

# Nanotechnology in the Advancement of Enhancing Bioavailability

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## ABSTRACT:

The nanotechnology is defined as the science that deals with the manipulations of matter on a scale of 1 to 100 nanometers, where a material can exhibit unique properties; whereas the bioavailability is defined as the rate and extent to which an administered drug substance is absorbed and becomes available at its intended biological site of action in body. There are several factors which resulting disturbance in the path of bioavailability such as solubility, dissolution rate, lipophilicity, molecular size, chemical stability, pka value, first-pass metabolism, gastrointestinal motility, and disease state, etc. there is a need to overcome the mentioned factors and it can be made possible with the use of Nanoparticulate nanomedicine (NNM), Nanoformulations like nanoemulsion, nanosuspension, Solid self-emulsifying drug delivery systems, and solid lipid nanoparticles (SLN) i.e Nanotechnology.

Keywords: Nanotechnology; Conventional and modern methodology, Quantum effect in nano –formulations; Challenges in adaptation of nanotechnology.

## INTRODUCTION:

In the recent times, one of the major challenges faced by the pharmaceutical industry included the poor solubility of water and inadequate bioavailability of drugs. Recent data shows that about 40% of commercial pharmaceuticals and the significant investigational drugs are struggling for the low solubility. This issue can lead to compromise with the bioavailability and therapeutic efficiency of dosages to achieve the desired pharmacological impact. Low bioavailability resulting in the consumption of higher drug dosages to achieve the desired therapeutic effects for the desired patients. Therefore, effectively retarded with the poor solubility and low bioavailability of drugs which has always been targeted point and a expressive challenge in pharmaceutical and medical research <sup>[1]</sup>. Nanomedicine delivery systems primarily surrounded with two fundamental aspects i.e based on pathological changes with nanotechnology-based structural modifications to control over drug release and increase in the drug stability which helps to prevent the premature degradation of the drug molecules before reaching the desired site in body. The common molecular abilities that impact drug solubilization to make it highly lipophilic and improve the strong intermolecular forces (Lindenberg et al., 2004) <sup>[2]</sup>. The involvement of nanotechnology has primarily transformed the landscape of pharmaceutical sciences and medicines in the 21st century. The nanotechnology delivers crucial limitations of conventional dosage forms. Traditional drug delivery systems, like tablets and capsules, frequently face several challenges including poor bioavailability, insufficient tissue distribution, and eagarless effects on healthy cells of body. Nanoscale manipulation of matter allows the formation of drug delivery systems that can overcome these limitations <sup>[3]</sup>. Recent research in pharmaceutical nanotechnology looking towards the development of intelligent drug delivery systems which will be capable of responding to biological functioning, target specified tissues, and maintain the therapeutic drug concentrations over a long period of time.

Nanotechnology has come up as a adaptable raise up surface that has the ability to provide competent, cost-effective and environmentally acceptable results to the global challenges facing society. There is a rapid increase in nanotechnology in the fields of medicine and especially in targeted drug delivery [4].

**History of Nanotechnology:** *R. Feynman* is known for his notable work in the field of nanotechnology and he is renowned as the father of nanotechnology (Fig.1).



Fig. 1 Richard Feynman.

The term nanotechnology taken from the Greek words, where ‘Nano’ referring to ‘a billionth’ and the word ‘technology’ is ‘the science of industrial art’. The end results of Nanotechnology or Nano scaled Technology is generally considered a size range below 100 nm i.e (a nanometer is one billionth of a meter,  $10^9$  m). Nanotechnology is an evident and dynamic field where over 50,000 articles have been published annually globally, and more than 2,500 patents are files such as the European Patent Office in recent years. It has the abilities to convert the Nanoscience to the working applications by assembling, measuring, and manufacturing the matters at the nanometer scale (Fig. 2), we can differentiate Nanoscience and nanotechnology as convergence of physics, materials science and biology deals with the manipulations of materials at atomic or molecular level and the ability to observe measures, manipulate, control the matter at nanometer level, respectively [13]. The summary of the history of nanotechnology are as follows-

1. The development of nanotechnology begins with the year of 1958 and the journey continues in the year of 1959 by R. Feynman who initiated thought processes involves in nanotechnology.
2. The term nanotechnology was used by Taniguchi for the first time in 1974.
3. IBM Scanning Tunneling Microscope was introduced in 1981.
4. 1st Nano medicine book ‘Nano medicine’ was published by R. Freitas.
5. National Nanotechnology Initiative was launched for the first time in the year 2000.
6. Feynman was awarded with a prize in 2001for developing the theory of nanometer-scale electronic devices and synthesis the characterization of carbon nanotubes and Nano wires, in Nanotechnology.
7. First policy conference was held on advance nanotech, the first center for nano mechanical systems was established in 2004, Feynman Prize in Nanotechnology was awarded for designing stable protein structures and for construction of a novel enzyme with altered properties.
8. The era of nanotechnology started with the year of 2011[4].

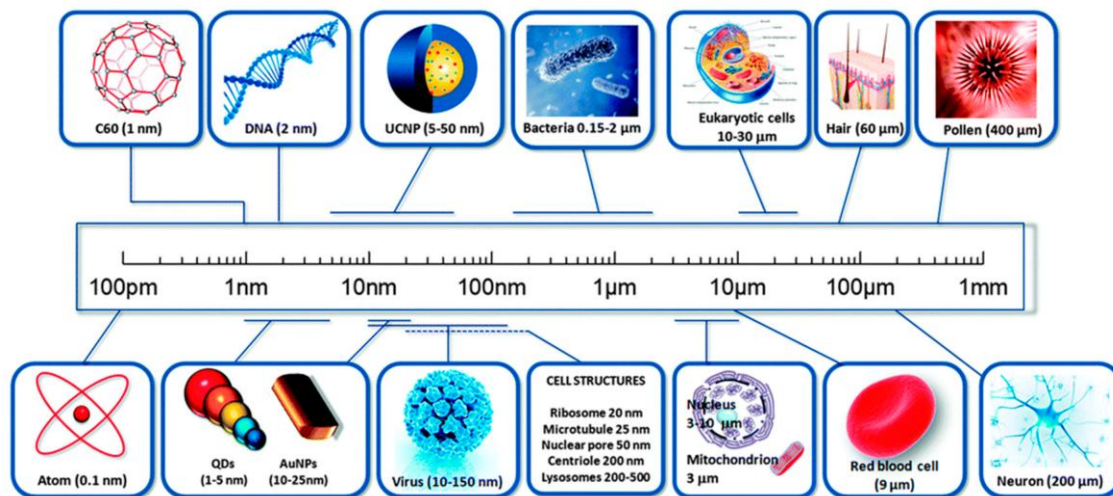


Fig. 2 Atomic or molecular level particles on nanometer scale [13].

### Bioavailability of drug:

Bioavailability defines as the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes reaches to the site of action. The BCS biopharmaceutical system was developed to understand drug’s bioavailability in a better way.

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE LIMITING STEP IN ABSORPTION	EXAMPLES OF DRUG
I	High	High	Well absorb	Gastric emptying	Quinine sulphate, Mefoquinine HCL
II	Low	High	Variable	Dissolution	Nifedipine, Diazepam
III	High	Low	Variable	Permeability	Isoniazid, Salbutamol
IV	Low	Low	Poorly absorb	Case by case	Doxycycline, Theophylline

Table 1: Biopharmaceutical classification system <sup>[5]</sup>

BCS classification system is depend upon the solubility and permeability in the gastro intestinal tract, drug substances are categorized in four BCS classes, as mentioned in Table 1. Due to low solubility, despite high permeability, BCS class II drugs are united with a slower dissolution rate in the GI tract, which results in the low bioavailability of drug. Low aqueous contrast responsible for low aqueous solubility, BCS-class IV drugs also has low permeability, result in less drug absorption. Whereas, BCS class IV drugs sometimes found less permeable to the membrane which result in the poor development of candidature. Since solubility and dissolution enlargement may not be enough to increase their bioavailability. However, these types of compounds unable to be neglected only because of their permeability issues. Therefore, class IV compounds had been developed with the current methods accepted by BCS class II drugs along with absorption enhancers. In the optimization stage, selecting a better drug candidate with more suitable physiochemical characteristics is another formulation development technique for class IV drugs. The development of various strategies to satisfy the biopharmaceutical properties and the advancement of knowledge in the drug delivery systems for oral administrations were both influenced by the formulations of BCS-classes II and IV drugs. 90% of new molecular entities come under BCS class II and IV <sup>[6]</sup>.

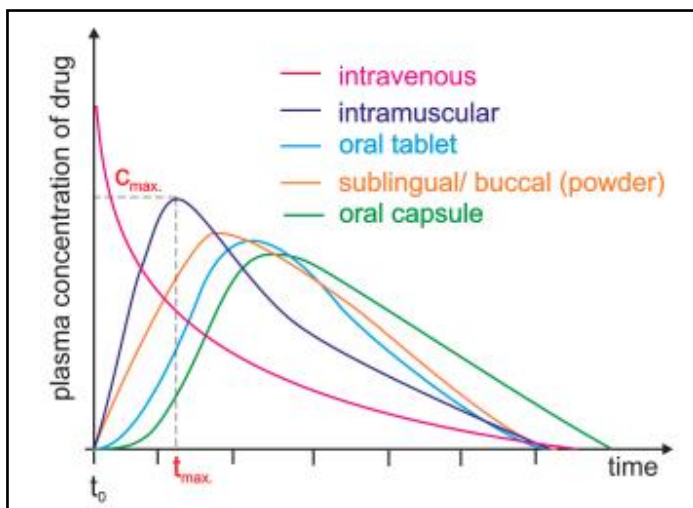
➤ **Necessity of a new review-** The physicochemical characteristics of the drug affect the passage into solution and or transfer across membranes, it includes the solubility in lipids, dissociation rate, pka, and the complex forming potency. After the administration of the drug these factors have influence on the dosage forms. There are several factors which influence the guidance of drug are disease conditions, genetic factors and age of the diseased state. Differences are depends upon the other parameters such as nutrition intake and, health, sex, changes in body during the pregnancy, and hormonal health, sleep-wake cycle of body. Resistance and body defense to toxic substances affects both the individuals and the dependent fetus in case of pregnancy. Diseases also influence the drug metabolism, its absorption and excretion which can only be cure with the food intake and significant fulfillment of nutritional requirements of the body.

Traditionally administration was done by swallowing, inhalation, absorption through skin or injection. Sometimes local administrations were preferred instead of general administration to overcome the treatment impact <sup>[7]</sup>. The advanced pills, robotic pills, liquid drugs are carried directly to stomach. Then the drug is injected into the stomach tissue whereas, the pill gets excreted through the gastrointestinal tract. The modes of micelles, nanoparticles and liposome help to deliver the drug substances at the desired destination or site in body. There are few assessment techniques for bioavailability of drugs such

as in vitro methods, in vivo methods, and pharmacokinetic studies. Almost all the techniques have some limitations and different reliability, resulting inaccuracy in bioavailability assessment. The proper technique need to choose, which will provide reliable and relevant results to overcome the difficulties due to the complexity of bioavailability.

Current advancement in nanotechnology and drug delivery technologies found revolutionary in the field of medicine by improving the bioavailability of drugs. Direct deliveries of drugs to the targeted tissues, drug nanoparticles can easily crosses the biological barriers like membrane barriers of the cell and reach the desired destination or site in the body. This allows the drugs to act more effectively and efficiently, resulting in patient-centered better results [8].

➤ **Scope of a new review-** The manipulation of drugs and other materials at the nanometer scale, the basic characteristics or properties and biological activities of the drug materials can be altered. These tools allows the control a control over the different properties of drugs or agents such as, alteration in solubility and blood pool retention time, controlled release over short or long duration of time, and triggered controlled release or site specific-targeted delivery of drug. By interacting with biological molecules at nano scale, nanotechnology broadens the field of research and application. The nano-devices interaction with bimolecular structure of the body made possible to be understand both in the extracellular and intracellular medium of the human cells. Changes at nano scale allow exploitation of physical characteristics of the drug different from the micro scale such as the volume or surface ratio of the material [8].



**Fig. 2 Plasma drug concentration vs. Time graph [8].**

One of the renowned applications of nanotechnology in medicine is the involvement of nanoparticles in the delivery of drug in the body. There are several applications of nanotechnology in medicine, such as transport of heat, light or other substances to specified cells, such as cancer cells. The nanoparticles are especially engineered to attract towards the specified disease in body, which allow it to treat directly those cells. These techniques reduce the harm to healthy cells in the body and enables early detection of disease. For example, nanoparticles that deliver chemotherapy drugs directly to cancer cells are under development [9].

➤ **Applications of nanotechnology:** The various applications of nanotechnology are as follows [12].

- The Nanobots are being employed in restoring the damaged cells and replace whole intracellular components as much as possible.
- Nanosensors help in the detection of oxygen and carbon dioxide concentrations in our body and the presence of hazardous substances to protect us from infectious conditions.
- Nanoparticles concentrate the radiation to increase treatment efficiency while maintaining healthy tissue in situations such as tumor-attracted radiation.
- It provides improvement in the efficiency of medicine by using the smart materials and nanoparticles for the drug delivery.

## METHODOLOGY FOR BIOAVAILABILITY ENHANCEMENT:

There are many processes are carrying from a long time in history for the enhancement of the bioavailability which are considered as traditional or conventional which had results but they had to be improved or developed with the changes in the generational issues or problems so that the modern methodology was developed in the recent years to withstand the newly developed problems and the futuristic development which felt need of the manipulations of the original structure of the dosage forms with the development of the nanotechnology in the field of medicine and introduced it through the means of nanoparticles. There are basically two types of methods for the enhancement of bioavailability i.e Conventional method and Nanoionization<sup>[9]</sup>.

### 1. Conventional method:

Conventional methods have been used for the enhancement of solubility of poorly soluble drugs for decades. Solid dispersion, prodrug formation, micronization, cyclodextrin inclusion complexes, cryogenic technology, and supercritical fluid technology these are the strategies falls under the groups of conventional methods.

**a. Particle Size Reduction:** The bioavailability of poorly soluble drugs is directly affected by the primary molecular size of the particles. The reduction of particle's size helps to an increase in surface area, which leads enhancement of the dissolution properties of the drugs as the contact angle with the solvent increases. The particle size reduction allows the solvent to diffuse rapidly.

Milling techniques, such as, jet mills, rotor-stator colloid mills, and other mills are used to reduce the particle size of drug raw materials. Thermal stress need be considered when there is a thermosensitive substance under spray drying. A micronization technique allows reduction of particles sizes less than 5 micrometer in diameter and uniform the overall particle sizes. There are several micronization techniques, such as milling, microprecipitation, supercritical fluid technology, and microcrystallization, and spray freezing into liquid, which changes the properties of the micronized drug substance<sup>[6]</sup>.

**b. Solid Dispersions:** Solid dispersion is a good technique for the enhancement of the solubility, absorption and therapeutic efficacy of drug in case of oral dosage forms. Solid dispersion is a group of solid materials where a hydrophilic matrix and a hydrophobic

Drug present in two different compartments. The molecular dispersion of one or more hydrophobic drugs in a hydrophilic carrier is considered as a solid dispersion. Solid dispersions is a method of choice for improving the solubility of dosage form within the pharmaceutical industry. Some hydrophilic carriers for solid dispersions are polyvinylpyrrolidone, hydroxy propyl methyl cellulose (HPMC), Polyethylene glycol, PEG 400, and Plasdone-S630. Pluronic-F68, sodium lauryl sulphate, and Tween-80 are used in solid dispersion formulation as a surfactant. In the mid-1960s the dissolution properties of eutectic melt composed of sulphonamide drug and a water-soluble carrier. Proper hydrophilic carrier in the solid dispersion can improve the solubility of celecoxib, halofantrine, and ritonavir like drugs<sup>[6, 10]</sup>.

**c. Prodrug:** Prodrug is an inactive, chemically modified parent drugs which are used to enhanced the solubility of aqueous substances and can be converted into the active parent drugs through the means of rapid biotransformation. The optimization and decrease or remove of first pass metabolism for pharmacokinetic profile of drug can be possible with prodrug.

There two types of prodrug formulations as- carrier-linked prodrug, where the parent drug is chemically connected to a prodrug molecule, and bio precursor prodrug. Carrier-linked prodrugs are classified as bipartite prodrug or tripartite prodrug due to the direct attachment of parent drug to the carrier by a spacer. Highly permeable HCV NS5B polymerase inhibitor was a prodrug methodology which was introduced to tackle the poor oral solubility.

Microsomes from the liver or the intestinal tissues simulated gastric fluids, plasma, and simulated intestinal fluids were used for in vitro assays to understand the bioconversion rates of structural prodrug derivatives. Rats were used for in vivo bioconversion to evaluate oral administration of prodrug. The carboxylic acid component has been readily converted to glycolic amide esters, which enhances the solubility in lipid-based self-emulsifying drug delivery system (SEDDS)<sup>[6]</sup>. Self emulsifying drug delivery systems are isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, and/or one or more hydrophilic solvents and co-solvents or surfactants. It helps to improve drug dissolution which alters the drug release, absorption at the gastro intestinal tract and can easily penetrate into the surfactant interfacial layer, which enhances its penetration through membrane barriers<sup>[10]</sup>.

## Pros and cons of conventional method:

### Pros-

- Faster dissolution and absorption rate with the reduction of the particle size.
- Improves the stability and manufacturability with the salt formation.
- Solid dispersion allows the enhancement of solubility and dissolution of poorly soluble drugs.
- Lipid based formulations improves the absorption of lipophilic drug and help to bypass the first-pass metabolism.

### Cons-

- Particle size reduction may cause physical in stability and manufacturing challenges.
- Salt formation results pH dependent stability and hygroscopicity.
- Solid dispersion may cause manufacturing difficulties and low drug loading capacity.
- Lipid-based formulations show gastrointestinal irritations and physical stability issues.

**2. Modern method:** Solubility and permeability of a compound are the most essential for the in-vivo absorption of drugs for oral administration.

**a. Nanosuspension:** A nanosuspension is a colloidal dispersion of nanoparticles of the drug particles. They are normally processed with a suitable method and stabilized by a certain stabilizer. In nanosuspension technology, the drug is maintained in the crystalline form with already reduced size of the particles, to enhance the dissolution rate and the improve bioavailability (Fig.2). Particle's size distribution of solid particles in nanosuspension is usually particle size ranging between 200 nm to 600 nm. There are major techniques used for nanosuspension preparations as <sup>[2]</sup>:

- Bottom-up technology (Precipitation).
- Top-down technology
- Media milling (Nanocrystals).
- High pressure homogenization in water (Dissocubes).
- High pressure homogenization in non aqueous media (Nanopure).
- Supercritical fluid method.
- Melt emulsification method.
- Nanojet technology.

**b. Solid self-emulsifying drug delivery systems (SSEDDS):** Solid self-emulsifying drug delivery systems are prepared by combining liquid, semisolid self-emulsifying ingredients into powders, or nanoparticles with differential solidification techniques these formulations are generally oils, surfactant, emulsion, dispersion, self-emulsifying drug delivery systems, solid-lipid nanoparticles and liposomes <sup>[2]</sup>.

### Case study:

• Rapamune (Sirolimus)- Rapamune® (Sirolimus) is targeted to rapamycin in mammals. It is used as an immunosuppressant and found effective in preventing acute rejection and help in preservation of renal function in kidney transplant recipients. Rapamune was a substitution for other immunosuppressant (85.4%). Post-marketing surveillance studies show that it hitherto unknown or unexpected safety issues, providing clinicians with valuable information about the drugs. Rapamune was effective against the kidney allograft rejection and preservation of renal function especially in kidney transplant that had begun to take Rapamune 1 year after transplantation. Rapamune had found safe so it was accepted for the prevention of kidney allograft rejection in Korea. Case study of Rapamune (Sirolimus) [a-  $p < 0.05$  between Sirolimus and Cis group, b- Glomerular filtration rate determined by iothalamate clearance at 1 month post-transplantation, R- acute rejection, Aza- azathioprine, Cic- cyclosporine, GFR- glomerular filtration rate, MMF- mycophenolate mofetil, thymoglobulin induction therapy]<sup>[11]</sup>

**c. Complexation with cyclodextrin:** Cyclodextrin is use as solubilizers for both the liquid-oral and parenteral dosage forms also it increases the solubility of the drug. Cyclodextrin complexation involves the formation of host-guest inclusion complexes with a weak intermolecular force attraction (Fig. 3). There are several methods which are designed for cyclodextrin complexation like freeze drying, spray drying co-precipitation of a cyclodextrin or drug solution with a

extrusion and grinding of slurry of drug in a mortar and pestle. The advantages of this technique included the easy applications on an industrial level, as they are restricted to water dispersible or water soluble carrier matrix material [14].

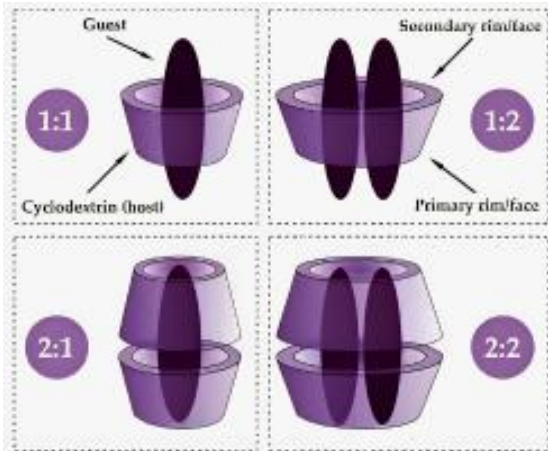


Fig. 3 Complexation of cyclodextrin [14].

**d. Solid lipid nanoparticles (SLN):** Solid lipid nanoparticles are colloidal drug carrier system like a nanoemulsion. But, the main difference is the lipid nature in which the liquid lipid part of emulsion is replaced with a solid lipid at 25°C. There are several methods of SLN preparation such as cold and hot homogenization, breaking of oil in water micro emulsion, high shear homogenization, and ultrasound dispersion. The high pressure homogenization method is considered to be the most effective with its key advantages such as: uniform particle size distribution, high particle content in the dispersions, avoidance of organic solvents, etc [2].

For shortening the medical methods, nanotechnologies found good one. The wearable monitors can be designed to transfer the data back to the hospital systems, simplifying elderly patient care, which often requires attention in remote places. Similarly, the nanomaterial made possible to control the circulating tumour cells. The technological industry uses individual atoms and molecules, Nanoscience, with futuristic possibilities for science, engineering, and technology. It can make an impact and influence the development, characteristics, and implementation of particular atoms and molecules [15].

**Quantum effect in nano-formulations:**

Quantum mechanics is considered the cornerstone for modern physics, allows a basic theoretical framework for understanding the behavioral nature of particles at nanoscale dimensions. The physical and chemical properties undergo several changes as the material is reduced to the nanoscale, due to quantum confinement effects, the motion of electrons and holes becomes restricted to the dimensions as compared to their de Broglie wavelength. The theoretical framework was presented for studying “Quantum Effects and Spectroscopy in Nanoscale Material Analysis” which covers the basic principles of quantum mechanics, the complication of spectroscopic methods, and their synergistic application in the examination of nanoscale materials. Quantum mechanics is a fundamental theory in physics, which describes the physical properties of nature at the scale of atoms and subatomic particles. The core of quantum mechanics is directly related to wave-particle duality, which shows that every particle or quantic entity may be partly describes both in the particles and waves. This duality is critical in nanoscale materials, where the confinement of particles in small dimensions result in the discrete energy levels, which is a phenomenon known as quantum confinement [16].

➤ **Quantum Dots:**

Quantum dots are crystalline semiconductors having a diameter less than 10 nm (Fig 4). “II-VI, IV-VI, or III-V semiconductors are used to make the highest-quality quantum dots”. The hydrophobic ligands present on the surface can be replaced with bifunctional ligands or the entire Quantum Dots can be coated with an amphiphilic polymer layer. Quantum dots allow a comprehensive foundation for building traceable drug delivery systems with the opportunities to enhance patient-centered outcomes to transform cancer treatment pharmacologically. In order to develop quantum dots or drug

nanoparticles preparation for targeted therapy in vivo. Carbon-based nanoparticles, also known as grapheme quantum dots (GQDs). Graphene quantum dots have superior physical, chemical, & biological properties; this allows the successful application of nanomedicine. This is a new class of carbonaceous forms that have gathered a lot of attention due to their remarkably high loading capacity, electrical fluorescent, chemiluminescent, photoluminescent, biocompatibility, and electro-chemiluminescent abilities. Quantum dots represent a promising frontier in nanotechnology for the revolutionary in targeted drug delivery in cancer therapy. This study was performed to provide a comprehensive understanding of how quantum dots can resolve the problem of targeted drug delivery in cancer therapy, it helps to reveal new opportunities for effective and personalized treatment [16]. Fluorescent semiconductor nanoparticles and quantum dots are considered as a versatile platform for designing and engineering of NDD vehicles. Combination of unique physical, chemical, and optical properties with quantum dots allows in-depth study for nanocarrier interactions with biological systems through real-time monitoring of nanoparticles, biodistribution, intracellular absorption of drugs, their release, and long-term nanocarrier belief. The theoretical view for quantum dots can model nanoparticle's cores as small as 2 nm in diameter, which provides a foundation for designing and testing of ultra-compact nanocarriers that readily elimination rapidly from the body through renal clearance. Example, Cho et al. demonstrated that multifunctional iron oxide or zinc oxide core or shell nanoparticles could effectively deliver carcinoembryonic antigen into in vitro, when transplanted in vivo, the tumour volume reduced in mice as compared to free antigen delivery [17].

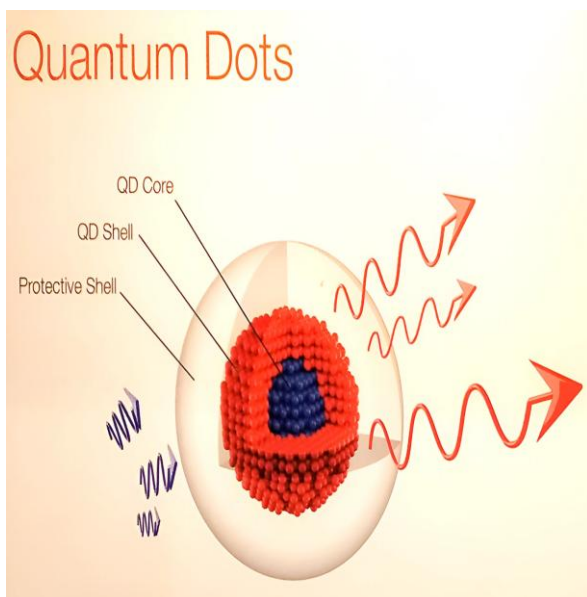


Fig. 4 Structure of Quantum dots [18].

#### CHALLENGES IN ADAPTATION OF NANOTECHNOLOGY:

Clinical translation of Nanoparticulate nanomedicine (NNMs) is an expensive and time-consuming process. This technology is more complex compared to the conventional formulation technology which contains dispersion of a free drug in a base (e.g., tablets, capsules and injections). One of the potential challenges could arise from the sample preparation process, where the variations in nanomaterial dispersion affect the spectroscopic measurements. The interpretation of spectroscopic data may cause complexation by overlapping signals from different quantum occurrence, which requires advanced analytical techniques to disentangle these effects [18]. Traditionally, Nanoparticulate nanomedicine development was completely based on a formulation-driven approach, but

the novel delivery systems firstly engineered and characterized from a physicochemical perspective. There is an alignment of NNM with a pathological application which results in the limitations for the clinical translation of the system which have been identified. Understanding of the relationship between biological and technological collaborations, included the understanding of the influence of disease's pathophysiology on nanomedicine administration, distribution, absorption and efficacy, also the biopharmaceutical relationship between delivery system's properties and in vivo behavior in animals versus humans which is important for the determination of the successful translation of NNMs. Researchers need to minimize the complexity of NNMs and to take into account the final dosage form for human use, for a formulation the potential need to be translated into a clinically applicable therapeutic form for administration or experimental considerations [19].

#### FUTURE DIRECTIONS:

The study reveals that the broader spectrum of quantum mechanics and nanomaterial research, enlightens their implications, asserting the initial hypotheses, and conceding the limitations (Fig. 5). The development of advanced computational models to predict spectroscopic properties based on the characteristics of material simultaneously enhanced the ability to design nanomaterial with customized properties [20]. Nanotechnology can provide the potential for standardized in vitro and in vivo

models and conduct safety tests for the development of new nanoparticles for the beneficiary effects to the human health [21].

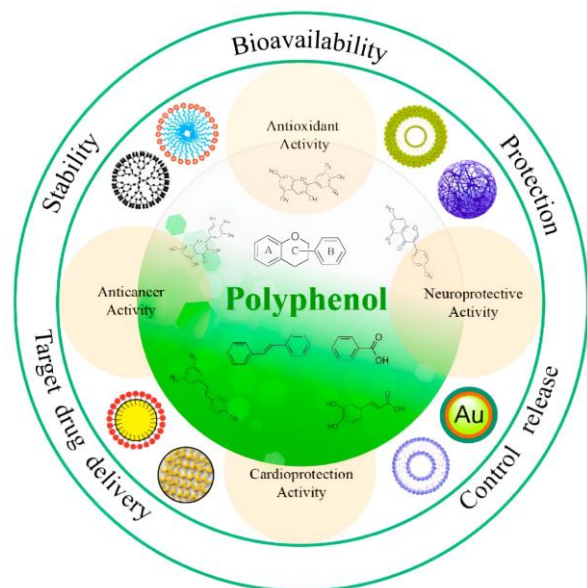


Fig. 5 Future of the Nanoformulations [21].

### CONCLUSION:

Finally it can conclude that the use of nanotechnology in the bioavailability enhancement and the various sections relating to the bioavailability found beneficial but there is safety as well as risk factors which are needed to be removed to run this enhancement processes in a proper resulting manner. The application of nanotechnology leads to the increase in bioavailability and bioactivity of medicinal substances by reducing the size of the particles, several surface modifications, and by attaching or entrapping the medicine. The process of manufacturing can be excellent and simple with the use of both conventional and commonly available nanotechnological

equipments.

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