and perhaps benefit from other, as of yet unproven treatment methods like

chemotherapy or biological therapy, a great deal of work has gone into understanding the basic biological mechanisms underlying the tumour.

Keywords: Adenoid cystic carcinoma, Fibroblast growth factor receptor 1, Molecular pathogenesis

Introduction:

The histology of head and neck tumours includes a small percentage—between 10% and 15%—of unusual tumours called adenoid cystic carcinomas (ACC). [1] These are the most common cancerous growths found in children, predominantly affecting areas such as minor salivary glands, the tracheobronchial tree, the esophagus, the lacrimal gland, and various sites beyond the head and neck, along with additional locations within these regions. [2,3]

Approximately 1% of all malignant tumours in the oral and maxillofacial region are adenoide cystic carcinomas (ACCs), a rare type of epithelial tumour. ACC is frequently categorised alongside salivary gland tumours, although being initially identified by Billroth as a "cylindroma." may appear anywhere mucous glands are present. The hard palate is the primary location of half of these tumours, although they can also originate in the tongue and other glandular regions that house minor salivary glands in addition to the large salivary glands. [3,4]

The vulva, oesophagus, cervix, external auditory canal, nasopharynx, lacrimal glands, breast, and Cowper glands are among the unusual sites. As the tumor's extended natural history, inclination towards perineural invasion, and propensity for local recurrence are well documented. Peak incidence occurs primarily in women between the fifth and sixth decades of life, despite the fact that it exhibits a wide age distribution Eleven, it is a very invasive, slowly developing malignancy that has a high recurrence rate. It is rare for lymphatic to expand to nearby lymph nodes. However, hematogenous spread happens frequently during the course of the illness. Twelve It has long been known that ACC spreads perineural. The Gasserian ganglion region was found to be the most often involved site (35.6%) in the literature. [5,6]

It is mainly made up of basaloid cells that have differentiated into myoepithelial/basal cells under the microscope. The three recognised morphologic patterns are solid, tubular, and cribriform. Among the crucial predictive the percentage of solid component in the tumour determines the histological grade, among other parameters. We report a case of ACC involving the small salivary glands of the hard palate together with a review of the literature regarding its prognostic, therapeutic, histopathological, and immunohistochemical features. [7,8]

Adenoid Cystic Cancer (ACC) is a less common type of tumor that has received limited research attention and offers few treatment choices. It is a rare cancer of the secretory glands known for its slow growth and tendency for perineural invasion, especially in cases where the

disease has progressed. Because of its sluggish growth, most treatment trials searching for a traditional response based on reliable tumour measurement criteria have shown disappointing results. There is an urgent need for new treatments. Understanding the pathophysiology and molecular characteristics of this disease has advanced recently in a number of ways. A detailed examination of the therapeutic options and current adenoid cystic carcinoma care is required in light of the new knowledge on ACC. [9,10]

The most typical place of genesis for ACC is the salivary glands. Only 1% of all malignant tumours of the head and neck region and 10% of all salivary gland neoplasms are ACCs, making them an unusual kind of tumor. In the latter instance, ACC happens more commonly in little salivary glands in contrast to larger ones. The head and neck region can also be the starting point for Adenoid Cystic Cancer (ACC), originating in areas like the tongue, paranasal sinuses, palate, nasopharynx, lacrimal glands, and external auditory canal. Furthermore, ACC can arise from secretory glands in other parts of the body such as the tracheobronchial tree, esophagus, breast, lungs, prostate, uterine cervix, Bartholin's glands, and vulva. Women had ACC at a 60:40 ratio, higher than in men, according to a recent population research. Little information is available regarding the potential predisposing variables (such as exposure, geography, ethnicity, or other factors) for the development of the disease because these tumours are rather uncommon. [11,12]

When compared to other carcinomas, ACCs usually grow more slowly and rarely disseminate to local and regional lymph nodes. However, local and distant recurrences are common after removal of the initial tumour. This high rate of recurrence probably represents the known propensity for hematogenous spread in the early phases of tumour development and perineural invasion with occult extension beyond surgical margins. The liver and bones are the next most prevalent locations for metastatic illness, then the lungs. There is ample documentation of both late relapses (more than five years after surgery) and accounts of fast tumour growth following protracted indolent illness. [13,14]

Molecular pathogenesis

The absence of reliable cell lines has complicated research into the pathophysiology of ACC. However, research on tumour tissues and, more recently, primary xenografts has yielded valuable information. Microarray analysis of tumour RNA showed that ACCs exhibit both high levels of the transcription factor Sox4 and genes linked to myoepithelial development. In addition to being a potential human oncogene, the latter generally controls embryonic development. Frizzled-7 and casein kinase 1-epsilon are two more overexpressed genes that are

linked to cancer and the Wnt/β-catenin signalling pathway. This would be in line with another study that found activating mutations in Wnt/β-catenin pathway components in ACCs. [15,16] Another notable finding is that ACC tumors frequently exhibit increased expression of EGFR, HER2, and/or fibroblast growth factor receptor 1 (FGFR1), along with substantial production of the receptor tyrosine kinase c-KIT. Each of these receptors has the potential to generate oncogenic growth factor signals, either through mutational activation or overexpression due to gene amplification. Consequently, it is believed that constitutive signaling occurs as a result of autocrine activation of these receptors.

The most convincing hints regarding the development of this tumour come from a recent sequencing of over eighty ACC genomes and a meticulous chromosomal analysis. It should come as no surprise that somatic gene alterations have been acquired in ACC tumours. Nonrandom increases or losses of particular chromosomal regions, maybe involving an ACC-specific chromosome 1p35–36 deletions. 6q24, 12q, and 14q have further deletions that occur often. The most intriguing alteration is a translocation between chromosomes 6q and 9p. This rearrangement involves the genes responsible for the transcription factors MYB and NFIB, with Persson *et al*. being the pioneers in uncovering this phenomenon. [17,18]

Up to 86% of these tumours have this translocation, which suggests that it is distinctive to ACC. This feature could be valuable for differentiating ACC tumors from other forms of carcinoma, like pleomorphic adenoma. One consequence of this rearrangement is the heightened expression of a MYB oncoprotein that remains largely intact, along with a fusion transcript potentially associated with the lack of a 3' negative regulatory element found in normal MYB mRNA. Tumorigenesis is subsequently encouraged by the dysregulation of MYB target gene expression that results from this. Since some ACCs have been reported to have mutations that appear to target NFIB, changes to this gene may also be significant.

Fewer overall genetic changes were discovered in ACC tumour genomes than in the majority of other carcinomas, according to thorough analyses. As a matter of fact, in a fraction of tumours, MYB translocations were the only alterations found. This aligns with the theory of deregulation. An important part of the pathophysiology of malignant tumours involves MYB. Merely a few number of mutations were common amongst the tumours that contained non-MYB gene changes; each tumour had its own unique mutational profile. It is interesting to see that oncogenes and tumour suppressor genes, which are commonly altered in other malignancies, were rare. In the two studies, for instance, only 3 of the 84 tumours had mutations in the p53 tumour suppressor gene, while 7 of them had mutations in the RAS or PI3K growth factor signalling proteins. [19]

Even if some mutations were exclusive to certain tumours or only occurred in a small percentage of them, the changed genes might be categorised according to their capacity to interfere with particular biochemical processes or cellular processes. This encompassed those who engage with the MYB transcription network, as well as genes that affect Notch, chromatin remodelling, DNA damage/checkpoint responses, FGF-IGFPI3K-regulated signalling pathways, protein kinase A pathway, and signalling pathways. Determining the precise role that every mutation plays in carcinogenesis may open up new avenues for targeted treatment. [20]

Surgery and radiotherapy

The recommended treatment for localized ACC involves surgical intervention aimed at achieving complete resection with clear surgical margins, while also preserving organ function. In cases of head and neck primary tumors, modified radical neck dissection is advisable only if cervical lymph nodes are clinically positive. Despite strict adherence to proper surgical protocols, recurrence rates over 5 to 10 years range from 30% to 75%.

Post-operative radiation is one method of preventing local relapses. Despite the paucity of data from randomised studies, the majority of practitioners believe that this type of treatment is helpful. In one retrospective study, patients who received radiation therapy after surgery had a 5-year local control rate of 78%, while those treated with surgery alone had a rate of 44%. Another study reported that individuals who underwent surgery with or without post-operative radiation had 10-year local control rates of 83% and 25%, respectively. In a separate retrospective analysis focusing on patients with submandibular ACCs, it was found that 82% of patients had local relapse-free survival at 67 months, compared to 70% for those who underwent surgery alone, indicating that the impact of postoperative radiation might not be as significant as previously believed. [21]

Chemotherapy

Systemic chemotherapy is not beneficial for many ACC tumours due to their poor growth kinetics. Nevertheless, a number of studies on chemotherapy have been carried out over time. Results for metastatic cancer typically indicate low response rates to cytotoxic treatment. sickness. For patients with ACC tumours, there is therefore no approved conventional systemic chemotherapy.

Targeted and novel agents

In light of cytotoxic chemotherapy's failure to treat advanced ACC, researchers have turned their attention to tailored treatments. Most of the medications that are presently undergoing clinical trials were chosen based on findings from pre-clinical research that was started prior to the ACC genome's elucidation. For instance, the discovery that 65–90% of ACCs

overexpress the well-known oncoprotein c-KIT (CD117) raised the possibility that this receptor may be a good target for therapy. When gastrointestinal stromal tumours (GIST) with mutant versions of c-KIT are treated with imatinib, a c-KIT inhibitor, response rates are high. Nevertheless, only 2 out of 42 ACC patients receiving imatinib in four phase II clinical trials showed objective tumour responses. Just three tumour responses were observed in 28 patients after adding cisplatin to imatinib, indicating that the combination did not improve the result. These unfavorable results suggest that activated c-KIT receptors are unlikely to be the main drivers of the malignant characteristics in ACC cells through signaling pathways. Moreover, sequencing data have consistently shown that ACC tumors express wild-type c-KIT. [22]

Targeting members of the EGFR family in ACC has also been shown to have potential benefits. A small molecule EGFR kinase inhibitor called gefitinib was used by Glisson and associates to treat eighteen patients with ACC. Despite the fact that none of the individuals showed an objective tumour response Thirteen (68%), had stable illness. In another study, twenty participants were administered cetuximab, a chimeric monoclonal antibody targeting the EGFR. Once again, despite 87% of individuals (20 out of 23) showing stable disease (SD), no objective responses were observed. A combination of cetuximab and chemotherapy (radiation and cisplatin for local disease, cisplatin+5-FU for metastatic disease) was also tested, revealing an objective response rate exceeding 40%. For localized disease, the overall survival rate was 100%, with a median progression-free survival (PFS) of 64 months; in contrast, the median PFS was 13 months, and overall survival was 24 months for metastatic disease. Agulnik and colleagues conducted a phase II trial targeting patients with tumors expressing HER2 or EGFR. Lapatinib, a medication that inhibits signalling by both receptors, was administered to those patients. There were no observable objective tumour responses. When considered collectively, these studies indicate that EGFR and/or HER2 signalling may have a small role in the malignant phenotype. [23]

Three phase II trials are assessing the anti-tumor activity of dovitinib. In the University of Virginia trial, two individuals exhibited metabolic responses, indicated by decreases in 18F-fluorodeoxyglucose (FDG) uptake in tumor tissues as assessed through positron PET (photoemission tomography). In 2013, there were also documented cases of several stable diseases and two objective tumor response. Since dovitinib acts as a multi-kinase inhibitor, it remains uncertain whether the positive initial outcomes are attributed to the inhibition of FGFR, the other targeted kinases, or a combination of these factors.

Ongoing investigations involve the evaluation of drugs targeting components downstream of activated FGFR and other growth factors, such as AKT, MAPK, and mTOR (see

table 2). In an initial report, vorinostat, a histone deacetylase inhibitor, was initiated, resulting in stable conditions in 25 out of 30 patients. A single, incomplete answer. Using Nelfinavir as a monotherapy, Hoover et al.'s Phase II clinical trial failed to find a meaningful clinical response in patients with advanced ACC. Nelfinavir targets Akt signalling. [24]

In summary, no medication has shown enough action in targeted therapy studies to be considered standard for treating advanced ACC. Dovitinib and vorinostat, the medicines, seem to produce responses in a small number of patients, whereas sunitinib may prolong PFS. percentage of the patient. Research on these and comparable targeted drugs may, in the future, provide evidence of clinically meaningful anti-tumor action.

Conclusion:

Despite being a relatively uncommon neoplasm, adenoid cystic carcinoma presents a challenge in our day-to-day practice because of endless unanswered questions about its progression and management. The best way to treat ACC is a topic of controversy, and there is a deficiency of of trustworthy data regarding ACC patients' clinical behaviour during therapy. To assess how well treatments, improve survival rates and quality of life, further clinical trials are required. We must keep a close eye on these patients for the rest of their lives due to the tumor's strong propensity to spread and, in rare cases, generate distant metastases even after achieving adequate locoregional control.

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A SURVEY ON DEVELOPMENT FRAMEWORK OF JAVA MOBILE APPLICATION USING ANT COLONY OPTIMIZATION ALGORITHM

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Abstract:

The application framework serves as a reusable design component, outlining the architecture of the application, defining dependency relationships, allocating responsibilities, and managing control flow across the entire design and collaborative components of a JAVA mobile application program. This paper aims to enhance readers' comprehension of JAVA by introducing the technology and presenting a practical application for JAVA mobile application development. To address a specific challenge, the paper employs a registration mechanism for validity verification. The identified problem is tackled using an ant colony optimization (ACO) algorithm. The paper simplifies the utilization of ACO by breaking down the problem into states, decision-making processes, and patterns. The research findings reveal that the algorithm determines stack allocation objects by analysing Java source code during the compilation stage, distinguishing these objects with extension instructions. During program execution, these objects are directly assigned in Java and automatically added when the program leaves its scope. In contrast, other Java objects continue to be allocated to the heap and are managed by the garbage collector for recycling purposes.

Keywords: Registration mechanism, Validity verification, Ant colony optimization (ACO) algorithm, Decision making, Stack allocation objects

Introduction:

JAVA technology has three main parts: J2EE, J2SE, and J2ME. J2ME is used a lot for making mobile apps [1]. Sometimes, we want mobile apps to start on their own, especially for big business apps. These apps often get information from a server [2]. Frameworks are like toolkits used to make apps. They help decide how different parts of the app talk to each other. Java programs can talk directly to the computer's insides [3], but doing that can make the app work only on certain types of computers. There's a special way to use outside tools that can make the app work on many types of computers [4]. This paper talks about a special tool called the Ant Colony Optimization (ACO) algorithm. It's like a problem-solving tool that helps make apps

work better. It keeps running and waits for a server to send information [5]. But, keeping the app always open uses the computer's resources and can make other apps slow. People who use this toolkit can start building specific things for their apps based on common things that are already built [6]. The toolkit gives default behaviours to apps, like how they should act. Developers can change these behaviours to make the app work the way they want. They also get special tools to help build apps. With this toolkit, apps can work on different types of computers, making them more open and easy to build. This makes building apps faster and cheaper [7]. The paper is about studying a toolkit used for making mobile apps with Java, and it uses a special problem-solving tool called the Ant Colony Optimization algorithm [8].

Methodology:

In this Chapter, we're talking about making apps start on their own using a wireless message system. It's like creating an app that automatically gets information when you connect to the internet. We've built a framework (like a toolset) that makes it easy for programmers. They just need to put the main information in the right place, and the framework does the rest. The framework supports different types of apps. For an app to get information, it needs to be set up correctly. Users can smoothly switch between apps on their devices. In the setup process, apps can say yes or no to requests and can even change the setup if needed. This way of setting up is active and quick. We're using a special problem-solving tool called the ant colony optimization algorithm. It helps the app make good decisions without taking too much time. It's like finding the best way to do things. We also have tools for handling when users touch the screen, and an app can show different things at the same time. Some special tools make sure the app is secure and only does what it's supposed to do. When making apps, it's important to understand how things work in that specific area. We turn these ideas into tools that help build the whole app. We focus on making the tools flexible, so it's easy for programmers to use them. The app can decide if it wants to get certain types of information or not, and it can change its mind if needed.

Result and Discussion:

The use and scope of mobile applications are constantly growing. Embedded systems are evolving towards hierarchy and modularization. The upper software of embedded applications is becoming less dependent on embedded hardware. To get the limits of active power, the programmer registers the real type of the object to the framework, creating this type of object. Although JAVA language allows type registration, it can't generate objects based on the registered type. Templates help solve this issue. When dealing with state values, if a state's lower limit is greater than the maximum or the upper limit is less than the minimum, the state is discarded. Otherwise, the state and its active power limits are recorded. The emulation client

sends information to the server, and the client's receiving program automatically activates to process the information. Applications need to decode data and convert it into raw data. With hardware advancements, mobile devices have more powerful functions, resulting in increased storage capacity. As applications run, they automatically process connections and optimize them over time. The ant colony optimization algorithm has characteristics like positive feedback and randomness in decision-making. When an application isn't running, application management software can listen for incoming connections. Upon detecting a connection request, the software calls the relevant method to start the application. In multi-document mode, file information acquisition is implemented in a higher-level document management class, not in the document class, to ensure consistency. Inbound connections can have static or dynamic addresses, consisting of an address (like an IP address) and a specified port. The technology allows the server to send information to the client independently, eliminating the need for a request. In information pushing, the server initiates events while it's feasible for the document management class to handle this operation, it may make the class redundant. Generating Java objects in native code can lead to the garbage collector considering them as unused and releasing them.

Conclusion:

In this chapter, we explore the development framework for JAVA mobile applications using the ant colony optimization algorithm. We analyse the message flow within the JAVA mobile application framework, which includes the flow of general command messages, user-adding command messages, and "activating" messages. Information is sent from the server to the mobile terminal, where the application program processes the received data. The ant colony optimization algorithm helps optimize time constraints, reducing the number of search states and the transfer path. This guides the ant search process and improves optimization efficiency. Additionally, we consider security constraints in the line. In mobile application development, we identify objects using extension directives, and access to object members is translated into direct access. These objects are directly assigned to Java during program execution. As mobile application development becomes more widespread, this chapter aims to provide valuable references for developers to creating mobile applications.

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BIOLOGICAL APPLICATIONS OF SELF-ASSEMBLING CYCLIC PEPTIDE NANOTUBES (SCPNs)

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Abstract:

The development of cyclic peptide which self-assembled through supramolecular interactions into tubular structures to form supramolecular cyclic peptide nanotubes (SCPNs) is the current area of research interest. A range of cyclic peptides have been identified to have such properties, including α-peptides, β-peptides, α,γ-peptides, and peptides based on δ- and ε-amino acids. Furthermore, the synthesis of cyclic peptides with diverse internal core radii permits a wide range of biological application including unique transport behaviors of ions, small molecules, such as water, ammonia, drugs and genes.

Keywords: Self-assembly, cyclic peptides, nanostructures

Introduction:

Supramolecular chemistry deals with the area of chemistry focusing on spatial chemical systems with spatially organized molecules *via* noncovalent interactions [Lehn *et al*., 2002]. Among, these interactions, hydrogen bonding, metal coordination, hydrophobic interactions, van der Waals interactions, π–π interactions, and electrostatic interactions are widely being used in the supramolecular chemistry. Self-assembling cyclic peptides (CPs) are bioinspired supramolecular building blocks, which stack into supramolecular cyclic peptide nanotubes (SCPNs), driven by β-sheet-like hydrogen bonding. In this chapter we focus on the biological application of self-assembling cyclic peptide nanotubes (SCPNs). Protein channels, peptides and metabolites embedded in cell membranes play a fundamental role in the transport of small molecules [Yang *et al.,* 2015]. These features are necessary for the regulation of intracellular processes and signaling cascades for biomedical and disease research initiatives. The propensity of cyclic peptides to stack into elongated structures has naturally led to the investigation of how they might form "channels" that either (a) allow transport of small molecules through the confined space of the internal core, (b) interact and insert into lipid membranes on account of potential binding with certain amino acid combinations, leading to structural disruption, or (c) interact uniquely with native peptide or lipid species in a biological environment to alter another

specific process. The occurrence of these behaviors has been investigated by various methods, starting with [Ghadiri *et al.,* 1994] who administered peptide nanotube assemblies to the phosphatidylcholine liposome model (with differing internal/external pH) and used fluorescence dye spectroscopy to track the collapse of the pH gradient, rationalizing formation of transmembrane channels to be the cause [Amorin *et al.,* 2012]. Furthermore, the synthesis of cyclic peptides with diverse internal core radii, self-assembly properties (length), and external functional chemistries permits a wide range of unique transport behaviors to be unearthed for ions (Na^+ , K^+ , or Ca^{2+}) and small molecules, such as water, ammonia, or glutamic acid. A further novel application was discovered by [Richman *et al.,* 2014] and [Chemerovski *et al.,* 2016] who determined that self-assembled cyclic α-alt(D,L)-peptides that formed fibrils were able to bind to and stabilize the nonamyloid-β region of α-synucleins, thereby preventing aggregation and the downstream pathways which lead to amyloidogenic diseases, for instance, Parkinson's or Alzheimer's [Wilk *et al.,* 2013]. Hence, the advantageous capability for producing diverse types of self-assemblies from such basic building blocks was clearly evident in the early years of research and laid the important groundwork for more advanced biological applications, which will next be evaluated.

Antibacterial treatments

One of the greatest challenges facing the healthcare system in recent years has been the emergence of "superbacteria" which have developed resistance to traditional antibiotic medications due to overuse by the general public [Theuretzbacher *et al*., 2013]. A major concern is that gradually, medications will lose their effectiveness and thus research is now driving toward finding alternatives to replace clinical treatments that will soon become obsolete. Cyclic peptide nanotubes have emerged as an attractive solution to these challenges as they exhibit strong antibacterial properties on both Gram-negative and Gram-positive bacteria.

[Lopez et al., 2001] presented the first report defining SCPNs as a class of novel antibacterial agents. They established that amphiphilic cyclic α-alt(D,L)-peptides composed from an alternating L-Trp and D-Leu segment and three consecutive hydrophilic amino acids were acting as ion transporters in lipid bilayer models and potentially also embed into bacterial membranes. A typical cyclic peptide cyclo-[D-Lys-L-Glu-D-Arg-L-Trp-D-Leu-L-Trp-DLeu-L-Trp-] exhibited potency against multiple Gram-positive and negative bacterial strains. [Lopez et al., 2001] hypothesized that this is caused by insertion into bacterial membranes, disrupting transmembrane ion channels and increasing permeability, which induces eventual cell death by a "carpet-like" mechanism.

Claro *et al.* [2020] have also used logic based prediction methods like computational simulation to model the interactions of various cyclic α-alt(D,L)-peptides with antimicrobial membrane targets, arguing that a combined analysis of biophysical characterization and coarse-grained molecular−dynamics (CG-MD) can support understanding of membrane/antimicrobial agent interactions. The two peptides studied, **1** (known antimicrobial activity with amphipathic sequence and three basic residues) and **2** (improved solubility from three Lys residues) were tested against DMPE and DMPG liposomal models in mixed ratios to elucidate the role of negatively charged membrane density. DSC, ATR-FTIR, and CG-MD were rigorously used to corroborate the previous speculation that hydrophobic peptide residues are critical for a significant effect against Gram-positive bacteria and the results suggest that the assembled peptides lay in parallel to membrane surfaces in most cases (Figure 1).

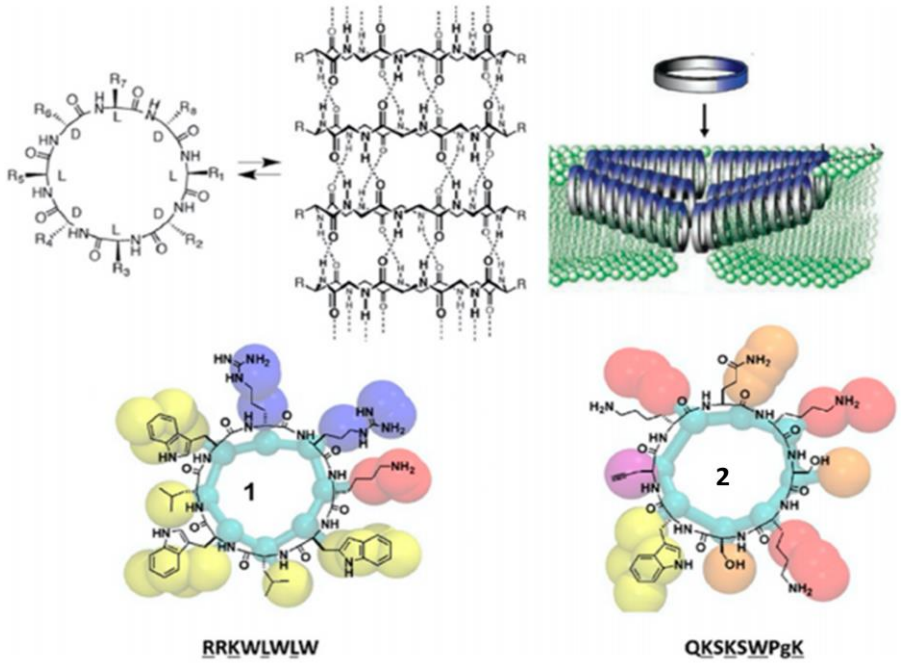

Figure 1: Chemical structures of two cyclic peptides 1 and 2 modeled by Claro *et al.* and illustration of the parallel conformation in which they are thought to lay in regard to membrane surfaces. [Claro *et al.*, 2020]

Cyclic peptide nanotubes have also taken inspiration from existing active compounds. [Motiei *et al.,* 2009] have observed the similarity in the design of cyclic peptides and mannopeptimycins, a class of cationic glycopeptide antibiotic materials with activity against Gram-positive bacteria [Hoffman *et al.,* 2007].

Anti-cancer drug delivery

Given the aforementioned ability of cyclic peptides to reversibly stack into tubular structures, to date, they have chiefly been explored as a possible tool for anticancer drug delivery

since their synthetic pliability, high aspect ratio, and supramolecular composition make them attractive materials for this type of application. In addition, the high aspect ratio has also attracted attention as a property which may improve the time of circulation and ensure better cellular uptake [Zhu *et al.,* 2019] and [Bauer *et al.,* 2004]. Hence, the elongated structures formed by cyclic peptides are of increasing interest for improving the bioavailability and activity of hydrophobic, poorly soluble anticancer actives, which are toxic but nonselective and can produce undesirable side effects.

More recently, our group has undertaken a considerable effort in studying cyclic peptide−polymer conjugate assemblies for drug delivery, largely by attaching biocompatible RAFT polymers with a range of functionalities that act as a handle for drug loading of different organometallic drugs. The first report of a singular cyclic peptide−polymer conjugate nanotubes by Blunden *et al.* employed RAFT polymerization to generate a statistical copolymer of poly(2-hydroxyethyl acrylate) (pHEA) and poly(2-chloroethyl methyl acrylate) (pCEMA) to compose the corona around a central cyclic peptide by attaching onto two azide functional handles within the sequence (Figure 2) [Blunden *et al.,* 2014].

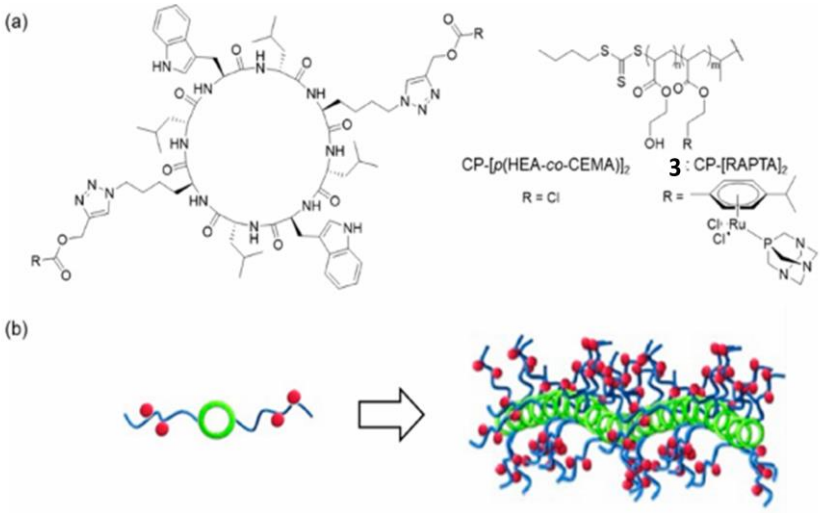

Figure 2: (a) Chemical structure of the drug-loaded cyclic peptide−polymer conjugate 3. (b) Scheme of the nanotube loaded with organometallic drug RAPTA-C (Blunden *et al.*, 2014)

The latter monomer moiety underwent a halogen exchange to iodide to enable rapid substitution with an amine group present on organometallic drug RAPTA-C, which is highly selective and effective toward in vivo metastatic cancers. After preparation of the final nanotubes in water (20 nm in diameter and ranging from 200 to 500 nm in length) administration to ovarian A2780 cells and the cisplatin resistant equivalent, compared the activity against the pure drug and a 10-fold increase in cytotoxicity (IC_{50}) for the macromolecular drug complex was found in

each case. Given that the drug was covalently bound to the carrier, this is even more remarkable since there may be less opportunity for the RAPTAC to detach and reach its target site.

Larnaudie *et al.* [2018] advanced knowledge regarding the *in vitro* behavior of the nanotubes by investigating the cytotoxicity, intracellular drug fate, and carrier selectivity of these conjugates. An organoiridium drug was complexed onto a 2-arm conjugate (D-Leu-L-Lys-D-Leu-L-Trp)$_2$ **4** using pHPMA as an example of a biocompatible polymer of clinical relevance. This was copolymerized with 5% of pyridine based 2-(3-(pyridin-4-ylmethyl)ureido)ethyl)methacrylate (PUEMA) monomer for ligation of a novel organoiridium drug and upon attachment to cyclic peptide and assembly in water, assessed for antiproliferative activity against A2780 cell line (comparing to the free drug and a polymer−drug conjugate control). Figure 3 shows the improved cytotoxicity and, more interestingly, the strong selectivity for cancerous cells over healthy human cells. Furthermore, poor delivery of the drug carrier into cells when incubating at low temperatures confirmed an energy-dependent endocytosis pathway for entry.

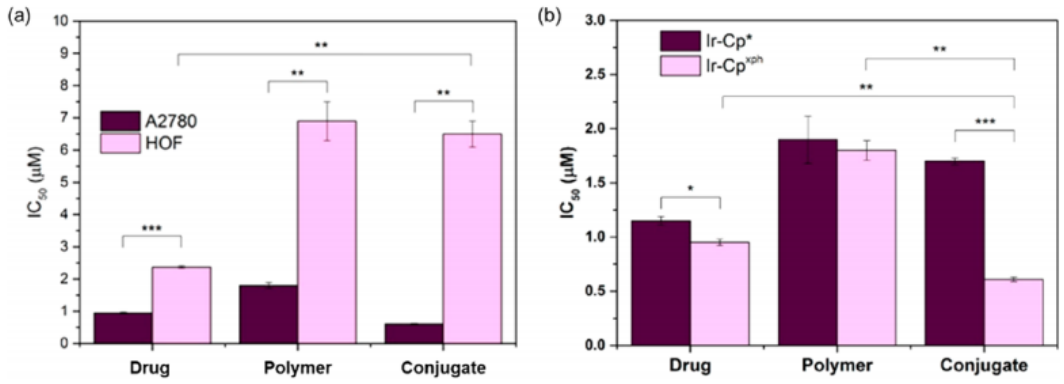

Figure 3: Cytotoxicity profile for the iridium drug-loaded conjugate 4 compared with free drug and drug-bearing polymer (a) and the antiproliferative effects on cancerous cells vs healthy cells (b), which suggest a favorable selectivity index (Larnaudie *et al.*, 2018)

Amphiphilic tubisomes **5** was synthesized by [Yang *et al.*, 2020]. Encapsulation of doxorubicin in the core followed by controlled release behavior through fine-tuning of a UV-responsive polymer as the hydrophobic polymer arm. Figure 4 illustrates the design of the cyclic peptide−polymer conjugates, which through synergy of hydrogen bonding and hydrophobic effect; assemble into cylindrical micelle type particles which can later disassemble upon photocleavage of the NMBA. Doxorubicin was loaded into the central cavity (10.3 wt %), and upon incubation with MDA-MB-231 cells, with UV irradiation for 20 min, a cytotoxicity profile similar to that of the free drug was determined. Although the cytotoxicity was not improved

upon, the responsive nature of the nanoparticle could be beneficial where the time-dependent release behavior exhibited a burst release that is favorable for some treatment types.

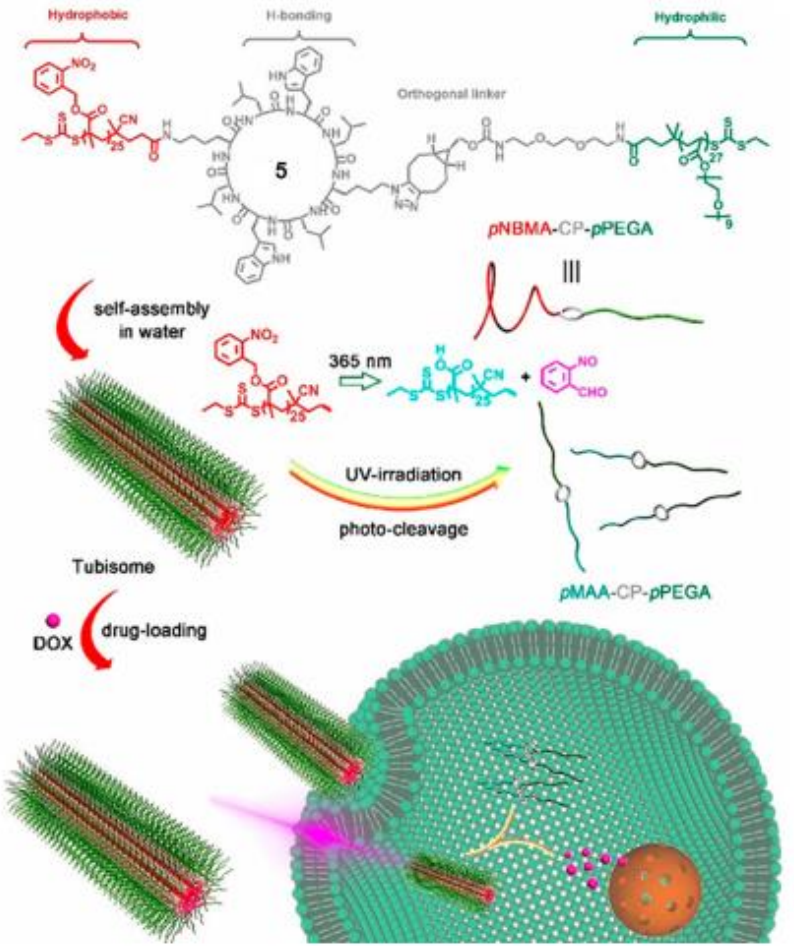

Figure 4: Chemical structure of asymmetric conjugate 5. The trigger responsive assembly into tubisomes can successfully deliver anticancer drug doxorubicin into cells (Yang *et al.*, 2020).

Gene delivery

In recent years, gene therapy has emerged as a powerful universal method of reprogramming genetic material to cure multiple diseases such as cancer, viral infection, or inherited disorders [Sung *et al.*, 2019]. By introducing new genetic code, or "knocking out" mutative genes at the cell nuclei, a positive impact on regulation of normal cellular functions can be observed. However, this therapeutic technique faces considerable challenges. It is highly dependent on the vector composition to preserve the integrity of the load, evade the immune response and target on a cellular level [Shi *et al.*, 2017]. To date, most nanotubular vectors for genetic transfer have been relatively large in size and use intermolecular binding between genetic material and different amino acid moieties to construct a loaded vector. Since peptide nanotubes are composed of closely stacked unimers, the presence of repulsive electrostatic forces is

unwelcome for producing supramolecular structures and, therefore, presents a significant difficulty when attempting to complex charged genetic loads. To date, a select number of cyclic peptide species have been studied for gene delivery applications.

A nonassembling cationic cyclic octapeptide **6** synthesized by [Li *et al*., 2016] was modified with a novel arginine analogue rationalized by molecular modeling to partake in enhanced binding with adjacent peptide backbones and overcome lysine residue charge repulsion (Figure 5). This was hypothesized to stabilize the assembly and form distinctive tubular structures in solution (pH 7.4). Complexation with calf thymus DNA did not alter the nanoparticle integrity (as confirmed by TEM and dynamic light scattering (DLS) and demonstrated the utility of the design for carrier purposes. Furthermore, transfection efficiency assay using green fluorescent protein (GFP) reporter labeling determined that transfection of HeLa and HEK-293 cell lines by SCPNs was on a comparable level to the commercially used polyethylene imine but occurred independently of active endocytosis pathways and was notably less cytotoxic.

Therefore, proper consideration of SCPNs for gene delivery therapies is surely a worthwhile avenue given their potential to resolve the setbacks of current medicines by avoiding endosomal entrapment and exhibiting fewer side effects on healthy cells. For instance, [Panigrahi *et al.,* 2018] reported stable peptide nanotubes capable of delivering siRNA at low concentrations to HCT-116 colorectal cancer cells (via caveolae and clathrin-mediated endocytosis) with capability matching that of lipofectamine, but further benefit from negligible cytotoxicity.

Hsieh *et al.* [2012] proposed that assembled cyclo-[(D-Trp-L-Tyr)$_{4}$-] nanotubes between 1 and 20 μm in length can act as an oral gene delivery vector to the stomach, duodenum, liver, or kidney where a strong binding constant (3.2 × 108 M−1) was calculated between plasmid DNA (pCMV-lacZ and pCMV-hRluc) and tyrosine peptide residues using fluorescence spectroscopy (Note: although this publication does not specify the size of the CP ring, based on the data provided we suggest it is an octapeptide). The shielding properties of the nanotubes were evident from the stability of plasmid to DNase 1, acidic conditions (pH 2 gastric acid simulation) and bile digestion for 50, 60, and 180 min respectively, indicating a broad potential for in vivo targets. Southern blot analysis and TM-rhodamine labeled DNA with intact genetic loads. The effect of this was apparent from β-galactose expression increasing by 41% in the kidney at 48 h, and 49%, 63%, and 46% at 72 h in the stomach, duodenum and liver respectively and bioluminescence imaging of ex vivo mouse organs gave confirmation of these accumulations (Figure 6).

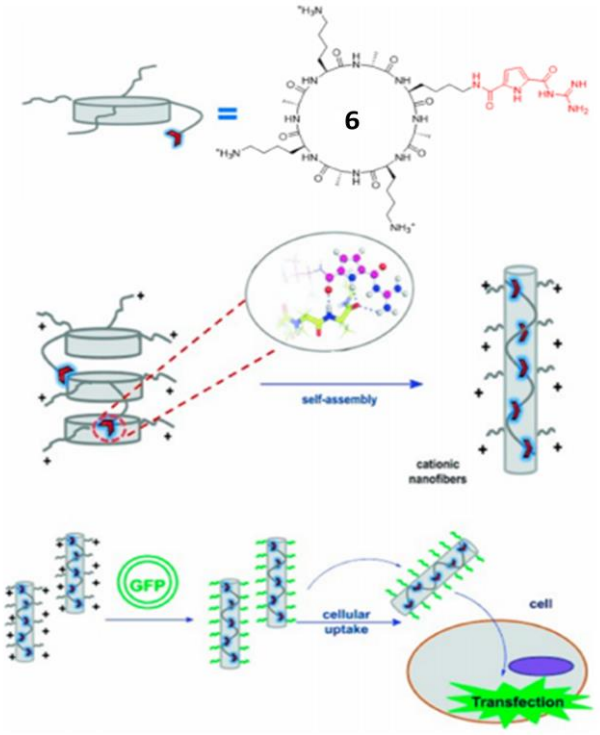

Figure 5: Chemical structure of the cationic cyclic octapeptide 6 and illustration of the assembling cationic nanotubes binding ctDNA and the process of fluorescent labeling with GFP to track cellular uptake and transfection efficiencies (Li *et al*., 2016)

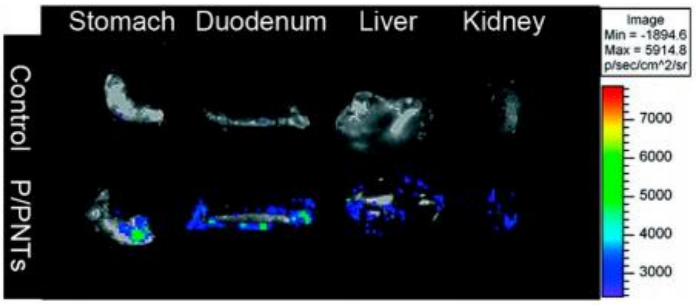

Figure 6: Ex vivo bioluminescence imaging of mice organs after oral administration of pCMV-hRluc: cyclo-[(D-Trp-L-Tyr)$_{4}$-] nanotubes for 48 h (kidney) or 72 h (stomach, duodenum, liver) (Hsieh *et al*., 2012)

Using this same peptide species, [Lee *et al.* 2015] investigated further gene delivery properties for treatment of corneal injury *via* atopical eye drop formulation administering the caspase 3 silencing shRNA to artificially induced epithelial debridement on nude mice. The known high aspect ratio and fast internalization rates of nanotubes are rationalized to be crucial features for this therapy, requiring good penetration through tightly packed layers of the epithelial matrix. Histological analysis of ThT stained nanotubes demonstrated that delivery into the epithelial layers and stroma had been achieved just 180 min after the first dosage. Notably, the material had even reached the nuclear region of corneal keratocytes, despite previous studies

suggesting a delayed DNA release. The successful uptake of the carrier could be translated to accomplishing a biological impact where caspase 3 apoptotic activity was calculated to be significantly lower in the treated tissue compared to native corneal wound control subjects. This result could be explored in the future for the prevention of permanent corneal damage and vision deterioration.

Antiviral applications

Transfer and replication of viral material is highly dependent on the low pH of endocytic vesicles, which trigger conformational protein changes needed for membrane fusion, lysis, and escape from these compartments prior to any degradation by other organelles. The appeal of cyclic peptide nanotubes due to their capacity to embed into membrane models is therefore amplified by the evidence of antiviral effects which [Horne *et al*., 2005] first discovered upon the rational design of octapeptide nanotubes, which could prevent the growth of adenovirus infection. A cyclo- [L-Ser-D-His-L-Lys-D-Arg-L-Lys-D-Trp-L-Leu-D-Trp-] **7** peptide demonstrated dose-dependent inhibition of adenovirus against HeLa cells (IC_{50} = 5 μM). [Horne *et al*., 2005] hypothesized that nanotubes block the development of acidic pH in endosomes due to transmembrane channel ion transport, preventing viral escape from these capsules (Figure 7).

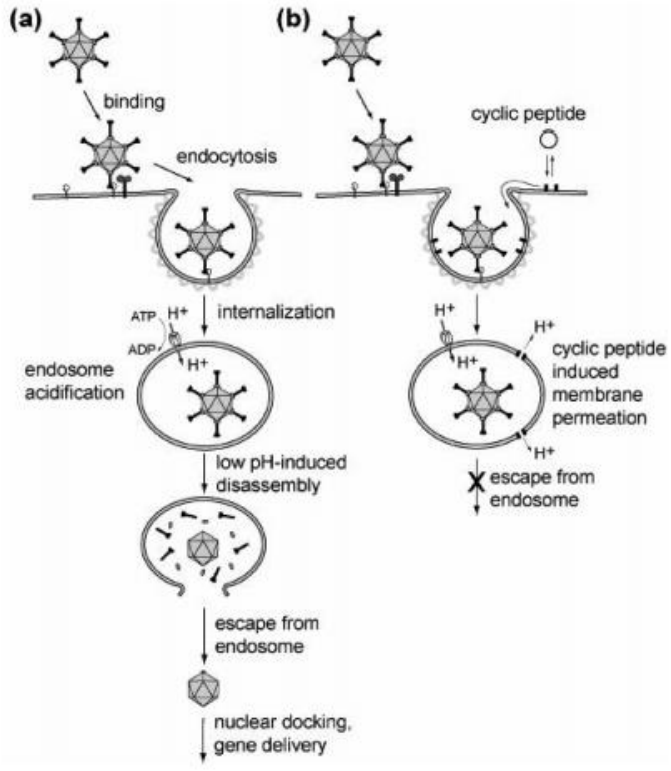

Figure 7. Illustration of the proposed mechanism of action for peptide 7 during the early phases of adenovirus infection cycle. In the absence of peptide (a), viral material is taken up via clathrin-mediated endocytosis, and the acidic environment can allow disassembly and escape. Administration of peptide (b) prevents the formation of an acidic endosomal environment and therefore limits the escape of the virus (Horne *et al*., 2005)

This was demonstrated by an experiment in which incubation of the peptide 4 h post Ad5-GFP infection did not prevent the escalation of the virus. This implied that the peptide does not impact transcription or translation processes but was vital for disrupting earlier processes like cellular entry or endosome formation. The influence of the assembled nanotube upon endosomal pH during infection was evaluated by fluorescence microscopy and imaging of carboxy-fluorescein labeled virus, namely the defective Ad2-tsl which has similar receptor properties to wild type adenovirus but cannot escape the endosome. The analysis revealed that the intracellular location of the virus remained the same in the presence or absence of the peptide, but the relative fluorescence was significantly different. Calculation of relative pH revealed the untreated cells tended toward stronger acidity (pH 5.3) compared to treated cells (pH 6.8), which corroborates the initial hypothesis of endosomal acidification being a primary target for nanotubes.

In addition, since [Ghadiri *et al*., 1993] initial investigation of cyclic peptide nanotubes, over 1200 octapeptide sequences have been amassed throughout the known literature. Of these, 144 were screened by [Montero *et al.* 2011] against HCV in an ELISA assay to afford the 9 most potent amphiphilic peptides, best described by having overall neutrality, positive charges adjacent to hydrophobic moieties, and Glu, Asp or Gln residues filling the cyclic ring. Further modifications to these compounds were made and compared to their linear analogues which had a very poor antiviral performance, as did N-methylated nonassembling cyclic peptides, corroborating previous thought that insertion of the elongated supramolecular structure into membranes is an essential component of the antiviral response. The screening also elaborated that while self-assembly is fundamental, this alone was insufficient for pronounced effects, and hence sequence specificity is also key to impart a balance between anti-HCV behavior and low toxicity to mammalian cells. [Montero *et al.* 2011] performed a time-dependent inoculation experiment and observed that antiviral activity was only possible when peptides were present during initial viral exposure or throughout the entire inoculation period, implying that a crucial early stage of cell entry was obstructed. Peptide dosage was kept constant and added to varying concentrations of HCV load in infected Huh-7 cells, either during or post inoculation period and susceptibility of binding versus post binding events to inhibition was compared to DMSO controls. A significant reduction in infectivity was clear during post binding processes, which corroborates the hypothesis that degradation of endosomal compartments is responsible for limiting viral spread. This remarkable feature to control viral spread suggests that this class of compounds could be used as part of a synergistic combination therapy with other antiviral compounds.

Conclusion:

To date, self-assembling cyclic peptides have demonstrated strong potential for a broad range of biological applications, and in many cases, might even be able to outperform or replace current highly regarded therapeutics. However, most of the materials studied for the aforementioned applications are cyclic α-alt(D,L)-peptides, and while the literature shows extensive optimization and the generation of large peptide libraries. Additionally, although there is some strong evidence of the biocompatibility of peptides and peptide− polymer conjugates, further tests are needed to assess long-term side effects of the materials in vivo and establish their chances of clinical success. These materials are an exciting opportunity for researchers to work across various disciplines and their synthetic pliability opens up a huge potential; the dual-purpose design of having both (1) specific peptide sequences capable of inducing targeted effects on peptide sensitive antibacterial or antiviral strains and (2) capability for extended supramolecular assemblies into nanoparticles that carry different types of cargo, have allowed these materials to merge the fields of small molecule therapies and macromolecular chemistry.

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RECENT ADVANCES OF VARIOUS NANOMATERIALS IN CANCER THERAPY

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Abstract:

Cancer is one of the diseases with a complicated pathological process. Problems with current chemotherapy include cytotoxicity, lack of selectivity, formation of multidrug resistance, and proliferation of stem-like cells. Materials with distinct optical, magnetic, and electrical characteristics that fall between 1 and 100 nm are called nanomaterials. There are numerous major categories where nanomaterials employed in cancer therapy. These nanomaterials, which target immune system, tumor microenvironment, and cancer cells, have been modified for a variety of cancer therapies in order to improve drug capacity and bioavailability, reduce toxicity, and improve selectivity. Over time, there has been a slight increase in the number of approved nano-drugs, despite an increase in studies. Additional research is required to better understand targeted drug delivery using nano-carriers, which can minimize the shielding impact of protein corona, improve permeability and retention effects, and reduce toxicity. In addition to discussing current barriers and restrictions that prevent the application of innovative nanomaterials from research to clinical settings, this chapter describes novel and developing nanomaterials that have been created for these purposes and offers recommendations for more effective application of nanomaterials in cancer therapy.

Keywords: Cancer therapy, Nanotechnology, Nanomaterials, Nano-drugs, Nano-carriers.

Introduction:

Many millions of cells make up the human body and are ultimately microscopic in nature. These cells are a living unit of life. Every cells plays a crucial part in daily activities. A normal cell must undergo apoptosis. These healthy cells develop into cancerous cells when they proliferate out of control. An imbalance in metabolism and aberrant signaling pathway leads to uncontrolled cell division and survival, called cancer (Sneeggen *et al.*, 2020). Rapid emergence of abnormal cells is one of the specific features of cancer. The most significant cause of death in cancer is due to metastasis. The most common cancer kinds are colorectal, lung, breast, and

prostate cancers. By 2030, the Global Cancer Observatory (GCO) projects that 30 million cancer patients would lose their lives to the disease (Globocan, 2018). Cancer not only has a high death rate but also imposes a heavy financial burden on society and the families of cancer sufferers. As a result, initiatives for cancer detection, treatment, and prevention are crucial (Sneeggen *et al.* 2020).

Modern techniques for diagnosing cancer include imaging techniques, lab examinations, and morphological examination of tissues and cells, which is typically regarded as quite trustworthy for the majority of cancer diagnoses, depicted in Fig. 1. Cancer diagnosis is further aided by pathological features such as IHC (immunohistochemistry) analysis, histological changes, mutational, and molecular genetics analysis (Pulumati *et al.,* 2023). Surgical resection, chemotherapy, radiation therapy, and biological therapy are common cancer treatments. While malignant solid tumors are removed surgically, especially while the cancer is still in its early stages, the results are positive. Multiple therapies, including radiation, chemotherapy, and surgery, are used in combined therapy (Mokhtari *et al.,* 2017). Chemotherapy has gained popularity throughout time since it is an easy and convenient way to treat cancer patients. Acute myelogenous leukemia, acute lymphoblastic, Hodgkin's and non-Hodgkin's lymphomas, small cell lung cancer, germ cell cancer, ovarian cancer, and choriocarcinoma are among the tumors that respond well to chemotherapy (Savage, 2020). Nevertheless, because chemotherapy can also suppress rapidly growing tissues and cells, such as bone marrow, gastrointestinal tract cells, and hair follicles, its indiscriminate cytotoxicity results in undesired side effects. Additionally, chemotherapy causes multi-drug resistance and may be linked to cancer stem cells. The non-specific and heterogeneous distribution of cytotoxic chemical agents used in chemotherapies promotes multi-drug resistance during the course of treatment. This non-specificity reduces the effectiveness of chemotherapy and makes it more difficult to stop tumor development, metastasis, and recurrence (Bukowski *et al.,* 2020; Mansoori *et al.,* 2017).

Lack of specificity, cytotoxicity, short half-life, poor solubility, multi-drug resistance, and the formation of stem-like cells are some of the issues with current chemotherapy. Photodynamic therapy, photothermal therapy, targeted therapy, molecular therapy, chemodynamic therapy, sonodynamic therapy, and nanomaterial-based chemotherapy are being employed in cancer treatment to address these drawbacks (Cheng *et al.* 2021). Furthermore, a significant amount of research has been conducted in recent years on a range of cancer treatment methods, including molecular therapy, immunotherapy, apoptotic regulations, signal modification therapy, nucleic acid-based therapy, and anti-angiogenesis therapy. Since the development of nanotechnology, there has been a great deal of study conducted in the hopes of

reducing the side effects of chemotherapy when using nanomedicines for cancer treatment (Ojha *et al.* 2022; Cheng *et al.* 2021). This chapter describes novel and developing nanomaterials that have been created for these purposes and offers recommendations for more effective application of nanomaterials in cancer therapy.

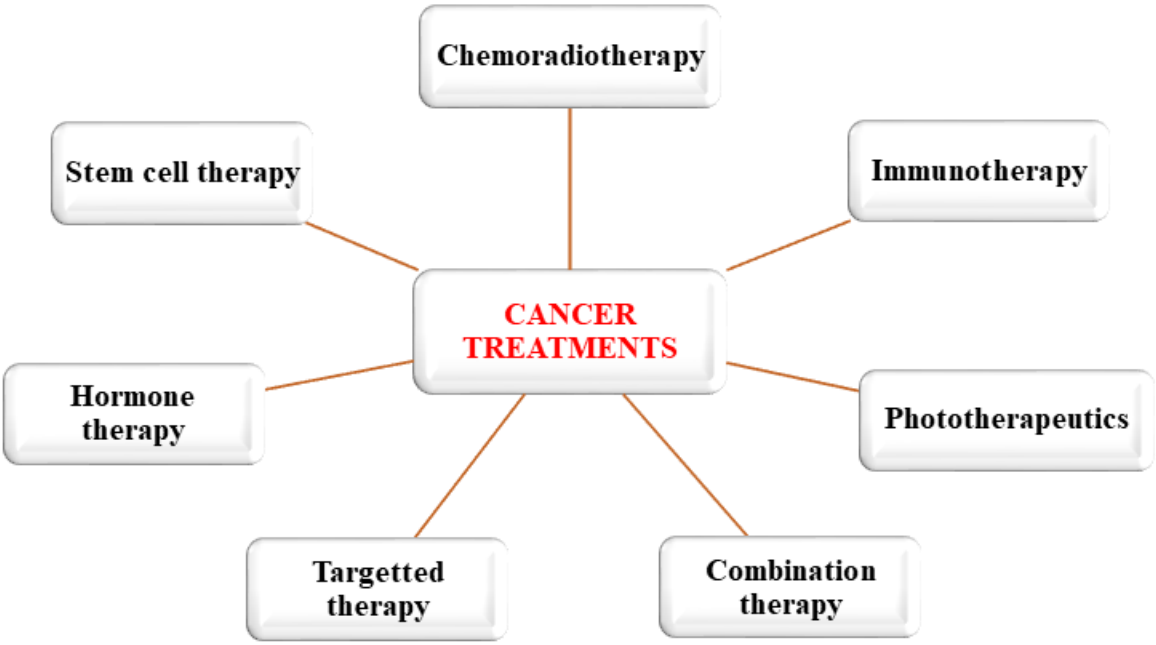

Figure 1: Various types of cancer treatments

Role of nanotechnology in cancer

With several types of nanoparticles (NPs) being utilized for molecular imaging nowadays, the use of NPs in cancer diagnosis and monitoring has garnered significant attention in the last few decades. Their advantages—small size, high atomic number, and strong biocompatibility—have made them more well-known in the field of cancer diagnostics and research recently (Baranwal *et al.*, 2023). Certain NPs, like semiconductors, quantum dots, and iron oxide nanocrystals, are employed in cancer treatment because they have unique optical, magnetic, or structural characteristics not found in other molecules. Early cancer detection has become feasible in cancer diagnostics thanks to the use of nanoparticle imaging of tumor tissue. High surface-to-volume ratios, improved electrical conductivity, superparamagnetic behavior, spectral shift of optical absorption, and distinctive fluorescence features are some of the common traits shared by typical nanomaterials (Cheng *et al.*, 2021). Nanomaterials can be used in medicine for controlled release and drug transfer. Notable characteristics also include enhanced biocompatibility and increased permeability, which allow passage across biological obstacles. These unique characteristics of nanomaterials imply their potential application in cancer treatments. A few nanomaterials have a high surface-to-volume ratio that allows them to

assemble with biomolecules or residues. This can improve the specificity of chemical drug complexes in targeted therapy, increasing the treatment's effectiveness while lessening the toxicity to normal cells (Mosleh-Shirazi *et al.*, 2022).

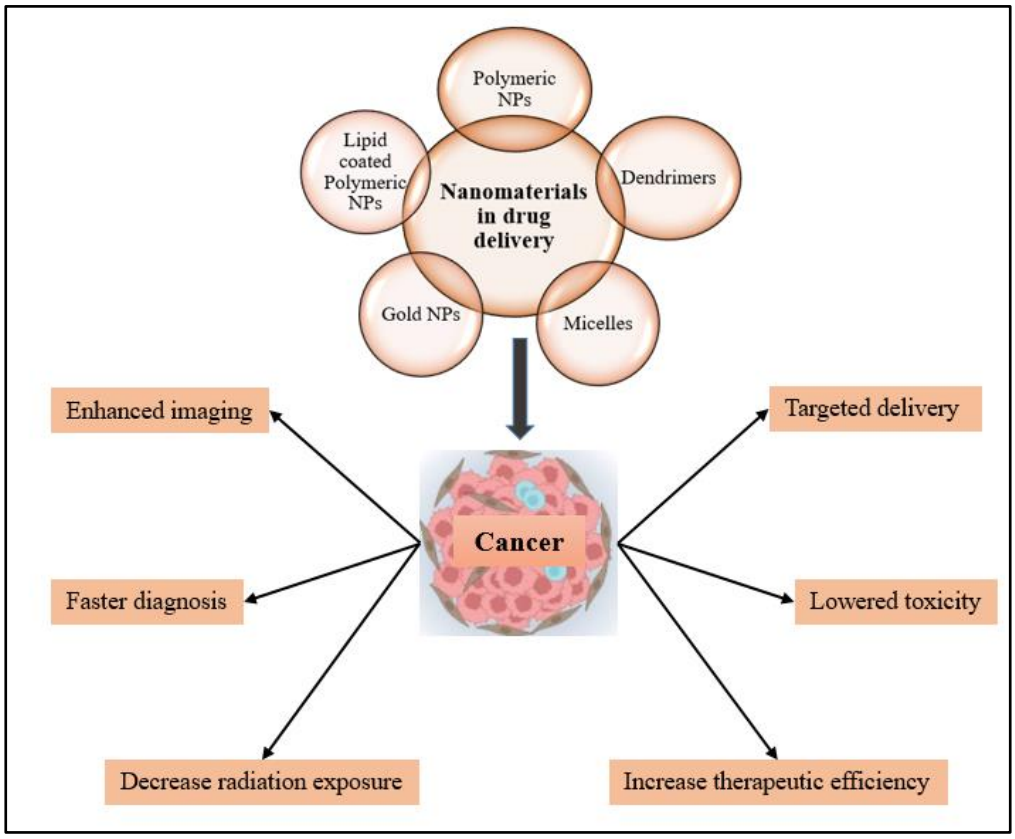

Figure 2: Advantages of using various nanomaterials in cancer therapy

Technically speaking, NPs are particles with a single dimension of less than 100 nm and special qualities that are typically absent from bulk samples of the same substance. The surface layer, shell layer, and core—which is essentially the central component of the NP and is typically referred to as the NP itself—make up the basic composition of nanoparticles, which is rather complex (Sousa *et al.*, 2021). These materials have become more important in interdisciplinary domains because of their remarkable properties, which include high surface-to-volume ratio, dissimilarity, sub-micron size, and improved targeting system. Developing or designing a medication or gene delivery system with superior ability to target tumor cells while sparing healthy normal cells is crucial for successful cancer therapy (Yao *et al.*, 2020). It increases the effectiveness of treatment, protecting healthy cells from the damaging effects of cytotoxicity. It can be accomplished by delivering NPs into the tumor microenvironment in a systematic manner, thereby indirectly targeting cancer cells. There should be several physiological and biological hurdles that these nanoformulations can overcome. These barriers consist of multiple layers and components (Tang *et al.*, 2021). In order to avoid unintentional targeting, these

realities enforce restrictions on the size, biocompatibility, and surface chemistry of NPs. Nevertheless, an NP medication molecule does not necessarily reach its subcellular target just because it internalizes into the cytosol. It takes specialized engineering and optimization to make cellular or nuclear targeting possible (Gavas *et al.,* 2021).

Nanomaterials in cancer therapy

1. Monoclonal antibody NPs

Currently, monoclonal antibodies are widely utilized to target many antigens on the surface of cancer cells with nanoparticles. Drug-targeting therapies can benefit from the fact that this antigen is expressed more in cancer cells than in healthy cells, which is what separates malignant cells from healthy ones (Wathoni *et al.,* 2022). Conjugating monoclonal antibodies to the nanoparticles reduces the systemic toxicity of the medication treatment because of improved drug targeting. Many nanoparticle systems, such as lipid-based nanoparticles, gold nanoparticles, super magnetic iron oxide nanoparticles, and other materials for active lung cancer targeting, have been coupled with monoclonal antibodies. Antibody–drug conjugates are created when monoclonal antibodies are coupled with cytotoxic medicines to further enhance the therapeutic efficacy of anticancer therapies; Better specificity and less toxicity can be obtained by using specific antigens that are expressed differently in malignant cells compared to normal cells to guide the drug combination (Peters and Brown, 2015). For instance, a monoclonal antibody called Trastuzumab (Herceptin) is used to treat breast cancers that express human epidermal growth factor receptor 2 (HER2). Studies utilizing Trastuzumab in the ADC system have been carried out, and the findings indicate that the therapeutic efficacy is enhanced when compared to Tmab used alone (Nieto *et al.,* 2020). An antibody-drug nanoparticle was created by Abedin *et al.* (2021). It has a surface modified with trastuzumab and a core loaded with paclitaxel (PTX). This novel NP, PTX, and trastuzumab were administered separately to two HER2-positive and one HER2-negative cell line. The results were encouraging: the NP complex exhibited greater anti-tumor efficaciousness than either PTX or trastuzumab alone, and comparatively lower cytotoxicity in human breast epithelial cell control was noted in the NP complex group (Abedin *et al.,* 2021).

2. Lipid based NPs

Lipid-based NPs are made of lipids and often take the shape of solid lipid NPs, liposomes, or nanostructured lipid carriers. There is a lot of interest in using these NPs in cancer treatment and drug development. Certain NPs have very minimal or no toxicity and can transfer both hydrophobic and hydrophilic substances (Chaudhuri *et al.* 2022). These NPs can also extend the therapeutic action time because of their controlled drug release and extended half-life.

Therapeutic carriers such as lipid NPs have been widely used, especially in the treatment of cancer (Sheoran *et al.*, 2022). By coupling these NPs with ligand monoclonal antibodies that are selective for particular receptors, they have also been made for active targeted distribution. The methods include double emulsion and thin-film dispersion were used to generate lipid nanoparticles that encapsulated PD-L1 ligand antibodies and trapped Adriamycin. Studies using A549 cells were conducted both *in vitro* and *in vivo*. The findings demonstrated that the intracellular derived fluorescence of the nanoparticles containing this ligand was significantly greater than that of the nanoparticles lacking the ligand at the same Adriamycin concentration. The results demonstrated that the experimental animals' tumor volume was reduced more by nanoparticles carrying an anti-PD-L1 ligand than by the Adriamycin-only group (Wathoni *et al.* 2022).

3. Polymeric NPs

Drug delivery systems utilizing polymeric NPs are becoming more and more popular as a way to address issues arising from, among other things, challenges in administering the medication in relation to the location of tumor cells and to lower the possibility of side effects on adjacent unaltered cells. Polymeric NP-based anticancer therapy is becoming more and more popular in research because it allows the therapeutic effect to be limited to cancer cells (Dristant *et al.,* 2023). Undoubtedly, the primary function of the small size is in cancer therapy, when the drug's accessibility is restricted. For instance, blood-brain barrier (BBB) is the primary barrier for brain. However, most of the time, this barrier can be removed since drug-loaded polymeric NPs can interact with receptors on a ligand-receptor basis (Yao *et al.,* 2020). *In vitro* attempts have been made to use polymeric NPs as carriers for genome-editing tools, and they are currently being used in the treatment of women's cancers and colorectal cancer (Fatima *et al.,* 2022). Polymeric NPs, particularly those made from d,l-PLGA, a copolymer that the Food and Drug Administration (FDA) has approved for use in active pharmaceutical component delivery systems, show promise for application in cancer therapy. These carriers have been shown to be effective against a range of cells and can operate through either an active or passive method (Alsaab *et al.*, 2022). Numerous research' findings indicate that polymeric NPs have a lot of promise for application as chemotherapeutic delivery systems in the treatment of glioblastoma multiforme, oral cancer, breast cancer, ovarian cancer, and colorectal cancer. Strong evidence suggests that treating and diagnosing oral cancer early can lower its death rate. Polymer fluorescent nanoprobes have several benefits, including excellent biocompatibility, high sensitivity, and non-invasiveness, which makes them perfect for imaging. Polymeric nanoagents serve as fluorescent probes or nanocontrast agents in the early detection and imaging of oral

cancer. Furthermore, polymeric NPs are presently being studied for their potential as gene therapy carriers. The fact that several PNPs are undergoing evaluation in clinical studies and that some have received FDA approval for treatment is also noteworthy (Begines *et al.*, 2020).

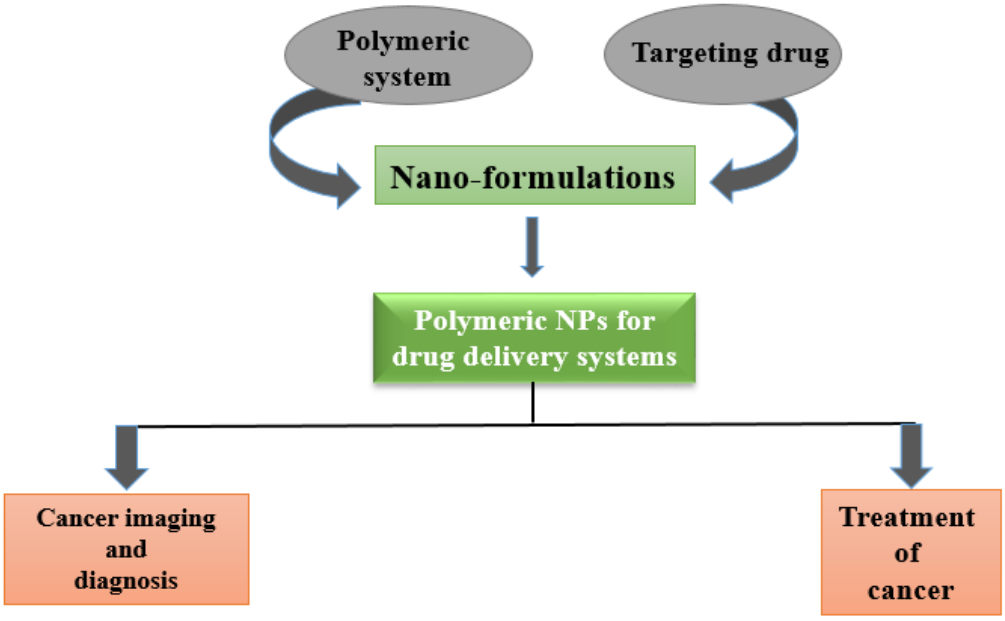

Figure 3: Outline of polymeric NPs in applications of cancer

4. Gold NPs

Effective radiosensitizers for use in medicinal applications including medication administration and cancer therapy are gold Nps. Using kilovoltage cone-beam computed tomography, image-guided NP-enhanced radiotherapy can use gold NPs as a contrast agent and dosage enhancer in biomedical and cancer therapy applications. Particle characteristics like size, content, shape, and surface chemistry can now be readily controlled by precision technology thanks to recent advancements in nanomaterial synthesis and fabrication techniques (Chen *et al.*, 2020). Additionally, the NP surface can have a biocompatible surface coating applied to it to offer stabilization under physiological conditions. Functional ligands are integrated into the NPs' surface chemistry to serve as coating, allowing them to simultaneously carry out a variety of molecular or cellular biological tasks (Chen *et al.*, 2020). Gold NP-based drug delivery has drawn a lot of interest due to its outstanding results. Despite the fact that Gold NPs have not received pharmacological approval for use in officially marketed nanomedicines, numerous investigations are being conducted in this area (Kong *et al.*, 2017). Many Gold NP-based nano-drugs in combination with other biomedical uses are under investigation, such as drug-conjugated Gold NPs made for tumor-targeting and cancer therapy (Jain *et al.*, 2012). Small interfering ribonucleic acids (siRNAs), proteins, peptides, plasmid deoxynucleic acids (pDNAs),

and chemotherapeutic medicines are among the pharmaceuticals for which Gold NPs are known to be an efficient nano-carrier.

In the treatment of oral cancer, gold nanoparticles are frequently used as drug carriers. In order to achieve increased antitumor efficacy, Liu *et al.* (2020) studied a gold NPs-DOX system (podoplanin antibody) as a nanoplatform integrating chemophotothermal treatment. Through active targeting, gold nanoparticles coupled with podoplanin antibodies can aid in the drug's and NPs' accumulation in the tumor site. Under acidic conditions in the endolysosomal compartments of tumor cells, the rate of DOX release increased. This could be because the acid-sensitive amide bond between PEGylated AuNPs and DOX was disrupted. Although Gold NPs are not currently being used extensively in clinical environment, studies on Gold NP-based medication delivery, gene therapy, photothermal therapy, and radiotherapy have demonstrated encouraging outcomes and may prove to be workable approaches in the future (Chung *et al.,* 2021). It is clear that Gold NPs will continue to be important in advancing the biomedical area, including medication delivery and cancer therapy, based on the positive current outcomes and anticipated future advancements.

5. Extracellular vesicles

Extracellular vesicles are phospholipid vesicles that are bilayer and usually range in size from 50 to 1000 nm. Different cell types continuously release extracellular vesicles that vary in size, origin, and composition. Extracellular vesicles are categorized into three main types based on their origin: apoptotic bodies, microvesicles, and exosomes. Exosomes are tiny, 40–200 nm particles. Extracellular vesicles are used in long-distance communications and contain DNA, RNA, and protein (Doyle and Wang 2019). Exosome NPs are natural carriers that can be paired with currently available anti-tumor compositions and techniques since their membrane shares identical lipids and chemicals with the cells from whence they originated. This allows exosome NPs to evade immune monitoring and internalize with target cells with ease. In both healthy and pathological physiological processes, including cell maintenance and differentiation, tissue regeneration, immunological regulation, and tumor growth, extracellular vesicles have been shown to be essential mediators of intercellular communication (Avgoulas *et al.,* 2023; Mukherjee *et al.,* 2022). It is well recognized that extracellular vesicles have a variety of roles in the processes that drive the development of tumors, such as angiogenesis, tumor invasion, progression, and metastasis, as well as tumor microenvironment modification. It has long been known that extracellular vesicles produced from tumor cells are essential in encouraging tumor microenvironment cells to exacerbate tumor growth. Low extracellular vesicle recovery and restricted cargo loading efficiency are issues with using engineered extracellular vesicles and,

particularly, direct engineering methodologies, which limit their use in cancer therapy to some attention (Wang *et al.,* 2023). A number of indirect intracellular modifications that involved the engineering of parent cells to modify extracellular vesicles have surfaced, improving cargo encapsulation and boosting extracellular vesicle mass production at the same time. Potential safety concerns are present, but the current limits are low isolation yield and insufficient purification of extracellular vesicles following donor cell modification. Furthermore, suitable analytical tools are needed because it is a problem to properly measure the active ingredients enclosed in extracellular vesicles (De Sousa *et al.,* 2023). Notwithstanding these difficulties, extracellular vesicle-based cancer therapy holds great promise and could advance cancer treatment in the future.

6. Nanoemulsions

Colloidal dispersions known as nanoemulsions are mostly employed as safe-grade excipient-based compounds with poor water solubility as medication delivery systems. Due of its great stability and solubility, this dosage form is made up of a heterogeneous dispersion of a nanoscale droplet in another liquid. The medication is shielded from deterioration and has a longer half-life in plasma thanks to the encapsulation (Sánchez-López *et al.,* 2019). For targeted applications, nanoemulsions can be coupled with antibodies or their fragments; this is particularly advantageous because antigen–antibody binding is both selective and specific. Numerous studies suggest that this conjugation results in drug-loaded nanoemulsions being successfully delivered to cancer cells and internalized. To become even more particular to cancer tissues, the nanocarrier–antibody combination may respond to stimuli (Chehelgerdi *et al.,* 2023). Comparing nanoemulsions to other drug carriers, their primary benefit is that they can be engineered to selectively target tumor cells while avoiding multidrug resistance (Sánchez-López *et al.,* 2019). This is an important advancement in the field of cancer therapy, as the fundamental obstacle still facing it is that the majority of anti-cancer medications fail because they are extremely toxic to healthy cells and tissues or even because the cancer cells acquire resistance to the treatment. Delivery by passive targeting capitalizes on the ERP effect, which is common in tumor tissues. But since active targeting employs particular targeting moieties for cancer cells in addition to the EPR effect, it may add even more advantageous aspects to the formulation (Subhan *et al.,* 2021). Compounds that oppose multi drug resistance processes can co-encapsulate, or bind, to the surface of multifunctional nanoemulsions.

7. Dendrimers

A certain class of macromolecules known as dendrimers have a specified hyperbranched topology. The highly branched and easily adjustable surfaces of dendrimers are their most

noticeable feature. A number of dendrimers, including 5-aminolevulinic acid, polypropylenimine, poly(ethylene glycol, 2,2-bis(hydroxymethyl) propionic acid, and triethanolamine, have been developed for use as cancer therapies. Compared to other nanomaterials, dendrimers have distinct properties such as a defined molecular weight, flexible and adjustable branching, a limited polydispersity index, and better solubility and bioavailability of hydrophobic medicines due to their distinctive structure (Abbasi *et al.,* 2014). Dendrimers can be effective nucleic acid nanocarriers because cationic dendrimers with positively charged surfaces can form compounds with nucleic acids. Despite their multifunctional properties, dendrimers have been shown to be toxic to biological membranes in the early stages of research (Abedi-Gaballu *et al.,* 2018). This is because the positive charge of dendrimers interacts with the negative charge of the biological membrane, creating nanoholes in the membrane. However, researchers have overcome this obstacle by creating biocompatible dendrimers and by using dendrimer surface engineering techniques like acetylation, peptide conjugation, and carbohydrate conjugation (Santos *et al.,* 2019). Anticancer medications can be delivered at the nanoscale to specific tumor sites using dendrimers. The characteristics of these biocompatible nanosystems make them suitable for transdermal drug administration, cancer treatment, and diagnostic applications (Chis *et al.,* 2020). Most anticancer medications on the market today cause systemic toxicity and adverse effects in addition to failing to distinguish between malignant and healthy cells. Dendrimers have proven to be effective in gene therapy and the active targeting of antineoplastic agents within malignant cells without posing any harm. Receptor-mediated dendrimer absorption is possible, and dendrimers can be selectively targeted toward cancer cells (e.g., by antibodies specific for tumor-associated antigens) (Chis *et al.,* 2020). They will therefore guarantee decreased systemic toxicity and selective intratumoral accumulation. Dendrimers have the potential to emerge as the newest class of effective anticancer treatment medicines if ongoing research in nano-oncology continues.

Conclusion:

While nanomaterials vary in composition, structure, hydrophobicity, magnetic, immunogenicity, and other characteristics, they always have a comparable size. Numerous studies have been conducted on cancer treatments based on these special qualities. Generally speaking, different nanomaterials can have their surfaces modified in different ways, and traditional anti-tumor chemical medications can frequently be loaded into various nanocarriers. It is imperative that researchers possess a thorough understanding of both the properties of therapeutic medicines and the attributes of the chosen nanoplatform. One approach could be to use antibody-modified extracellular vesicles to deliver essential gene therapy molecules to

specific cancer cells. extracellular vesicles, for example, are biocompatible vesicles that can evade immune surveillance and integrate easily with target cells. It is also crucial to take into account testing nanomaterials in models that are closer to the *in vivo* environment. In conclusion, it is noted that advances in nanobiotechnology and cancer therapy development will lead to a breakthrough in clinical translation for the treatment of cancer, a fatal disease, and more medications based on nanomaterials will help patients with cancer.

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NANOTECHNOLOGY ADVANCEMENTS: BIOSYNTHESIS ROUTES, CHARACTERIZATION AND BIOMEDICAL APPLICATIONS OF ZINC OXIDE NANOPARTICLES

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Abstract:

This study delves into recent strides in biosynthesis, characterization, and the biomedical applications of zinc oxide nanoparticles (ZnONPs). Biosynthesis methodologies have emerged as sustainable alternatives to conventional synthesis routes, harnessing biological organisms such as bacteria, fungi, plants, and algae for eco-friendly ZnONP production. These methods have several advantages, such as less of an adverse effect on the environment and avoidance of hazardous chemicals. Characterization techniques such as X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), and spectroscopic analyses, are pivotal in unveiling the structural, morphological, and physicochemical characteristics of ZnONPs. The applications of ZnONPs traverse drug delivery, cancer treatment, environmental remediation, and biomedicine. From antimicrobial coatings and photovoltaic devices to drug delivery systems and biomedical sensors, their adaptability underscores their significance in surmounting critical challenges and propelling technological innovations. In this review, the synthesis, characterization, and applications of ZnONPs epitomize a dynamic domain within nanotechnology. Sustained research endeavours aimed at refining synthesis methodologies, augmenting characterization techniques, and exploring nascent applications will further amplify the potential and impact of zinc oxide nanoparticles across multifarious technological domains.

Keywords: Zinc Oxide Nanoparticles, Biosynthesis, Characterization, SEM, TEM, XRD.

Introduction:

Nanotechnology has emerged as a revolutionary field with profound implications across various disciplines, including materials science, electronics, medicine, and environmental science. Among the myriad nanomaterials, zinc oxide nanoparticles (ZnONPs) have garnered significant attention due to their unique properties and versatile applications. This review explores the recent advancements in the biosynthesis, characterization, and biomedical applications of zinc oxide nanoparticles. Zinc oxide nanoparticles hold immense potential in

biomedical applications owing to their biocompatibility, low toxicity, and photocatalytic properties. Their synthesis via biological routes has gained prominence due to its eco-friendly nature and cost-effectiveness compared to conventional chemical synthesis methods Sirelkhatim *et al.* (2015). Biological synthesis methods utilize various biological agents such as bacteria, fungi, plants, and algae to produce ZnO nanoparticles. These methods not only offer sustainable approaches but also facilitate the production of nanoparticles with controlled size, shape, and surface properties. Characterization of zinc oxide nanoparticles is crucial for understanding their physicochemical properties, stability, and potential interactions with biological systems Jamdagni *et al.* (2018). Advanced techniques such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), X-ray diffraction (XRD), dynamic light scattering (DLS), Fourier-transform infrared spectroscopy (FTIR), and UV-visible spectroscopy are commonly employed for the comprehensive characterization of ZnO nanoparticles. These techniques provide insights into nanoparticle morphology, crystalline structure, surface chemistry, and optical properties, which are essential for their biomedical applications. The biomedical applications of zinc oxide nanoparticles encompass a broad spectrum, including drug delivery, cancer therapy, tissue engineering, and imaging Wahab *et al.* (2016). ZnO nanoparticles exhibit remarkable antibacterial, antiviral, and anticancer properties, making them promising candidates for combating infectious diseases and cancer Sirelkhatim *et al.* (2015). Moreover, their tunable properties enable the targeted delivery of therapeutic agents to specific tissues or cells, thereby minimizing off-target effects and enhancing treatment efficacy. Additionally, zinc oxide nanoparticles have shown potential in biosensing applications for the detection of biomolecules and pathogens with high sensitivity and specificity. In recent years, extensive research efforts have been directed towards exploring the biomedical applications of zinc oxide nanoparticles and addressing key challenges related to their synthesis, characterization, and biocompatibility. This review aims to provide a comprehensive overview of the current state-of-the-art in the biosynthesis, characterization, and biomedical applications of zinc oxide nanoparticles, highlighting recent advancements, challenges, and future perspectives.

Biosynthesis of zinc oxide nanoparticles:

Zinc oxide nanoparticles ZnONPs can be synthesized by various methods such as mechanical, chemical, and biological routes. From those methods, biological methods of producing ZnONPs is frequently utilized worldwide because of its low toxicity and valuable properties of biological sources utilized. Some of the common biological routes used for production of ZnONPs are detailed as follows.

Microbial mediated biosynthesis:

Synthesis of zinc oxide nanoparticles (ZnONPs) using microbial-mediated biosynthesis utilizes microorganisms such as bacteria, fungi, and algae to produce nanoparticles (table 1) Sharma *et al.* (2019). This eco-friendly approach offers several advantages over conventional methods, including cost-effectiveness, scalability, and the ability to produce nanoparticles with controlled size and morphology Singh *et al.* (2015). In this process, microorganisms function as both reducing and capping agents, facilitating the reduction of metal ions to form nanoparticles, and stabilizing them to prevent agglomeration Raliya and Tarafdar (2014). The choice of microorganism and reaction conditions play a crucial role in determining the size, shape, and properties of the synthesized nanoparticles. For example, bacteria like *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli*, as well as fungi like *Aspergillus*, *Fusarium*, and *Saccharomyces* species, have been successfully used for the biosynthesis of ZnONPs Husseiny *et al.* (2015) Bharde *et al.* (2006). These microorganisms can be easily cultured and manipulated to optimize the synthesis process. Several studies have reported the use of various microbial species and their byproducts, such as enzymes and proteins, for the synthesis of ZnONPs with different applications in biomedicine, agriculture, and environmental remediation.

Table 1: Various microbial sources used for synthesis of ZnONPs.

Microbial Source	Microbial Part Used	Biosynthesis Method
Bacillus subtilis	Whole cell	Intracellular
Escherichia coli	Cell-free extract	Extracellular
Pseudomonas aeruginosa	Cell-free extract	Extracellular
Lactobacillus acidophilus	Cell-free extract	Intracellular
Streptomyces sp.	Cell-free extract	Intracellular
Aspergillus niger	Biomass	Intracellular
Fusarium oxysporum	Biomass	Intracellular
Candida albicans	Cell-free extract	Intracellular
Saccharomyces cerevisiae	Cell-free extract	Intracellular
Rhodococcus sp.	Biomass	Intracellular

Plant mediated biosynthesis:

Plant-mediated biosynthesis of zinc oxide nanoparticles (ZnONPs) involves the utilization of various plant extracts (table 2) as reducing and stabilizing agents, making it an environmentally friendly and sustainable approach Husseiny *et al.* (2015). The process typically entails mixing zinc precursor solutions with plant extracts rich in phytochemicals, such as

flavonoids, phenolics, and terpenoids, under specific pH and temperature conditions Al-Khayri et al. These phytochemicals function as reducing agents, converting the zinc ions into ZnONPs, while the plant extracts play a vital role in stabilizing the synthesized NPs, preventing their agglomeration, and ensuring their uniform dispersion Sundrarajan *et al.* (2015). The mechanism of synthesis involves the reduction of zinc ions by phytochemicals, followed by nucleation and growth of ZnONPs. Factors such as the type of plant extract, concentration of phytochemicals, pH, and temperature influence the size, shape, and properties of the synthesized NPs. For example, higher concentrations of phytochemicals and alkaline pH conditions tend to result in smaller-sized NPs Ramesh *et al.* (2021). Characterization techniques like X-ray diffraction (XRD), transmission electron microscopy (TEM), and Fourier-transform infrared spectroscopy (FTIR) are commonly used to analyse the synthesized ZnONPs and confirm their crystalline structure, size, and chemical composition Alaghemand *et al.* (2018). Plant-mediated biosynthesis offers several advantages over conventional chemical methods, including cost-effectiveness, scalability, and reduced environmental impact.

Table 2: Various plant sources used for synthesis of ZnONPs.

Plant Source	Plant Part Used	Biosynthesis Method
Aloe vera	Leaf	Aqueous leaf extract
Green tea	Leaf	Aqueous leaf extract
Neem	Leaf	Aqueous leaf extract
Basil	Leaf	Aqueous leaf extract
Turmeric	Rhizome	Aqueous rhizome extract
Ginger	Rhizome	Aqueous rhizome extract
Rosemary	Leaf	Aqueous leaf extract
Pomegranate	Peel	Aqueous peel extract
Onion	Bulb	Aqueous bulb extract
Banana	Peel	Aqueous peel extract

Enzyme mediated biosynthesis:

Enzyme-mediated biosynthesis of zinc oxide nanoparticles (ZnONPs) offers a sustainable and eco-friendly approach to nanoparticle synthesis. Enzymes act as biocatalysts, accelerating the reaction rate and facilitating the formation of well-defined nanoparticles Meer *et al.* (2022). One of the most commonly used enzymes (table 3) in this process is urease, which hydrolyses urea to produce ammonia and carbonate ions. These ions then react with zinc ions to form ZnONPs. Urease-mediated biosynthesis of ZnONPs has been widely studied due to its simplicity

and efficiency Barsainya & Singh (2018). Other enzymes, such as alkaline phosphatase and lipase, have also been employed for the synthesis of ZnONPs, each offering unique advantages in terms of reaction kinetics and nanoparticle properties Ahmed *et al.* (2016).

Table 3: Various enzymes used for synthesis of ZnONPs.

Enzyme	Source	Biosynthesis Method
Urease	Fungi, yeast, bacteria	Microbial fermentation
Protease	Bacteria, fungi	Aqueous enzyme extraction
Cellulase	Fungi, bacteria	Enzyme-assisted hydrolysis
Amylase	Bacteria, fungi	Enzymatic hydrolysis
Laccase	Fungi, bacteria	Enzyme-mediated synthesis
Phytase	Bacteria, fungi	Solid-state fermentation
Catalase	Bacteria	Enzyme-assisted synthesis
Peroxidase	Plants, fungi, bacteria	Enzyme-catalysed reaction
Glucose oxidase	Fungi, bacteria	Enzymatic oxidation
Chitinase	Fungi, bacteria	Enzymatic degradation

Characterization of Zinc oxide nanoparticles:

Zinc oxide nanoparticles (ZnONPs) can be characterized by using various analytical techniques to validate their physical and chemical properties. Some of the analytical techniques employed for characterization are detailed below.

Scanning Electron Microscopy (SEM)

Characterization of zinc oxide nanoparticles using scanning electron microscopy (SEM) provides valuable details about the morphology, size distribution, and surface characteristics of these nanoparticles. In SEM analysis, a beam of electrons scans the surface of the sample, generating high-resolution images that reveal the topography and structure of the nanoparticles. The morphology of zinc oxide nanoparticles can vary significantly depending on the synthesis method and conditions. For example, nanoparticles synthesized by the sol-gel method often exhibit spherical shapes, while those prepared using hydrothermal methods may have rod-like or flower-like structures. SEM images also help in determining the size distribution of nanoparticles, which is essential for understanding their properties and behaviour. Additionally, SEM can be used to study the surface characteristics of zinc oxide nanoparticles, such as the presence of defects, cracks, or impurities, which can impact their performance in various applications. Several studies have employed SEM to characterize zinc oxide nanoparticles. For

instance, a study by Mohd Zain *et al.* (2020) used SEM to investigate the morphology and size distribution of zinc oxide nanoparticles synthesized via a precipitation method. The SEM images revealed that the nanoparticles were uniform in size and exhibited a spherical morphology with an average diameter of 50 nm. Similarly, Huang *et al.* (2008) utilized SEM to analyse the surface morphology of zinc oxide nanoparticles prepared by a hydrothermal method. The SEM images showed that the nanoparticles had a rod-like structure with an average length of 200 nm and a diameter of 50 nm.

Transmission Electron Microscopy (TEM)

Characterization of zinc oxide nanoparticles (ZnONPs) using transmission electron microscopy (TEM) is a crucial technique for understanding their morphology, size, and structure. TEM offers high-resolution imaging, allowing researchers to visualize individual nanoparticles and their characteristics. To prepare samples for TEM analysis, ZnONPs are typically dispersed in a suitable solvent and then deposited onto a TEM grid. The grid is then placed in the TEM chamber, where a beam of electrons passes through the sample. The interaction of the electrons with the sample produces an image that can be analysed to determine the size, shape, and distribution of the nanoparticles. In addition to imaging, TEM can also be used for selected area electron diffraction (SAED) analysis, which provides information about the crystal structure of the nanoparticles. SAED patterns are formed when electrons are diffracted by the crystal lattice of the sample, producing a pattern of spots that can be used to determine the crystal structure of the nanoparticles. This information is valuable for understanding the properties of the nanoparticles and their potential applications. Several studies have demonstrated the effectiveness of TEM in characterizing ZnONPs. For example, a study by Salahuddin *et al.* (2015) used TEM to investigate the size and morphology of ZnONPs synthesized using a hydrothermal method. The TEM images revealed that the NPs were uniform in size and exhibited a hexagonal shape, confirming the successful synthesis of ZnONPs.

UV-Visible Spectroscopy (UV-Vis)

UV-Vis spectroscopy is a powerful technique used in the characterization process due to its simplicity and effectiveness. In UV-Vis spectroscopy, the absorption of light by ZnO nanoparticles provides valuable information about their electronic structure, bandgap energy, and particle size. The absorption spectrum typically shows a sharp absorption peak in the UV region, known as the excitonic peak, corresponding to the bandgap of ZnO. The position and intensity of this peak can be used to determine the size and morphology of the nanoparticles. Additionally, UV-Vis spectroscopy can also be used to monitor the stability and aggregation of ZnO nanoparticles in solution, providing insights into their behaviour under different conditions. One

of the key advantages of using UV-Vis spectroscopy for ZnO nanoparticle characterization is its non-destructive nature, allowing for repeated measurements without altering the sample. This makes it particularly useful for monitoring changes in the nanoparticles over time or in response to different environmental factors. Furthermore, UV-Vis spectroscopy is a relatively simple and cost-effective technique, making it accessible to researchers in various fields. Several studies have utilized UV-Vis spectroscopy for the characterization of ZnO nanoparticles. For example, Wang *et al.* (2018) used UV-Vis spectroscopy to investigate the size-dependent optical properties of ZnO nanoparticles synthesized via a sol-gel method. They observed a blue shift in the excitonic peak with decreasing particle size, indicating quantum confinement effects. Similarly, Khan *et al.* (2019) utilized UV-Vis spectroscopy to study the stability of ZnO nanoparticles in different pH environments, revealing the influence of surface charge on nanoparticle aggregation.

X-Ray Diffraction (XRD)

Characterization of zinc oxide nanoparticles (ZnONPs) using X-ray diffraction (XRD) is used for understanding their structural properties. XRD provides valuable information about the crystalline structure, phase purity, crystal size, and lattice parameters of ZnONPs. The XRD pattern of ZnONPs typically exhibits sharp diffraction peaks corresponding to the crystal planes of the hexagonal wurtzite structure (JCPDS card no. 36-1451). The intensity and position of these peaks can be used to determine the crystallite size of ZnONPs using the Scherrer equation, which relates the peak broadening to the crystallite size. Moreover, XRD can be used to identify any additional phases or impurities present in the ZnONPs sample. For instance, the presence of zinc hydroxide or zinc carbonate can be detected based on characteristic peaks in the XRD pattern. Additionally, the XRD data can be analysed to calculate the lattice parameters of ZnO, providing insights into the structural distortion or strain in the crystal lattice. Several studies have employed XRD for the characterization of ZnONPs. For example, Huang *et al.* (2008) used XRD to investigate the crystal structure and size of ZnONPs synthesized via a sol-gel method. They found that the average crystallite size of the ZnONPs was approximately 15 nm. Similarly, Bekele *et al.* (2021) utilized XRD to analyse the phase purity and crystal structure of ZnONPs prepared by a hydrothermal method, revealing a high degree of crystallinity and wurtzite structure.

Fourier Transform Infra-Red Spectroscopy (FTIR)

Characterization of zinc oxide nanoparticles using Fourier-transform infrared spectroscopy (FTIR) provides details about their structural and chemical properties. FTIR is a powerful analytical technique that measures the absorption of infrared radiation by a sample,

revealing information about its molecular composition and structure Tauc *et al.* (1966). In the context of zinc oxide nanoparticles, FTIR is used to identify functional groups on the nanoparticle surface, analyse chemical bonding, and detect impurities or contaminants. In FTIR analysis of zinc oxide nanoparticles, the characteristic peaks in the spectrum can be attributed to various vibrational modes of the molecules present. For example, the stretching vibrations of O-H bonds from surface hydroxyl groups typically appear around 3200-3600 cm^-1, while the bending vibrations of these groups occur around 1600-1700 cm^-1. The presence of Zn-O bonds, which are indicative of the zinc oxide structure, can be confirmed by peaks in the region of 400-600 cm^-1 Serpone *et al.* (1995). Furthermore, FTIR can be used to study the interaction of zinc oxide nanoparticles with other molecules, such as organic compounds or polymers. For instance, changes in the FTIR spectrum of zinc oxide nanoparticles after surface modification or functionalization can provide information about the nature of the bonding between the nanoparticles and the modifying agent.

Biomedical applications of Zinc oxide nanoparticles:

Zinc oxide nanoparticles finds potential applications in various biomedical fields. Some of the biomedical applications are summarized as follows.

Tissue engineering

Zinc oxide nanoparticles (ZnONPs) have for various applications in tissue engineering due to their unique properties. These nanoparticles possess excellent biocompatibility, low toxicity, and antimicrobial properties, making them suitable for use in tissue engineering scaffolds and implants. One of the key advantages of ZnONPs is their ability to enhance the mechanical properties of biomaterials. When incorporated into scaffolds, ZnONPs can improve the strength and durability of the scaffold, making them suitable for load-bearing applications such as bone tissue engineering Wiesmann *et al.* (2021). ZnONPs also exhibit photocatalytic properties under ultraviolet (UV) light, which can be utilized for on-demand drug release in tissue engineering. By incorporating ZnONPs into scaffolds, researchers have been able to achieve controlled release of growth factors and drugs, leading to enhanced tissue regeneration and healing Al-Tememe *et al.* (2021). Moreover, ZnONPs have been shown to promote cell adhesion, proliferation, and differentiation. Studies have demonstrated that ZnONPs can enhance the attachment and growth of various cell types, including osteoblasts, fibroblasts, and endothelial cells, which are crucial for tissue regeneration Anjum *et al.* (2021). Furthermore, ZnONPs possess antimicrobial properties, which can help prevent infections in tissue engineering constructs. The ability of ZnONPs to inhibit the growth of bacteria makes them a promising candidate for developing infection-resistant biomaterials Zayed *et al.* (2021).

Environmental bioremediation

Zinc oxide nanoparticles (ZnONPs) have utilized for environmental bioremediation due to their properties such as high surface area, reactivity, and stability. In bioremediation processes, ZnONPs can be utilized for the removal or degradation of various pollutants including heavy metals, organic compounds, and pathogens from contaminated environments. ZnONPs have been shown to effectively adsorb heavy metals like lead, cadmium, and chromium from aqueous solutions, thereby reducing their concentrations to safe levels Gnanasangeetha and Prathipa, (2019). Additionally, ZnONPs have photocatalytic properties that can be harnessed for the degradation of organic pollutants under UV light irradiation Ibrahim *et al.* (2021). This photocatalytic activity can help in the degradation of various organic contaminants including pesticides, dyes, and pharmaceuticals, making it a versatile tool for environmental cleanup. Moreover, ZnONPs have been reported to exhibit antimicrobial properties, making them effective in controlling microbial populations in contaminated environments. Studies have demonstrated the effectiveness of ZnONPs in inhibiting the growth of bacteria, fungi, and viruses, thus reducing the risk of disease transmission Ashajyothi *et al.* (2016). This antimicrobial activity can be particularly beneficial in the remediation of contaminated water sources. Furthermore, ZnONPs have been explored for their potential in enhancing the biodegradation of pollutants by microorganisms. Studies have shown that ZnONPs can enhance the activity of certain enzymes involved in the degradation of organic compounds, thereby accelerating the bioremediation process Singh and Borthakur. (2018). This synergistic effect of ZnONPs and microbial activity holds great promise for the remediation of contaminated environments. Their unique properties make them effective in adsorbing heavy metals, degrading organic pollutants, controlling microbial populations, and enhancing biodegradation processes.

Drug delivery

Zinc oxide nanoparticles (ZnONPs) have gained significant attention in recent years due to their potential applications in drug delivery systems. These nanoparticles possess unique physicochemical properties, such as high surface area, biocompatibility, and ease of surface modification, making them promising candidates for targeted drug delivery. One of the major advantages of using ZnONPs in drug delivery is their ability to encapsulate a wide range of drugs, including hydrophobic and hydrophilic compounds, through various encapsulation techniques such as co-precipitation, sol-gel, and microemulsion methods Jeevanandam *et al.* (2018). Furthermore, ZnONPs have been shown to enhance the stability and bioavailability of drugs, thereby improving their therapeutic efficacy. The surface of ZnONPs can be functionalized with targeting ligands, such as antibodies or peptides, to achieve targeted drug

delivery to specific cells or tissues. Additionally, ZnONPs exhibit inherent antimicrobial properties, which can be advantageous in combating infections at the site of drug delivery El-Kattan *et al.* (2022). Moreover, ZnONPs have been investigated for their potential to overcome multidrug resistance (MDR) in cancer cells. Studies have shown that ZnONPs can inhibit the efflux pumps responsible for MDR, thereby enhancing the sensitivity of cancer cells to chemotherapeutic drugs Nabil *et al.* (2020). Overall, the versatile properties of ZnONPs make them promising candidates for the development of advanced drug delivery systems with improved therapeutic outcomes.

Cancer treatment

Zinc oxide nanoparticles (ZnONPs) have emerged as potential agents for cancer treatment due to their unique physicochemical properties, including small size, high surface area to volume ratio, and inherent cytotoxicity towards cancer cells. These nanoparticles can be synthesized using various methods, such as sol-gel, precipitation, and hydrothermal methods, allowing for control over their size, shape, and surface properties, which are crucial for their anticancer efficacy Jiang *et al.* (2018). One of the key mechanisms through which ZnONPs exert their anticancer effects is via the induction of oxidative stress. Upon entering cancer cells, ZnONPs generate reactive oxygen species (ROS), leading to DNA damage, lipid peroxidation, and cell death Sharma *et al.* (2011). Additionally, ZnONPs have been shown to inhibit the proliferation of cancer cells by inducing cell cycle arrest and apoptosiss Bai *et al.* (2017). Moreover, ZnONPs can be functionalized with targeting ligands, such as antibodies or peptides, to specifically target cancer cells while minimizing off-target effects on healthy tissues Hassan *et al.* (2017). This targeted approach enhances the efficacy of ZnONPs in killing cancer cells while reducing the risk of toxicity to normal cells. Furthermore, ZnONPs can be used in combination with other anticancer agents, such as chemotherapeutic drugs or radiation therapy, to enhance their therapeutic effects. Studies have shown that ZnONPs can sensitize cancer cells to radiation therapy and reduce the multidrug resistance of cancer cells to chemotherapeutic drugs Sharma *et al.* (2012).

Biomedical imaging

Zinc oxide nanoparticles (ZnONPs) have emerged as significant candidates for various imaging applications. These nanoparticles possess excellent biocompatibility, low toxicity, and high photo stability, making them suitable for use in various imaging techniques such as fluorescence imaging, magnetic resonance imaging (MRI), and photoacoustic imaging. In fluorescence imaging, ZnONPs can be functionalized with fluorescent dyes or biomolecules to target specific tissues or cells, allowing for high-resolution imaging with minimal background

interference Nabil *et al.* (2020). Moreover, the piezoelectric properties of ZnONPs make them ideal for photoacoustic imaging, where they can convert light energy into sound waves, enabling deep tissue imaging with high spatial resolution Dolai *et al.* (2022). Additionally, ZnONPs can be coated with paramagnetic materials for enhanced MRI contrast, improving the detection sensitivity of this imaging modality Nguyen *et al.* (2019). Furthermore, the small size and large surface area of ZnONPs allow for efficient drug delivery, making them ideal candidates for theragnostic applications Kanagamani *et al.* (2021). Overall, the unique properties of ZnONPs make them promising candidates for a wide range of imaging applications, with potential implications in diagnosis, monitoring, and treatment of various diseases.

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TECHNIQUES FOR CREATING EXPERT SYSTEMS

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Abstract:

The process for building expert systems is the subject of scientific study. The primary elements and guiding concepts of expert systems are the topic of this essay. Following that, expert system development stages are taken into consideration. The stages of development for expert systems are similar to those for other information systems and include identification, conception, formalisation, execution, adjustment and testing, and application. This article discusses particular stages in the evolution of expert systems.

Keywords: Artificial intelligence, expert systems, information systems, technique, and system

Introduction:

Expert system research has advanced to the point where it is now able to formulate fairly broad scientific and methodological guidelines for building them. ES is a sophisticated piece of software that relies on specialised knowledge and can offer workable answers to unique issues within a specific field of study. [1] In most situations, the findings of earlier years' research in the field of artificial intelligence can be used to explain the effective application of ES in a variety of domains that are hard to define or lack a precise algorithmic explanation. [2] The following guidelines provide a succinct explanation of expert system:

- The size of the knowledge base and its capacity to be expanded with fresh knowledge are the main factors that affect how effective ES is; methods for finding a solution are less crucial.
- Experience has taught us that generic extraction alone is not sufficient.
- The knowledge used in the ES, which is based on the expertise of a human, is mostly heuristic (empirical), hazy, partial, and indeterminate. In actuality, this is congruent with the nature of the field being studied. [3]
- The user must engage in a structured conversation because of the low level of problem solving and the heuristic nature of the knowledge. [4]

Every system needs to be set up in a specific order. Typically, the implementation of expert systems involves the following steps:

- The identification;
- Conceptualization,
- Formation,
- Realisation (Execution),
- Adjustment, and Testing,
- Followed by Application and Testing.

It was observed that the phases in the system's design were in use within the time period indicated. Let's now examine each of these stages in isolation.

Resources and Techniques

Identification

The creative ES's objectives and the problems that need to be handled are revealed at the identification stage. In this situation, it is important to make a clear distinction between the system's intended use and the problems it will resolve. The creation of expert knowledge, enhancing problem-solving quality in relation to the expert-person's answer, automating the expert-person's extensive work, and expanding the dissemination of expert knowledge can be seen as the key objectives of the ES. [5]

You can identify significant aspects of the issue during the identification phase. These factors include the nature and scope of the issue, the people involved in the design process, the timeline for the project, and the technical tools needed. The identification of the problem's nature and scope is the most pertinent of them. The necessity to simplify the initial aim and setting often becomes apparent in the following steps. Experience has proven that the researcher can have a better understanding of the intricacy of the overall problem if they initially concentrate on a number of straightforward issues, temporarily put the ultimate objective on hold, and find a workable solution. [6]

During the identification process, the knowledge engineer and the expert collaborate closely. The informal description of the problem is clarified by the knowledge engineer in collaboration with the expert. The subject matter expert provides a thorough explanation of the issue, outlining both the solution and the concepts that underpin it. After multiple iterations of debate, the knowledge engineer and expert receive a final and informal description. By defining crucial components for the description of information, participants identify and describe the knowledge required to solve a problem. [7]

The most valuable resource is time. A knowledge engineer, who is an expert, must invest many months to create the initial iteration of a functional system. Additional time may be needed

if any of them have trouble understanding other concepts and procedures. It is also crucial to provide technical and instrumental means. Both are promised to be accessible for at least two years. Additionally, it's critical to keep in mind that software functions as an essential component of hardware tools. It should be highlighted that a collaborative design method is now being used to build ES, notably dynamic ES, and that this process involves key users.

Conceptualitation

The concepts, linkages, and management techniques required to describe the challenges found are made clear during the conceptualization phase. Special attention is given to the following:

- The core ideas behind the theories and techniques employed;
- The hierarchy of relationships, cause-and-effect relationships, part-complete relationships, etc.;
- the type of limits;
- The types and structure of knowledge used. [8]

It is advisable to create a thorough protocol of the expert's decision-making and behaviour during the process of resolving at least one issue in order to ascertain the listed characteristics of the issue. A protocol like this gives the knowledge engineer vocabulary terms (things) and some rough descriptions of the tactics employed. The expert's. The protocol also assists in addressing a number of queries that come up throughout the process. The knowledge engineer examines queries pertaining to the description of knowledge and approach to solutions at this level. The selection of specific procedures and approaches is not taken into consideration at this time, though. [9]

The accurate depiction of information is what matters most at this point. Researchers typically work hard to present their findings in their entirety. Experience, however, demonstrates that, as in the previous step, moving quickly to the next stage while utilising a shorter description is more beneficial. Before a qualified doctor or engineer is created in the field of medicine, which is taken as a subject, the facts (such as syndromes, diseases, and symptoms) related to the subject (such as the connection between symptoms and diseases) are first accurately and completely determined.

Forming

The formulation phase's goal is to express the fundamental ideas and connections that resulted from conceptualization in any recognised formal language.

Three important elements determine the formal description:

- From the search space's structure;
- From the model of the problem-solving procedure;
- From the problem's data characteristics. [10]

There are numerous models that can be used to describe the problem-solving process. Models based on math and behaviour can both be applied in this situation. Building the crucial relationships and knowledge is possible if the behavioural model can support decision-making. You can arrange the output using the mathematical model. The connections between the knowledge base's components should be routed and reflected. The primary problems in the formation process stem from the structuring of the primary problem, particularly the structuring of the general problem associated with the sub-problems; structuring declarative and procedural knowledge; and consist of structuring the subject area based on the hierarchy of classes and structuring application programmes based on the "part / complete" hierarchy.

Realization (Execution)

The implementation phase's goal is to produce one or more ES prototypes that address the specified issue. The final product fit for industrial use is then created at a specific stage in accordance with the findings of the testing and trial operation phase. The process of creating a prototype entail programming its elements (or choosing them from tools that already exist) and putting them on hold until all test samples and the knowledge base's organisational structure are well understood. This challenging portion of the labour is put off until the subsequent phases, though. The process of acquiring knowledge should start with the creation (or selection of) instruments that enable you to work with a straightforward management structure and a straightforward description of the knowledge you want to acquire.

This method enables you to get started on particular sub-problems as soon as feasible and decide whether further information is necessary to resolve them. After the project begins, the ES-1 expert system's initial prototype ought to show up. A crucial step in the building of an ES is the production of a prototype. The prototype may have some pieces that are incorporated into the finished ES, but this may not have been the primary objective. The most important thing is to make sure that the concepts, approaches, and methodologies used in the prototype developed by ES are evaluated for their suitability to the issues at hand.

The ES-2 variant experimentation enables for the identification of system flaws and the development of methods to fix them. Depending on the complexity of the subject matter, the adaptability of the selected image, and how closely the control mechanism relates to the issue at

hand, this iterative process may take several months. It might be essential to produce an ES-3 version in some circumstances.

Iterative design, in general, is a strategy to the development of the system as a succession of successful prototype approximations rather than as a single, monolithic, integrated system. When features of a system are not exact enough, iterative design is particularly beneficial. Designers learn about new system needs after they begin a project since similar projects are not sufficiently developed in terms of system analysis. The expenditures to modify the system and the subsequent work plan are minimal if the design is carried out iteratively. On the other hand, if the development of a complete system is started right away, the project's process may result in the discovery of new system requirements that raise questions about the project's viability.

Tuning and testing

In each stage of the creation of the application system prototype, the setup and testing phase is covered. Even though system testing is thought regarded as the last phase. The verification of the system and its compliance with the requirements (conceptual testing-validation) are particularly important throughout the prototype process because it is marked by major modifications to the project and changes in the specifications of the system of application. In addition to the ES design process, these two problems need to be addressed simultaneously. Even though ES testing is distinct from conventional testing, the verification process (logic testing) and conceptual testing (although ES testing is different from traditional testing) can both be understood as beta testing phases according to typical software system testing technology. A subject-matter expert must be consulted in order to test the ES, even if the basic requirements of a standard software system permit the programmer to undertake this task without restriction.

Experts approach ES testing from three perspectives:

- Initial data testing;
- Logical testing of the knowledge base;
- Conceptual testing of the application system.

Verifying the accuracy of the factual data that will be examined is part of the testing of primary data. The data collection utilised during testing ought to include all potential scenarios examined by the ES. Without regard to the topic matter, logical testing of the knowledge base identifies logical mistakes (excess, periodic, and conflict rules; rules of omission and intersection; unrealized conditions). The testing method can be automated due of these faults' formal nature. To validate (verify) the entire knowledge base and set of rules, there are numerous instruments at our disposal. The verification process is carried out manually, nevertheless, if the

chain of rules employed in the extraction process (rules 3 to 10) is not very longstop examine the system's overall structure, conceptual testing is done. It is currently impossible to test the application without involving system end users.

Test operation and application

During the test step, a variant created for various initial data values is executed, and its quality is assessed. Together with a subject-matter specialist, the researcher conducts this stage. Depending on the results of the testing, it may be decided to redesign one stage or another or to change the conventional ideas, attitudes, and connections. Trial stage must affirm or refute the following.

Decisions made by the system are considered acceptable by experts;

- The rules of extraction are complete, error-free and unambiguous;
- The decision-making sequence coincides with the expert's intervention;
- The system can explain its decision quite clearly;
- In the testing phase, the system can solve possible problems - from the simplest to the most difficult that can be expected within the boundaries of the subject area.

It is difficult to determine the system's quality once it has undergone testing. A knowledge engineer, who is the system's primary researcher, a subject-matter expert, and the average user, can all assess the same system in various ways. The correctness and comprehensiveness of the extraction rules are of primary concern to the expert, the overall effectiveness of the system is of primary concern to the knowledge engineer, and the usability of the system and the significance of the results are of primary concern to the average user. Demonstrates whether the ES created at the period of practical application is appropriate for use by common users.

A few of these include:

- Working with ES is not tiring;
- The system can be adapted to users of different skill levels;
- The system maintains the working state in case of user misbehaviour.

Conclusion:

ES needs to be a "specialist" in a specific area. In order to obtain a directional solution path, there should be both general and specific extraction rules. The ES must also adhere to general guidelines for intellectual conduct. The tenets of "symbolic thinking" serve as the foundation for rules of intellectual conduct. Additionally, after the creation of expert rules, the original formulation of the problem should be updateable. A better examination of automated activities will be possible thanks to user participation in the cooperative design process.

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NANOTECHNOLOGY IN NASAL DRUG ADMINISTRATION: NANOEMULSION INNOVATIONS

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Abstract:

Nanotechnology in nasal drug administration has emerged as a promising frontier, revolutionizing drug delivery systems with its precision and efficiency. Nanoemulsions, in particular, represent a significant innovation in this field, offering numerous advantages such as enhanced drug solubility, stability, and bioavailability. Nanoemulsions are colloidal dispersions of oil and water stabilized by surfactants or other emulsifying agents, typically with droplet sizes ranging from 20 to 200 nanometers. Their small particle size facilitates rapid absorption and penetration across the nasal mucosa, bypassing barriers that traditionally hinder drug delivery. One of the key benefits of nanoemulsions is their ability to encapsulate both hydrophilic and hydrophobic drugs, widening the scope of therapeutic agents that can be delivered nasally. This versatility opens avenues for targeted delivery of drugs to the central nervous system, offering potential treatments for neurological disorders and brain injuries. It can be tailored to achieve controlled drug release kinetics, ensuring sustained therapeutic levels and minimizing fluctuations in drug concentration. This controlled release profile not only improves efficacy but also reduces side effects associated with conventional drug delivery routes. It can be engineered to incorporate targeting ligands or functionalized nanoparticles, enabling site-specific delivery and enhanced cellular uptake. This targeted approach holds promise for personalized medicine, where treatments can be tailored to individual patient needs.

Keywords: Intranasal, Blood-brain barrier, Drug delivery, Nano-emulsions, Brain Delivery.

Introduction:

A blood-brain barrier (BBB) is the term used to describe the central nervous system's (CNS) microvasculature, which separates the brain from the rest of the body. Arteriole-capillary-venule-level CNS vessels are continuous, non-fenestrated, and capable of regulating the exchange of chemicals, ions, and cells intermediate between blood and the brain [1]. The BBB's robust barrier ability enables it to shield the CNS from viruses, poisons, and outside influences. The unique characteristics of the brain endothelial cells (BECs), which make up the blood vessel

walls, determine how the BBB functions as a barrier. BECs vary from endothelial cells in non-neural tissues in that they are polarized cells locked together via gap junctions that effectively limit vesicle-mediated transcellular fluxes (transcytosis and pinocytosis) [1,2] and the extracellular flow of substances (molecules and ions). The expression of influx transporters, which are particular messengers that deliver substances across the Blood-brain barrier into the brain, and efflux transporters, whose role is the removal of lipophilic toxins capable of passively diffusing through the cell membrane, are two types of systems of transport that are characteristic of BECs [1].

Understanding the mechanisms that control the Blood-brain barrier during health and how they change during disease includes illustrating the difference that a few scientists have correctly put into evidence and can provide crucial support to finding the right medicinal therapies for an array of different neurological conditions [3,4]. Several serious pathologies that affect the nervous system, including neuro infections, Parkinson's disease, Alzheimer's disease, multiple sclerosis, prolonged age-related neurological illnesses, cerebral ischemia, and others, are referred to as neurodegenerative conditions. Health statistics show that the prevalence of CNS illnesses is rising quickly globally, along with medical costs [5]. The medication can be delivered locally using techniques like focused ultrasound, catheter infusions, intra-cerebroventricular or intra-parenchymal infusions, intracerebral delivery with mini-pumps, focused ultrasound approaches, or external magnetic field-based methodologies for direct delivery to the brain. All of these procedures are, however, extremely invasive and dangerous, especially given the requirement for surgical treatment [6], and a lot of them are inappropriate in situations involving numerous or chronic treatments. Because of these factors, several efforts have been undertaken to develop methods for the transport of active compounds to the specified location without using the blood-brain barrier. Using non-traditional administration routes and creating drug formulations with qualities suited for the best possible administration through these routes are both components of a plan for brain targeting. Bypassing the Blood-brain barrier, intra-nasal drug delivery is a comfortable, non-invasive method of administering medicinal substances into the brain [8, 9-12]. Many benefits, including improved patient compliance, excellent safety, amazing ease of administration, quick onset of action, and less systemic exposure, characterize such drug delivery system pathways [7]. Additionally, medicines can evade hepatic first-pass metabolism when administered through the nasal mucosa. Hence, nasal dosages are frequently ten times less powerful than oral doses. Hence, nasal drug delivery is more promising than oral or intravenous drug delivery for delivering drugs directly to the brain [13].

General distinguishing features of nano-emulsions

Oil-in-water (O/W) or water-in-oil (W/O) mixture of two immiscible fluids is known as nanoemulsions. Liquids stabilized by the use of the proper surfactant(s) and co-surfactants [14], with an average globule size of about even though top size limits of as large as 300 nm [16] have already been recorded in the literature. NEs may have a large or a small droplet size that is much lower than the light wavelength that is visible or is transparent or has a milky-white appearance ranging from transparency [15]. NEs can be created in a variety of dosage forms, including solutions, creams, gels, foams, tablets, sprays, etc., and can be given via many methods, including injectable, ophthalmic, and oral.

The small droplet size of NEs prevents destabilizing phenomena including coalescence, creaming, and sedimentation, and as a result, they have a higher surface area than other formulations and exhibit long-term physical stability. Drug stability issues (oxidation, pH, hydrolysis, and enzymatic activity at the mucosal region, in biological settings) can be resolved with NEs [14,17]. According to the Noyes-Whitney equation [18], this determines the production of particles with an extraordinarily high surface and a noticeably improved rate of drug dissolution. Nano-emulsion can also be employed to transport natural materials [19,20] and to cover up the bitter or disagreeable taste of medications [18].

Several approaches that fit into two main groups—high-energy techniques and low-energy methods—can be used to prepare NEs. In instances involving high-energy procedures, such as sonication and high-pressure homogenization (HPH), the formation of the tiny droplets requires a mechanical system that produces disruptive manifestations breaking up the oil and water phases to produce the droplets, a process that uses a lot of energy. Microfluidic, ultrasonic, or HPH are the techniques employed [17]. To create small droplets without using a lot of energy, low-energy technologies use specialized physicochemical processes including phase inversion point and emulsion inversion temperatures. The droplets are formed in low-energy ways when the system experiences a phase inversion in response to modifications in composition or temperature and then moves via a reduced surface stress state [16].

Typically, fractions of natural oils including sesame oil, cottonseed oil, soybean oil, coconut oil, and others that can be categorized as long-chain, medium-chain, and short-chain triglycerides are used to prepare NEs, either alone or in combination [18]. The absorption of the medication is influenced (sometimes significantly) by the type of oil components utilized in the formulation phase of NEs. In order to elucidate this feature for oral NE delivery, numerous studies have been conducted. For instance, it has been claimed that NEs produced with medium- and long-chain triglycerides increase the absorption of curcumin [23].

Moreover, it has been shown that a number of NEs exhibit spontaneous lymphatic uptake (avoiding first-pass metabolism) [18], and it is likely that this behavior is highly influenced by the makeup of the lipidic phase. Surfactants are frequently used as emulsifiers in the formation of nanoemulsions, however, peptides and fats are additionally employed. Tweens, spans, bile salt, sorbitan monolaurate, and lecithin [24-27] are frequently used in the formation of nanoemulsions. Poloxamers [28], sodium dodecyl sulfate [29], casein [30], starch derivatives, gums [31] and block copolymers e.g., Poly ethylene glycol [32] are surfactants that are also used in the preparation of nanoemulsions. NEs can be stabilized with co-surfactants including polyols, ethanol, and glycerin [33]. They can be used separately or together.The choice of surfactants is important since toxicology and pharmacokinetics may be affected by this decision; for instance, poloxamer 188 causes kidney toxicity at concentrations greater than 0.5 percent in injectable nanoemulsions [18].

General recapitulation of nanoemulsions for intra-nasal delivery

Intranasal administration is frequently an alternative to oral medication, according to a broad review of the current research on nanoemulsions for nose-to-brain delivery. In reality, several medications can have issues with oral administration if the substance is meant to reach the brain. In vivo tests have demonstrated that CNS distribution via nasal mucosa occasionally performs as well as parenteral treatment.

Risperidone, an antipsychotic drug that belongs to the class of benzisoxazole derivatives, was one of the clearest manifestations in the field of nanoemulsion entering the brain by administration into nasal mucosa. Oral formulations are plagued by a limited bioavailability issue. Utilizing Capmul MCM as a lipid medium and polyoxyethylene sorbitan monolaurate 80 as a surfactant, risperidone nanoemulsion was manufactured. After incorporating chitosan into it and agitating the dispersion for an hour, risperidone bio-adhesive nanoemulsion was developed. Technetium (99mTc) labeling was used to determine the biodistribution in the bloodstream and in the brain after nanoemulsion and liquids were given intravenously and orally in in-vivo investigations on Swiss albino rats [34].

Ergoloid mesylate, an antiaging chemical made up of the methane sulfonate salts of the three alkaloids dihydroergocristine, dihydroergocornine, and dihydroergocryptine was formulated as "submicron emulsion" [35]. The primary emulsifier in use was egg lecithin. Male Sprague-Dawley rats were used in in vivo investigations to examine the effects of nasal and intravenous infusions of ergoloid mesylate "submicron emulsions" and drug solutions which in turn increases bioavailability in NEs.

The use of NEs to transfer anti-HIV medications to the brain is an important application. The brain serves as a sort of "anatomic reservoir" where HIV viruses can restart the infection. Protease inhibitor saquinavir mesylate is active against HIV-type 1. Yet, due to its poor solubility in water, its bioavailability is minimal. Saquinavir has limited blood-brain barrier permeability and is a substrate for P-glycoprotein and cytochrome P450. Saquinavir mesylate-containing nasal oil in water nanoemulsion was created utilizing the spontaneous emulsification process and Capmul MCM as the oil phase. The drug assay, globule size, and zeta potential of nanoemulsion were all characterized. Studies on ex vivo permeation were conducted using freshly removed sheep nasal mucosa. When compared to a simple drug suspension, nanoemulsion demonstrated increased drug penetration [17].

Conclusion:

Formulations known as nanoemulsions have grown increasingly important in the discipline of nanotechnology. Its size renders them suited for transport tothe brain. To retard nasal clearance, mucoadhesive polymers like chitosan serve a dual purpose as anexcipient as well as enhance permeation through the nasal mucosa. The oral medicines for the CNS, which can have issues that are typically connected to the properties of the drug, are frequently replaced by intranasal administration. A promising method for drug transport through the nose to the brain and for brain targeting in the treatment of neurodegenerative illnesses.

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SYNTHESIS OF PLANT-MEDIATED SILVER NANOPARTICLES USING PAPAYA FRUIT EXTRACT AND THEIR CHARACTERIZATION

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Abstract:

The present study reports a novel ecofriendly method for the synthesis of silver nanoparticles using papaya fruit extract as a capping agent and reducing agent .Boiled, crushed air dried unripe papaya fruit extract was utilized for reducing silver nitrate. The colorless mixture turned in to brown yellow color and shown UV-visible spectra characteristic of silver ion. The FTIR spectroscopy indicated the role of different functional groups. Ag-Np also characterized by X–ray diffraction method revealed the crystalline nature and the average size of silver nanoparticles was 30 nm as determined.

Keywords: Silver nanoparticles, unripe papaya fruits, characterization.

Introduction:

The field of nanoparticles is one of the most active areas of research in modern material Science. Nanoparticles exhibit completely new or improved properties based on specific characteristics such as size, distribution and morphology. New application of nanoparticles and nanomaterials are emerging rapidly [1, 2, 3]. Nano crystalline silver particles have found tremendous applications in the field of high sensitivity bimolecular detection and diagnostics [4], antimicrobials and therapeutics [5, 6], catalysis [7] and micro-electronics [8]. However, there is still need for economic, commercially viable as well of environmentally clean synthesis route to synthesis silver nanoparticles. A number of approaches are available for the synthesis of silver nanoparticles such as reduction in solution [9], chemical and photochemical reactions in reverse micelles [10], thermal decomposition of silver compounds[11], radiation assisted[12], electro chemicals[13], sonochemicals[14], microwave assisted process[15], and recently via green chemistry route [16,17,18]. Sometimes the synthesis of nanoparticles using various plant materials and their extract can be beneficial over other biological synthesis process which involves the very complex procedures of maintaining microbial cultures [19, 20].

The use of environmentally benign materials like plant leaf extract [21], bacteria fungi[22, 23], and enzymes[24] for the synthesis of silver nanoparticles offers numerous benefits of eco-friendliness and compatibility for pharmaceutical and other biomedical applications as they do

not use toxic chemicals absorbed on the surface that may have adverse effect in the medical applications. Green synthesis provides advancement over chemicals and physicals method as it is cost effective, environmentally friendly, easily scaled up for large scale synthesis and in this method there is no need to use high pressure, energy, temperature and toxic chemicals. Silver has long been recognized as having inhibitory effect on microbial present in medical and industrial process [25, 26]. The most important application of silver and silver nanoparticles is in medical industry such as topical ointments to prevent infection against burn and open wounds [27]. Nanomedicine is an emerging field expanding rapidly because of the development and incorporation of new nanocomposites into range of products and technologies. In recent years, the application of nanoparticles in medicine has increased and expanded to the fields of molecular imaging [28], drug delivery [29], diagnosis and treatment of cardiovascular diseases [30], healing [31] and development of medical devices with antimicrobial properties [32].

New applications of nanomaterials are emerging rapidly in bio medical science [33]. This decade has witnessed the inception of new significant technological products particularly based on nanotechnology. Nanoparticle synthesis is being widely explored since they exhibit unique size and shape dependent properties for applications in optics, electronics, catalytic system, magnetic and biomedical fields such as HIV, cancer cell, cytotoxicity and Genotoxicity [34]. Apart from this recently the anti-tumor effect of AgNPs has been reported against different cancerous cell lines[35]. Nanoparticles with the size range 1 and 1000 nm are mainly explored for the diagnosis and treatment of human cancers, which led to the new discipline of nano-oncology[36]. However, the microbial mediated synthesis of nanoparticles are not industrial feasible as it requires expensive medium and maintenance of highly septic condition [37]. In this context, plant mediated nanoparticles synthesis seems to be a cost-effect as well as eco-friendly method. Moreover, nanoparticles synthesis from plants with medicinal properties proves to be beneficial in treating various ailments in a better and easy way. On such plant is Papaya, a tropical fruit often seen in orange-red, yellow-green and yellow-orange hues with a rich orange pulp whole plant parts fruits, roots, bark, peel, seeds and pulp are known. To have medicinal properties it has been used for the treatment of numerous diseases like Warts, corns, sinuses, eczema, cutaneous tubercles, blood pressure, dyspepsia, constipation amenorrhea, general debility, expel thread worms and stimulate reproduction organs[38]. It also effectively treats and improves all types of digestive and abdominal disorders [39, 40]. Leaves of papaya, one of the plant parts with numerous medicinal values have the history of streaming and eating with spinach in Asia [41]. It has found to the have a significant effect on various tumor cell lines and tea extract of

leaves found to have antimicrobial, ease menstrual pain, relieve nausea and antispasmodic activities[42].

Materials and Methods:

1. Plant material and preparation of the extract:

Green unripe Papaya (*Carica papaya*) fruits were used to make the aqueous extract unripe papaya fruit weighing 25g were thoroughly washed distilled water, dried, cut into fine pieces and were crushed into 100 ml sterile distilled water and filtered through Whatman No.1 filter paper. The filtrate was further filtered through 0.6 μm sized filters. Similarly fully ripped papaya fruits and green leaves were also used to prepare the extract.

2. Synthesis of silver nanoparticles:

1mM aqueous solution of silver nitrate was prepared and used for the synthesis of silver nanoparticles, 10 ml of papaya fruit extract was added into 90 ml of aqueous solution of 1mM silver nitrate for reduction into Ag ions and kept at room temperature for 5 hours.

Figure 1: Synthesis of silver nanoparticles

Result and Discussion:

UV spectroscopy:

Silver nanoparticle appear brown in color in aqueous medium as a result of surface of plasma on vibration. In previous studies similar color change was observed. Synthesis of silver nanoparticle in sterile distilled water was confirmed by using UV-spectrophotometer in a range of wavelength from 257 nm. As a fruit of *Carica papaya* was mixed in aqueous solution of silver ion. The reduction of pure silver ions to silver nanoparticles was confirmed by measuring UV-spectrum of the reaction media. The spectroscopic band of silver nanoparticle solution was found to be close to 0.515nm which confirms the synthesis of silver nanoparticle. This absorption strongly depends on the particle size, chemical surrounding and dielectric medium.

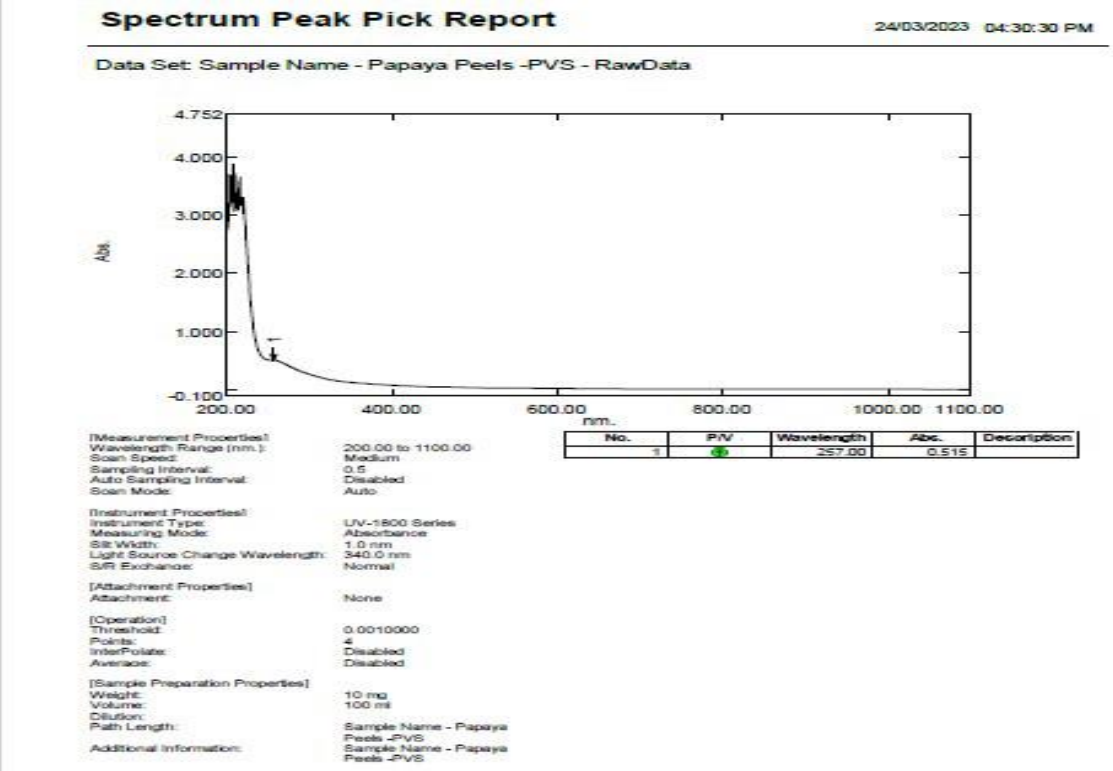


Figure 2: UV spectroscopy

FTIR analysis:

To investigate the functional group of *Carica papaya* fruit extract responsible for synthesis and stabilization of silver nanoparticle, a IR study was carried out and the spectra are shown in figure. It shown a number of absorption peak, reflecting the complex nature of the extract. A peak at 3361.11 cm^{-1} is result from the stretching of alcohol and phenol (-OH). The absorption peak at 2927.10cm^{-1} could be due to (C-H) stretching of alkane functional group. The absorption peak at 2068.74 cm^{-1} could be due to isonitriles (R-N=C) stretching of functional group. The absorption peak at 1884.58 $cm^{-1}$and 1819.25 cm^{-1} could be due to C=O stretching of acid anhydrides(-CO-O-CO-) functional group. The absorption peak at 1632.81 cm^{-1} could be due to C=C functional group. The absorption peak at 1596.37 cm^{-1} could be due to N-H in plane bending stretching of $R\text{-}NH_2$ amines and their salts functional group. The absorption peak at 1396.56 cm^{-1} could be due to asymmertic C-H bending of $\text{-}CH_3$ alkanes functional group. The absorption peak at 1082.11 cm^{-1} could be due to C-S stretching. Fruit of *Carica papaya* extract are mainly involved in reduction of silver ions to silver nanoparticles. In IR spectra of synthesized silver nanoparticle bands of absorbance around bands are matching to fruit extract IR spectrum. This denotes coumarones and tannis from fruits extract may responsible for reducation and stabilization of silver ions to silver nanoparticles.

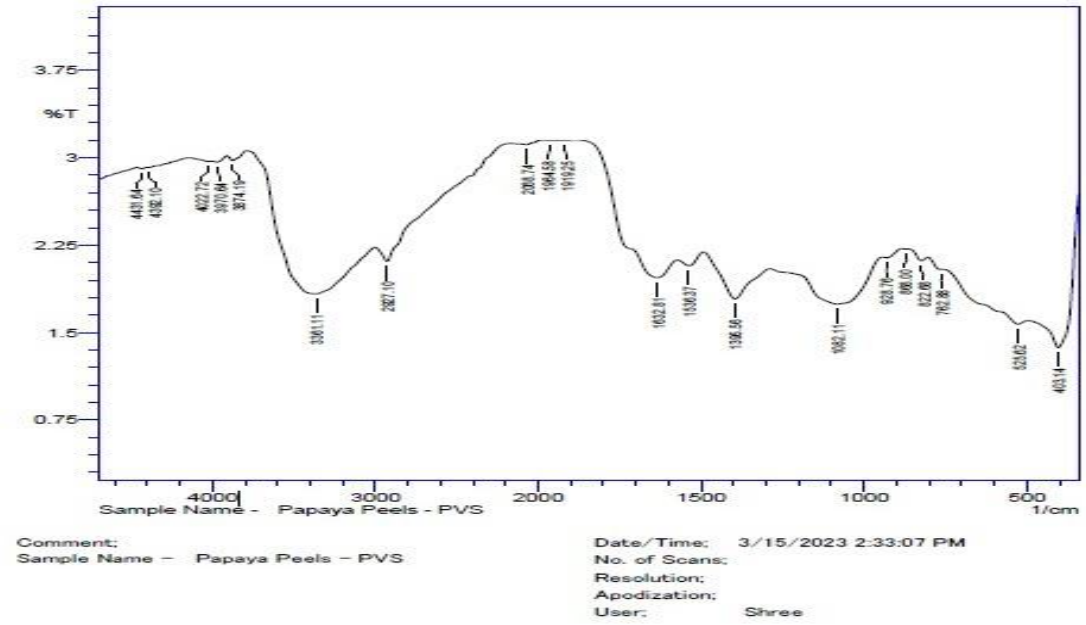


Figure 3: FTIR analysis

X-Ray Diffraction:

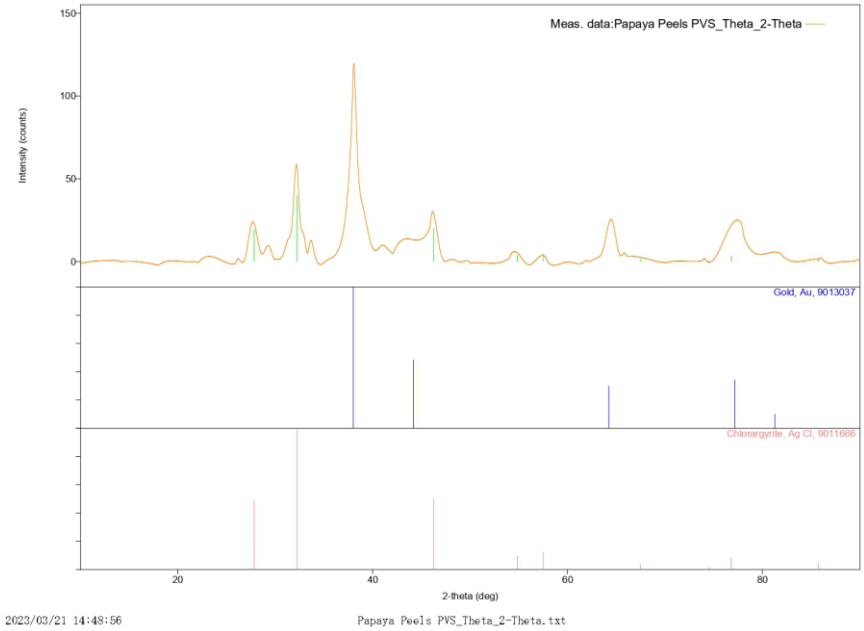


Figure 4: X-Ray Diffraction

Crystallographic structure, grain size, and preferred orientation in polycrystalline or powder solid samples were characterized by X-ray diffraction (XRD) analysis. The XRD patterns of synthesized silver nanoparticles are shown in Fig.4 and 5. Silver nanoparticles synthesized from fruit extract of *Carica papaya* showed Bragg Reflection peaks at 38.01, 44.18 ,64.25, 77.16, 81.28 and 97.54 in the 2h range between 10–80 which can be indexed to the (111), (200), (220), (311), (222), (400) planes of face centered cubic (fcc) crystal, respectively. The full width at half maximum (FWHM) values were used to calculated the size of the nanoparticles synthesized from fruit extract of *Carica papaya* was calculated using Scherres

equation where Scherrers constant value =0.94 was selected due to the cubic and crystalline nature of the nanoparticles They have a good match with the standard diffraction pattern of JCPDS No. 89-3722, revealing that the synthesized silver nanoparticles are composed of pure crystalline silver and the particle size is approximately 30 nm. The peak corresponding to (111) plane is more intense than the other planes, suggesting that the (111) plane is in the major orientation.

PDF Card No.: 9013037 Quality:C

Sub-File Name:

Formula: Au

Name: Gold I/Ic (RIR)= 26.34

Crystal System: Space Group: F m -3 m(225) Dmeas:

Cell Parameters: a= 4.0970 b= 4.0970 c= 4.0970

Alpha= 90.000 Beta= 90.000 Gamma= 90.000

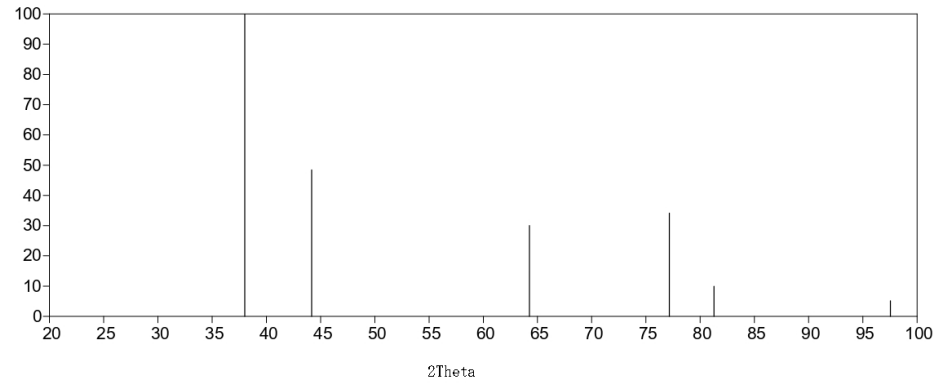
Volume= 68.770 Z= 1

Reference:

Radiation: Wavelength=

2Theta range: 38.01 - 97.54

Database comments:



No.	2Theta	d-Value	Intensity	h	k	l	No.	2Theta	d-Value	Intensity	h	k	l
1	38.01	2.365	100.0	1	1	1							
2	44.18	2.049	48.4	2	0	0							
3	64.25	1.449	30.0	2	2	0							
4	77.16	1.235	34.1	3	1	1							
5	81.28	1.183	9.9	2	2	2							
6	97.54	1.024	5.1	4	0	0							

Note: 2theta are calculated with wavelength = 1.54059

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Figure 5: X-Ray Diffraction

Conclusion:

In conclusion, it has been shown that the papaya fruit extract bioreduces aqueous Ag+ ions. the formation of silver nanoparticles with rather well defined dimensions as a result of the reduction of metal ions using papaya fruit extracts. However, there is a lack of testing and clarity

surrounding the other plant parts' potential as reducing and capping agents, such as fruit. Our current investigation revealed that fruits can serve as a valuable source for the synthesis of silver nanoparticles. There are numerous benefits to using this green chemical approach to synthesize silver nanoparticles, including simplicity of scaling up the process and economic viability. Their average particle size is 30 nm, and they are crystalline, uniform, spherical, and monodispersed nanoparticles.

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STEALTH LIPOSOMES: ENHANCING DRUG DELIVERY EFFICIENCY

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Abstract:

Liposomes, spherical vesicles composed of lipid bilayers enclosing an aqueous core, have garnered significant interest in drug delivery due to their versatile properties. Stealth liposomes, a specialized type of liposome coated with hydrophilic polymers like polyethylene glycol (PEG), have emerged as a promising solution to evade immune recognition and prolong circulation in the bloodstream. This explores the mechanisms of stealth liposome transportation and their distinct characteristics, including prolonged circulation time, reduced immunogenicity, enhanced stability, and targeted delivery. Various polymers used in stealth liposome formulations and methods of preparation are discussed. Evaluation parameters such as particle size, encapsulation efficiency, and in-vitro drug release are examined. Furthermore, the pharmaceutical applications of stealth liposomes in cancer therapy, vaccines, diagnostic imaging, and lung infections are elucidated, highlighting their potential to revolutionize drug delivery strategies for improved therapeutic outcomes.

Keywords: Stealth Liposomes, Phospholipids, Vaccines, Cancer therapy, Diagnostic imaging

Introduction:

Liposomes are spherical vesicles composed of lipid bilayers that enclose an aqueous core. These lipid bilayers typically consist of phospholipids, which are amphiphilic molecules containing a hydrophilic head group and hydrophobic tails. When dispersed in water, these lipids spontaneously self-assemble into closed vesicles due to their hydrophobic tails interacting with each other and their hydrophilic heads interacting with water molecules. The composition of conventional liposomes can vary depending on the specific application and desired properties. Common phospholipids used in liposome formulations include phosphatidylcholine, phosphatidylethanolamine, and cholesterol, which can be modified to alter liposome stability, permeability, and targeting abilities. Structurally, liposomes can range in size from tens to hundreds of nanometers in diameter. They can be unilamellar, consisting of a single lipid bilayer, or multilamellar, with multiple concentric lipid bilayers separated by aqueous compartments [1]. Liposomes may also have different surface properties, such as being negatively or positively charged, or modified with targeting ligands or stealth coatings to improve circulation time in the bloodstream. Conventional liposomes have a wide range of applications, primarily in drug delivery. They can encapsulate hydrophilic drugs within their aqueous core or hydrophobic drugs

within the lipid bilayers, protecting them from degradation and improving their solubility and bioavailability. Liposomes can be used to deliver a variety of therapeutic agents, including chemotherapy drugs, antibiotics, antifungals, and vaccines. Additionally, liposomes have applications in gene therapy, where they can deliver nucleic acids such as DNA or RNA to target cells. They were first described by British hematologist Alec D. Bangham in 1961 [2]. He discovered that certain lipids could self-assemble into closed structures when in contact with water, forming spherical vesicles. Bangham's work laid the foundation for further research into liposomes. Initially, liposomes were primarily studied for their ability to model biological membranes and their potential applications in drug delivery. In the 1970s, researchers began exploring the use of liposomes as carriers for drugs and other therapeutic agents [3]. Over the years, liposome technology has evolved, leading to the development of various types of liposomes with different properties and applications. These include stealth liposomes, which have a protective coating to evade detection by the immune system and prolong circulation in the bloodstream, and ligand-targeted liposomes, which are designed to selectively bind to specific receptors on target cells.

Stealth liposomes

It also known as stealth nanoparticles or stealth liposomal formulations, are a specialized type of liposome engineered to evade detection by the immune system and prolong circulation in the bloodstream. The development of stealth liposomes was prompted by the recognition that conventional liposomes are rapidly recognized and cleared by the body's immune system, leading to rapid clearance from circulation and limiting their effectiveness as drug delivery vehicles. To resolve this problem, stealth liposomes are typically coated with hydrophilic polymers such as polyethylene glycol (PEG), which creates a protective layer around the liposome surface [4]. This PEGylation alters the liposome's surface properties, making it less prone to recognition and clearance by the reticuloendothelial system (RES) and extending its circulation time in the bloodstream. The development of stealth liposomes has led to significant advancements in drug delivery technology, as it allows for improved delivery of therapeutic agents to target tissues or cells. By prolonging circulation time, stealth liposomes increase the likelihood of accumulation at the target site, enhancing drug efficacy while minimizing off-target effects and reducing systemic toxicity. The mechanisms underlying the stealth effect of PEGylated liposomes involve steric hindrance and reduced opsonization. The hydrophilic PEG chains create a hydrated layer around the liposome surface, which sterically hinders the interaction of opsonins (proteins that promote phagocytosis) with the liposome, thereby reducing recognition by macrophages and other immune cells [5]. Additionally, the PEG layer may also mask immunogenic epitopes on the liposome surface, further reducing immune recognition and clearance.

Mechanism of transportation through stealth liposomes

Firstly, stealth liposomes exploit the prolonged circulation time afforded by their surface modification with hydrophilic polymers, such as polyethylene glycol (PEG). This extended circulation allows stealth liposomes to evade rapid recognition and clearance by the immune system, particularly by the reticuloendothelial system (RES), which includes macrophages in the liver and spleen [6]. As a result, stealth liposomes can persist in the bloodstream for longer periods, increasing the likelihood of reaching their target tissues or cells. Once in circulation, stealth liposomes can passively accumulate at target sites through a phenomenon known as the enhanced permeability and retention (EPR) effect. This effect is commonly observed in solid tumors and inflamed tissues, where leaky vasculature and impaired lymphatic drainage result in increased extravasation and retention of macromolecules, including liposomes. Stealth liposomes take advantage of this phenomenon to accumulate preferentially in these regions, thereby improving drug delivery to diseased tissues while minimizing exposure to healthy tissues. Additionally, stealth liposomes can actively target specific cells or tissues through surface modification with targeting ligands or antibodies. These ligands bind to receptors overexpressed on the surface of target cells, facilitating the uptake of stealth liposomes into the cells via receptor-mediated endocytosis. This targeted delivery approach enhances the therapeutic efficacy of stealth liposomes by ensuring precise localization and accumulation of drugs within the desired cellular compartments [7,8].

Characteristics of stealth liposome

Stealth liposomes possess several key characteristics that distinguish them from conventional liposomes and contribute to their enhanced performance as drug delivery vehicles:

Prolonged circulation time: Stealth liposomes are coated with hydrophilic polymers, such as polyethylene glycol (PEG), which create a protective layer around the liposome surface. This PEGylation helps to evade rapid recognition and clearance by the immune system, particularly by the reticuloendothelial system (RES), thereby prolonging their circulation time in the bloodstream [9].

Reduced immunogenicity: The surface modification of stealth liposomes with hydrophilic polymers also helps to mask immunogenic epitopes on the liposome surface, reducing their recognition and clearance by the immune system. This enhances their biocompatibility and reduces the likelihood of triggering immune responses, making them suitable for repeated administration [10].

Enhanced stability: Stealth liposomes exhibit improved stability in physiological environments, which is essential for maintaining the integrity of the encapsulated cargo during circulation and delivery to the target site. The hydrophilic PEG coating provides a protective barrier that helps to prevent aggregation, degradation, and premature release of the encapsulated drugs [3].

Enhanced tumor accumulation: Stealth liposomes use the increased permeability and retention (EPR) phenomenon to accumulate quietly at tumour locations. Solid tumours' leaky vasculature and inadequate lymphatic drainage enable stealth liposomes to extravasate predominantly into tumour cell membranes, resulting in increased medication concentrations at the target location while minimising exposure to healthy tissues [4].

Targeted delivery: Stealth liposomes can be enhanced with ligands that target or the antibodies to enable targeted destruction of certain cells or organs. These molecules bind to receptors that are excessively expressed on the outermost layer of target cells, allowing stealth liposomes to enter the cells by receptor-mediated endocytosis [11]. This targeted delivery approach enhances the specificity and efficacy of drug delivery while minimizing off-target effects.

Polymers use in stealth liposome

Stealth liposomes are typically coated with hydrophilic polymers, with polyethylene glycol (PEG) being the most commonly used. These polymers form a protective layer around the liposome surface, shielding it from recognition and clearance by the immune system and prolonging its circulation time in the bloodstream. Other polymers that have been investigated for use in stealth liposomes include:

Polyvinyl alcohol (PVA): PVA is another hydrophilic polymer that has been used to coat liposomes for stealth purposes. It provides steric hindrance, preventing opsonization and uptake by the reticuloendothelial system (RES) [12].

Polysaccharides: Certain polysaccharides, such as dextran and hyaluronic acid, have been explored as coating materials for stealth liposomes. These polysaccharides offer biocompatibility and can also contribute to targeted delivery through specific interactions with receptors on target cells [12].

Poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA): It is a synthetic polymer that has been investigated for its potential use in stealth liposomes. It offers excellent biocompatibility and can be conjugated to targeting ligands for enhanced specificity in drug delivery [13].

Poly(lactic-co-glycolic acid) (PLGA): PLGA is a biodegradable polymer commonly used in drug delivery systems. While not as hydrophilic as PEG, PLGA-coated liposomes have been developed for sustained release and improved stability.

Poly(acryl amide) (PPA): It is a synthetic polymer that has been explored for its potential use in stealth liposomes. PAAm is a water-soluble polymer that can form a hydrophilic coating on the surface of liposomes, similar to PEGylation. This coating helps to shield the liposomes from recognition and clearance by the immune system, prolonging their circulation time in the bloodstream. Additionally, PAAm can provide steric hindrance, preventing opsonization and uptake by phagocytic cells, such as macrophages in the liver and spleen [14].

Poly (2-methyl-2-oxazoline): Poly(2-etyl-2-oxazoline) and poly(2-alkyl-2-oxazoline) are versatile polymers with several uses, including thermosensitive materials, sensors, and drug delivery systems. They all have longer blood circulation times and lower uptake by the liver and spleen [14].

Method of preparation

Thin film hydration technique

In this method, lipid components such as solution of phospholipids (distearoyl phosphatidylcholine) are dispersed in a solvent that is organic, resulting in a thin layer on the container's surface. The film is then hydrated with an aqueous solution containing the drug of interest, resulting in the formation of multilamellar vesicles (MLVs). These MLVs can be subsequently downsized to form small unilamellar vesicles (SUVs) using techniques such as sonication or extrusion. Hydrophilic polymers, such as PEG, can be included in the lipid film to coat the liposomes during hydration, forming stealth liposomes [15].

Hand shaken method

The production of liposomes necessitates the introduction of lipid molecules into a watery setting. When dry lipid membranes come into contact with moisture, the lamellae expand and give rise to myelin structures. Mechanical disruption, such as vertexing, trembling swirling, or pipetting, disturbs these myelin forms and closes exposed hydrophobic edges, causing liposomes to develop. The manual agitation method can generate sizable multilamellar liposomes [16].

Reverse phase evaporation method

This technique starts with dissolving lipids and the drug in an organic solvent. Next, an aqueous phase containing the hydrophilic polymer is added [17]. The mixture undergoes evaporation under reduced pressure, creating a water-in-oil emulsion. Removing the organic solvent afterward yields stealth liposomes that encase the drug within a hydrophilic polymer coating.

Liposome extrusion method

Liposomes prepared by thin-film hydration or reverse-phase evaporation can be further processed using extrusion techniques to achieve uniform size distribution and smaller particle sizes. In this method, liposome suspensions are passed through a series of polycarbonate membranes with defined pore sizes under controlled pressure, leading to the formation of small and homogenous stealth liposomes [18].

Detergent depletion method

The detergent depletion approach creates various liposome and proteoliposome compositions. Various approaches may be used to remove detergents from a detergent-lipid miceller, resulting in homogenous liposomes. This approach is suitable for any triglycerides

beneath their phase transition temperature. Only some detergents are suitable for the detergent depletion approach. The most often used detergents are sodium cholate, alkyl (thio) glucoside, and alkyloxy polyethylenes [15]. Mix micelles by adding a very concentrated detergent combination to multivesicular vesicles. The final quantity of the detergent should be greater than the critical micelle concentration (CMC).

Probe sonication method

The sonicator tip is directly submerged in the liposome dispersion. This approach requires a significant amount of energy to disperse fat. To prevent overheating at the tip, submerge the vessel in an ice/water bath. Up to one hour of sonication can de-esterify more than 5% of lipids. Additionally, the probe sonicator might cause titanium to pollute the solution [18].

Bath sonication method

A tube containing liposome dispersion is put in a bath sonicator. This approach allows for easier temperature control of the phospholipid dispersion compared to sonication directly with the tip. Sonicated materials can be stored in a sterile container or an inert environment, unlike probe devices. The liposome's lipid bilayer can fuse with other bilayers, such as cell membranes, to distribute its contents. Liposomes can carry DNA or medications that would otherwise not pass through the membrane by encapsulating them in a solution [17].

Evaluation parameters of Stealth liposome

Particle size and size distribution: The size of stealth liposomes is a crucial parameter as it influences their biodistribution, circulation time, and cellular uptake. Techniques such as dynamic light scattering (DLS) or electron microscopy are used to measure the average particle size and assess size distribution [18].

Zeta potential determination: Zeta potential is an indicator of the surface charge of liposomes, which affects their stability and interaction with biological systems. Stealth liposomes are often formulated to have a neutral or slightly negative surface charge to minimize non-specific interactions with cells and proteins [18].

Lipid quantification and chemical stability: The concentration and purity of phospholipids and cholesterol were measured using HPLC or cholesterol oxidase. TLC was used to test the purity of raw phospholipids and their hydrolysis throughout liposome synthesis and storage. Enzymatic measurement of non-esterified fatty acid levels was also performed [19].

Encapsulation efficiency: This parameter measures the percentage of drug encapsulated within the liposomal carrier. High encapsulation efficiency is desirable as it ensures maximal drug loading and minimizes wastage of the therapeutic agent. Encapsulation efficiency can be determined using various analytical techniques, such as high-performance liquid chromatography (HPLC) or ultracentrifugation [19].

***In-vitro* drug release:** *In-vitro* drug release experiments were carried out using a dialysis method for both uncoated and stealth-coated liposomes. To remove any free drug molecules, uncoated liposomes underwent pre-dialysis in buffered saline using dialysis tubing. Subsequently, 2ml of either uncoated or stealth-coated liposomal suspension was mixed with 2ml of blank marine plasma and placed into the same dialysis tubing. These dialysis cassettes containing the uncoated and stealth-coated liposome suspensions were then submerged into two separate beakers, each filled with 50ml of HBS (Hepes-buffered saline). The beakers were then placed in a water bath set to 37°C for incubation. Samples were carefully withdrawn from the beakers at various time points (0, 5, 15, 30 minutes, 1 hour, 4 hours, 6 hours, 10 hours, 24 hours, and 48 hours) and replaced with an equal volume of fresh HBS [20].

Stability: The stability of stealth liposomes is crucial for maintaining their integrity and drug encapsulation properties during storage and administration. Stability studies assess parameters such as physical stability (e.g., size, aggregation, and morphology), chemical stability (e.g., drug degradation), and colloidal stability (e.g., zeta potential). Accelerated stability testing and long-term stability studies under relevant storage conditions are typically performed to evaluate liposome stability over time [20].

Pharmaceutical application of stealth liposome

Stealth liposome in cancer therapy

They offer several benefits in cancer therapy. They utilize the EPR effect to passively accumulate in tumor tissues, enhancing drug delivery. Additionally, they have prolonged circulation in the bloodstream, avoiding immune clearance and increasing the likelihood of reaching tumors [15,21]. Furthermore, they minimize off-target effects and systemic toxicity by reducing exposure to healthy tissues through a protective polymer coating. Liposomal formulations can also release drugs in a controlled manner, maintaining therapeutic concentrations in tumors. Finally, stealth liposomes enable combination therapy by co-delivering multiple agents, targeting various pathways in cancer progression for improved efficacy. Doxil®, a PEGylated liposomal formulation of doxorubicin, has been extensively studied in clinical trials for various types of cancer, including ovarian cancer, breast cancer, and Kaposi's sarcoma. Clinical studies have demonstrated improved safety profiles and reduced cardiotoxicity compared to conventional doxorubicin, along with comparable or superior antitumor efficacy. Doxil® has been approved for the treatment of metastatic breast cancer, ovarian cancer, and AIDS-related Kaposi's sarcoma. Marqibo®, a liposomal formulation of vincristine, has been investigated in clinical trials for the treatment of relapsed or refractory acute lymphoblastic leukemia (ALL) [22].

Stealth liposomes for vaccines

Stealth liposomes serve as efficient carriers for vaccine antigens, facilitating their delivery to antigen-presenting cells (APCs) like dendritic cells, macrophages, and B cells, thus augmenting immune activation. The prolonged circulation time in the bloodstream, due to their stealth properties, enables sustained antigen presentation and interaction with APCs, fostering robust and enduring immune responses [23]. Moreover, liposomal formulations can be designed for controlled antigen release, ensuring optimal antigen concentrations over time, enhancing immune cell stimulation, and promoting long-lasting immunity. Engineered for targeted delivery, these liposomes can be modified with ligands or antibodies to direct vaccines to specific tissues or cell populations, improving antigen uptake and immune activation. Additionally, liposomal formulations can incorporate immunostimulatory molecules or adjuvants to further enhance vaccine potency by activating innate immune pathways and promoting robust adaptive immune responses. With improved stability and shelf life, stealth liposomes protect antigens from degradation, making them advantageous for vaccines targeting infectious diseases, especially in resource-limited settings or those requiring cold-chain storage. Clinical trials have evaluated the use of cationic liposome-based vaccine adjuvants, which possess stealth properties due to PEGylation, for enhancing immune responses to various vaccines, including influenza and human papillomavirus (HPV) vaccines [24].

Stealth liposomes in diagnostic imaging

Stealth liposomes possess unique characteristics that make them promising tools in diagnostic imaging. Their stealth properties enable prolonged circulation in the bloodstream, allowing them to accumulate in target tissues for an extended period. This prolonged circulation enhances the opportunity for imaging agents encapsulated within liposomes to reach and accumulate within specific anatomical sites, thereby improving imaging sensitivity. Moreover, these liposomes can be customized for targeted tissue delivery by modifying their surface with targeting ligands or antibodies. This facilitates precise delivery of imaging agents to sites of interest, enhancing imaging specificity and enabling accurate visualization of pathological processes [25]. Additionally, stealth liposomes can encapsulate imaging agents such as contrast agents or fluorescent dyes, improving their stability and circulation time in vivo. These agents emit specific signals detectable by various imaging modalities, including MRI, CT, PET, and fluorescence imaging, thereby significantly improving imaging contrast and sensitivity. Furthermore, stealth liposomes are investigated for theranostic applications, where diagnostic imaging is combined with therapeutic capabilities. By incorporating both imaging agents and therapeutic drugs within the same liposomal carrier, stealth liposomes enable simultaneous imaging and treatment of diseases, offering the potential for personalized and targeted healthcare approaches seamlessly integrating diagnostics and therapy [26].

Stealth liposomes in deliver drugs into the lung infections

It provides a targeted approach for delivering drugs to treat lung infections, exploiting the pulmonary route efficiently. Their stealth properties enable prolonged circulation in the bloodstream, facilitating accumulation in the lungs and delivery of therapeutic agents to infected tissues [27]. Encapsulation within liposomes protects drugs from degradation and immune clearance, ensuring potency and efficacy while minimizing systemic exposure and side effects. Additionally, liposomal formulations can be engineered for controlled drug release, optimizing efficacy and reducing dosing frequency. Furthermore, stealth liposomes enable combination therapy by co-delivering multiple agents for synergistic effects against lung infections, enhancing treatment efficacy [28]. Various stealth liposome formulation with their study stage and applications are described in table 1.

Table 1: Formulation of stealth liposomal drug delivery in different stage.

Stealth Liposome Formulation	Study Stage	Description	References
Doxil® (PEGylated liposomal	Clinical Trials	Doxil® is a PEGylated liposomal formulation of doxorubicin. has been approved for the treatment of metastatic breast cancer, ovarian cancer, and AIDS-related Kaposi's sarcoma.	[29,30]
Marqibo® (Liposomal Vincristine)	Clinical Trials	Marqibo® is a liposomal formulation of vincristine. It has been investigated in clinical trials for the treatment of relapsed or refractory acute lymphoblastic leukemia (ALL).	[31,32]
Cationic Liposome-Based Adjuvants	Preclinical Studies	Possessing stealth properties due to PEGylation, enhance immune responses to various vaccines, including influenza and human papillomavirus (HPV) vaccines.	[33]
Liposome-Based Diagnostic Imaging	Preclinical Studies	Utilize stealth properties for prolonged circulation, allowing for enhanced accumulation at target tissues and improved imaging specificity.	[34]
Stealth Liposome for Lung Infections	Preclinical Studies	Exploit the pulmonary route efficiently, delivering therapeutic agents to infected tissues while minimizing systemic exposure and side effects.	[28]

Conclusion:

In conclusion, liposomes represent versatile and promising vehicles for drug delivery, offering various advantages such as enhanced stability, controlled release, and targeted delivery. The development of stealth liposomes has revolutionized drug delivery technology, particularly in cancer therapy, vaccine delivery, diagnostic imaging, and treating lung infections. By prolonging circulation time and evading immune detection, stealth liposomes improve drug delivery efficiency while minimizing off-target effects and systemic toxicity. They enable precise targeting of specific tissues or cells, controlled release of therapeutic agents, and combination therapy for synergistic effects. With ongoing research and development, stealth liposomes hold immense potential for advancing personalized and targeted approaches to healthcare, addressing critical needs in disease diagnosis and treatment.

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NANOPARTICLES IN FOOD INDUSTRY: APPLICATIONS AND CHALLENGES

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Abstract:

Nanotechnology has potential applications in the food industry, particularly in food packaging, fortification, preservation, and sensory enhancement. Nanoparticles, with their unique physicochemical properties, offer significant benefits. However, challenges like poor stability, solubility, and bioavailability pose challenges. Encapsulation can help overcome these issues. This chapter analyses recent advancements in the use of nanoparticles in food industries, focusing on their potential applications as active ingredients or packaging materials. It also discusses potential adverse effects of these nanomaterials. By examining recent advancements and projections, this chapter aims to contribute to a comprehensive understanding of the opportunities and limitations of nanoparticles in the food industry.

Keywords: Nanoparticles; Nanotechnology; Food Industry; Food Safety Standards; Food Processing; Food Packaging.

Introduction:

Small, highly surface-to-volume particles with distinct physicochemical characteristics, nanoparticles have sizes between 1 and 100 nanometers. Their macroscale dimensions may be used to categorize them: 0D corresponds to nanomaterials, 1D to nanofibers and wires, 2D to nanosheets and thin films, and 3D to bulk materials. Chemical nature may also be used to categorize nanomaterials, with four primary groups being carbon, ceramic, metal, and polymeric compounds. While nanotechnology creates structures, devices, and systems at the nanometer size, nanoscience investigates phenomena and manipulates materials at the atomic, molecular, and macromolecular scales. Nanotechnology methods are being used to generate high-performance delivery vehicles for biologically active compounds originating from food. Due to their potential to improve food quality, safety, and functioning, they are widely sought after by a variety of businesses, including the food industry. To increase mechanical strength, barrier qualities, and the antibacterial and antioxidant effects of food packaging materials, nanoparticles can be used. Additionally, by encapsulating and distributing bioactive substances, vitamins, and minerals, they may be utilized to fortify food while improving the stability and bioavailability of

those ingredients. Additionally, nanoparticles have antibacterial qualities that prevent the growth of pathogens and bacteria that cause food to deteriorate. They can alter the flavor, texture, and appearance of food goods to improve their sensory qualities and increase customer acceptability. Additionally, they perform as exact delivery systems, enabling the targeted and regulated release of flavors, bioactive chemicals, and functional substances to certain locations within food matrices or the human body.

Types of nanoparticles used in food industry

Across all phases of food production, processing, and packaging, nanoparticles contribute significantly to improving food quality, safety, and functionality. The antibacterial qualities of metallic nanoparticles, which are derived from metals including copper, zinc, gold, and silver, are utilized in food packaging. Titanium dioxide, zinc oxide, and iron oxide make up metal oxide nanoparticles, which shield food from UV deterioration and stop the growth of microorganisms. The stability and bioavailability of nutrients, tastes, and bioactive chemicals are increased when they are encapsulated and delivered via lipid-based nanoparticles. In addition to improving biodegradable packaging, polymer nanoparticles regulate component release. Chemically, mechanical strength, and sensory qualities are enhanced by carbon-based nanoparticles. Pottery nanoparticles improve mouthfeel and texture while strengthening food packaging materials. Food imaging and sensing, quality assurance, and labeling are among the areas where quantum dots find use.

Table 1: An overview of the various types of nanoparticles used in the food industry, along with their descriptions and applications

Types of Nanoparticles		**Applications**
Metallic Nanoparticles	Nanoparticles composed of metals such as silver, gold, copper, and platinum.	▪ Food packaging for antimicrobial properties ▪ Food preservation to inhibit microbial growth ▪ Catalysis in food processing
Metal Oxide Nanoparticles	Nanoparticles consisting of metal oxides such as titanium dioxide (TiO2), zinc oxide (ZnO), and iron oxide (Fe2O3).	▪ UV protection in food packaging ▪ Antimicrobial effects for food preservation ▪ Enhancing sensory properties of food products

Lipid-based Nanoparticles	Nanoparticles composed of lipids, including liposomes, nano emulsions, and solid lipid nanoparticles (SLNs).	▪ Encapsulation and delivery of bioactive compounds ▪ Controlled release of Flavors and nutrients ▪ Improving bioavailability of fat-soluble vitamins
Polymer Nanoparticles	Nanoparticles made from synthetic or natural polymers, such as poly(lactic-co-glycolic acid) (PLGA) and chitosan.	▪ Controlled release of active ingredients in food supplements ▪ Enhancing stability and solubility of bioactive compounds ▪ Designing biodegradable food packaging materials
Carbon-based Nanoparticles	Nanoparticles composed of carbon, including fullerenes, carbon nanotubes, and graphene.	▪ Food packaging for barrier properties and mechanical strength ▪ Enhancing sensory attributes of food products ▪ Improving food processing efficiency
Ceramic Nanoparticles	Nanoparticles made from ceramics such as silica (SiO2) and alumina (Al2O3).	▪ Reinforcing food packaging materials ▪ Improving thermal stability and mechanical properties of food products ▪ Enhancing texture and mouthfeel of food formulations
Quantum Dots	Semiconductor nanoparticles with unique optical and electronic properties.	▪ Food labelling and tracing for quality control ▪ Detecting foodborne pathogens and contaminants ▪ Developing novel food imaging and sensing technologies

Applications of nanoparticles in food industry

Nanotechnology can revolutionize food production by targeting pesticides, controlling pharmaceuticals, and improving animal health. It can also revolutionize food processing with self-cleaning antimicrobial machines and faster fluid transport systems. However, a seamless transition from existing packaging to nano-packaging is necessary for successful marketing,

considering functional and aesthetic characteristics. Few applications of nanotechnologies are listed below and shown in Fig.1.

- **Food packaging:** The barrier qualities of packing materials can be improved by nanoparticles, especially metal oxides like zinc oxide and titanium dioxide, which can prolong the shelf life of perishable food items. Their antibacterial qualities prevent the formation of mold and bacteria, lowering the possibility of contamination and spoiling. Additionally, these nanoparticles serve as UV filters, preventing sunlight-induced deterioration of food items that are sensitive to light. Antioxidants, antimicrobials, and oxygen scavengers are examples of active substances that may be added to active packaging systems to improve the quality and safety of packed foods. Food packaging materials can incorporate sensor nanoparticles, including carbon nanotubes and quantum dots, to monitor food safety and quality indicators in real time. Additionally, by assuring product freshness and safety, these nanoparticles may be utilized in smart packaging systems that react to outside stimuli or changes in the environment, improving food preservation, reducing waste, and improving the consumer experience.
- **Food fortification:** Food fortification is a process that adds essential nutrients to food products to address nutritional deficiencies and improve public health. Nanotechnology, specifically nanoencapsulation of bioactive compounds, has been shown to enhance the efficacy of food fortification and promote enhanced nutrient absorption. Nanoencapsulation encapsulates bioactive compounds, such as vitamins, minerals, antioxidants, and omega-3 fatty acids, within nanoscale carriers, protecting them from degradation, oxidation, and interactions with other food components. This process enhances stability by shielding them from environmental factors, ensuring nutrient integrity and bioavailability throughout the food product's shelf life. It also enables targeted delivery of bioactive compounds to specific sites within the gastrointestinal tract, facilitating efficient absorption.

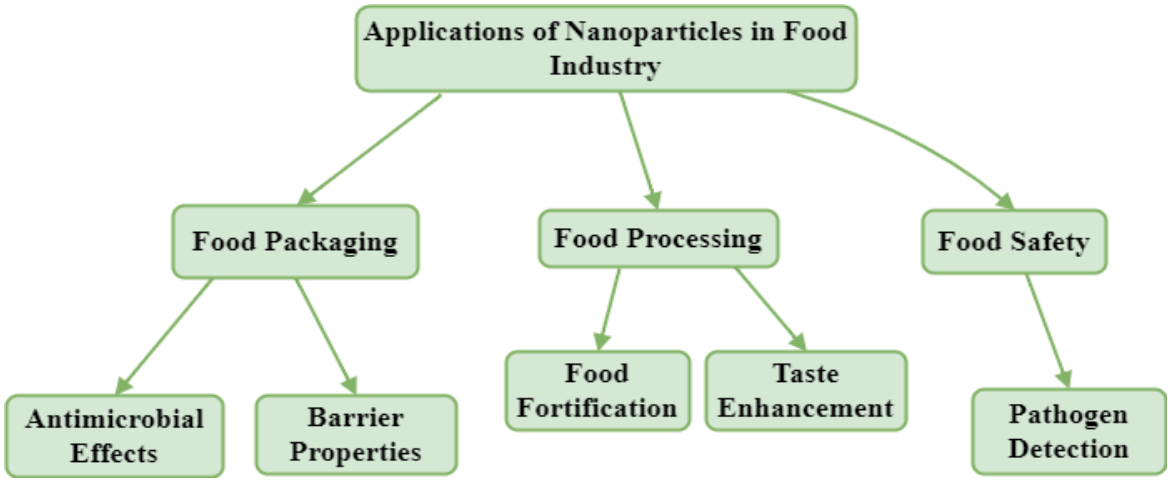

Fig. 1: Applications of Nanoparticles in Food Industry

- **Nanoencapsulation** also enhances bioavailability by improving solubility, dispersibility, and absorption kinetics. It also facilitates enhanced nutrient absorption by promoting optimal interactions between nutrients and biological systems, including the gastrointestinal tract. This allows for prolonged residence time of nutrients within the gastrointestinal tract, facilitating efficient nutrient uptake and utilization. However, safety, regulatory compliance, and consumer acceptance must be considered when incorporating nano encapsulated bioactive compounds into fortified food products.
- **Food safety:** Nanoparticles, particularly silver nanoparticles, have antimicrobial properties that prevent microbial contamination and extend the shelf life of perishable food products. They preserve food quality and freshness by inhibiting microbial growth, delaying enzymatic reactions, and minimizing oxidative processes. This leads to prolonged storage stability and reduced food waste, benefiting both consumers and food manufacturers. Nanoparticles can also be used to modify the texture and rheological properties of food products, enhancing their sensory attributes and consumer appeal. They can optimize viscosity, suspension stability, and gelation properties, resulting in desirable textures. Additionally, nanoparticles can enhance the flavor profile and taste perception of food products by masking off-flavors, stabilizing volatile compounds, and controlling flavor release kinetics. This results in a more consistent and intense flavor sensation throughout consumption.

Challenges and limitations

Nanoparticles pose significant toxicity concerns in various applications, including the food industry. They have a high surface area-to-volume ratio, which can lead to increased reactivity and potential toxicity. They may interact differently with biological systems, causing potential adverse effects. The biocompatibility of nanoparticles depends on factors like composition, size, shape, surface chemistry, and charge. They can enter the body through inhalation, ingestion, dermal contact, and injection, raising concerns about systemic absorption and distribution. The potential health effects of nanoparticles depend on their physicochemical properties, concentration, exposure duration, and route of exposure. Regulatory agencies face challenges in evaluating the safety of nanoparticles and establishing guidelines for their use in food products. Addressing toxicity concerns requires comprehensive risk assessment, toxicity testing, and regulatory oversight to ensure the safe and responsible use of nanotechnology in food packaging, additives, and processing.

The use of nanoparticles in the food industry presents several challenges, including regulatory uncertainty, safety concerns, consumer perception, cost considerations, technical challenges, sustainability, ethical considerations, and potential for nanoparticle migration.

Regulatory frameworks are still evolving, and lack of standardized testing protocols can create uncertainty for manufacturers and regulatory agencies. Nanoparticles may pose toxicity, biocompatibility, and long-term health effects, and their behavior in complex food matrices and the human body is not fully understood. Consumer acceptance of nanoparticle-based food products remains a challenge, and cost considerations may hinder the production and incorporation of nanoparticles. Technical challenges include precise control over particle size, morphology, and surface properties, and environmental sustainability concerns include the potential impact on ecosystems and natural resources. Ethical considerations, including informed consent, labeling transparency, and equitable access to nanoparticle-enhanced foods, are also crucial.

Table 2: The challenges of nanoparticles in the food industry:

Challenges of nanoparticles in the food industry	
Toxicity	Nanoparticles may pose health risks when ingested in large quantities. Their small size allows them to penetrate biological barriers more easily, raising concerns.
Regulatory Uncertainty	There's limited regulatory framework governing the use of nanoparticles in food. Uncertainty exists regarding safety standards and labeling requirements.
Stability	Nanoparticles can exhibit instability in food matrices, affecting their functionality and potential benefits.
Agglomeration	Nanoparticles tend to agglomerate, diminishing their surface area and altering their behavior and effectiveness in food applications.
Cost	The production and incorporation of nanoparticles into food can be expensive, potentially limiting their widespread adoption in the industry.
Perception and Acceptance	Consumer perception regarding the safety and necessity of nanoparticles in food products may affect acceptance and market viability.
Toxicological Assessment	Nanoparticles require thorough toxicological assessment to evaluate their potential health effects upon ingestion, including acute and chronic toxicity studies.
Risk of Bioaccumulation	Some nanoparticles may accumulate in the body over time, raising concerns about long-term health effects and the potential for bioaccumulation in the food chain.

Allergenicity	Nanoparticles could trigger allergic reactions in sensitive individuals, necessitating allergenicity testing to identify potential risks associated with their use.
Environmental Impact	Consideration must be given to the environmental impact of nanoparticles, including their potential for accumulation in ecosystems and effects on non-target organisms.
Interactions with Food Components	Nanoparticles may interact with food components, altering taste, texture, and nutritional properties, necessitating comprehensive studies to assess their impact.

Risk assessment & regulatory framework

The food industry relies on risk assessment and regulatory frameworks to ensure the safe and responsible use of nanoparticles as mentioned in Table 3. These include hazard identification, exposure assessment, toxicity assessment, and risk characterization. Regulatory agencies like the FDA and EFSA oversee the safety and regulation of nanoparticles in food products, establishing guidelines, standards, and regulations. Manufacturers must conduct safety assessments, label food products transparently, and obtain pre-market approval or authorization before introducing nanoparticle-based food products. International harmonization is crucial for global trade and consistency in safety evaluation and risk management practices.

Regulatory Framework	
Novel Food Regulations	Nanoparticles in food often fall under the purview of novel food regulations, which require comprehensive safety assessments prior to market approval.
Labeling Requirements	Many regulatory bodies mandate labeling requirements for food products containing nanoparticles to inform consumers and facilitate informed choices.
Risk Assessment Guidelines	Regulatory agencies provide guidelines and frameworks for conducting risk assessments of nanoparticles in food, ensuring their safety for human consumption.
Maximum Permissible Limits	Some regulatory authorities set maximum permissible limits for nanoparticles in food products to mitigate potential health risks associated with their use.
Post-Market Surveillance	Post-market surveillance mechanisms enable regulatory agencies to monitor the safety and efficacy of nanoparticles in food products after they enter the market.

Conclusion:

Improving food safety, functionality, and quality may all be accomplished using nanoparticles in the food sector. Application areas include food processing, production, packing, and preservation because to their special physicochemical qualities. It is necessary to handle obstacles including cost considerations, customer perception, safety concerns, and regulatory difficulties. The synthesis of sustainable nanoparticles, improved functions, consumer acceptability and education, safety and regulatory compliance, and cooperative research activities are some of the prospects for the future. Risk assessment, regulatory monitoring, stakeholder transparency, and interdisciplinary cooperation are all necessary for these endeavors. Nanoparticles in the food business have a bright future ahead of them, despite these obstacles.

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