A Review on "Dispersion characteristics of nanoparticles in Blood flow modelling"

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Abstract

In recent years, there has been done a lot of research in the field of drug delivery using a particulate carrier "nanoparticles" [1]. Nanoparticles played a very significant role in the treatment of many challenging and chronic diseases(cancer, asthma, hypertension, HIV, diabetes, neurological disorders and many cardiovascular diseases) as they have ability to penetrate the tissues and deliver the drugs to the specific sites and provide controlled release therapy with minimized side effects [1,2,3]. Also, acts very suitable carriers for the efficient delivery of drugs to the targeted cells as they can be directly injected into the blood stream through blood flow. This targeted and sustained delivery of nanoparticles has helped in improving the utility of drugs and reduced the drug related toxicity. Recently they have been widely used for delivering drugs, proteins, polypeptides, vaccines, nucleic acids, genes and many more [4]. Their dispersion characteristics (size, shape, surface charge etc.) also helped in delivering drugs to the tumour sites. We can improve their drug delivery by manipulating their characteristics and properties. Further, their ability to target and enter tissues is based on their behaviour under blood flow [5,6] and also their subcellular size, controlled and sustained release therapy result into their comprehensive study as a particulate carrier in the various biomedical fields [4]. Moreover, this review highlights the potential of nanoparticles formulation, advantages and characterization and their biomedical applications [1].

Keywords: Nanoparticles, drug-delivery, blood flow, characterization, cancer therapy, cardiovascular diseases.

Introduction

In recent times, many practices of medicine have been done in research field to fight against various challenging and incurable diseases. Also, various new medications have been developed for the treatment of complex conditions efficiently but at the same time some of them cause severe side effects that do not always outweigh the risk [7]. Although there has been done an extreme progress in recognizing targeted or infected sites and for making more efficient drug molecules and their carriers but still there is the need of improvement in drug delivery system and targeting [8]. The distribution of various cargo elements to the tissues through blood flow is extremely used in the drug delivery [5]. Over the years, various carrier system has been introduced for the controlled delivery of these bio molecules/drugs, out of which nanoparticle drug based system has gained remarkable attention in this field [9]. Moreover this review aims to explore the dispersion characteristics of nanoparticles in blood flow.
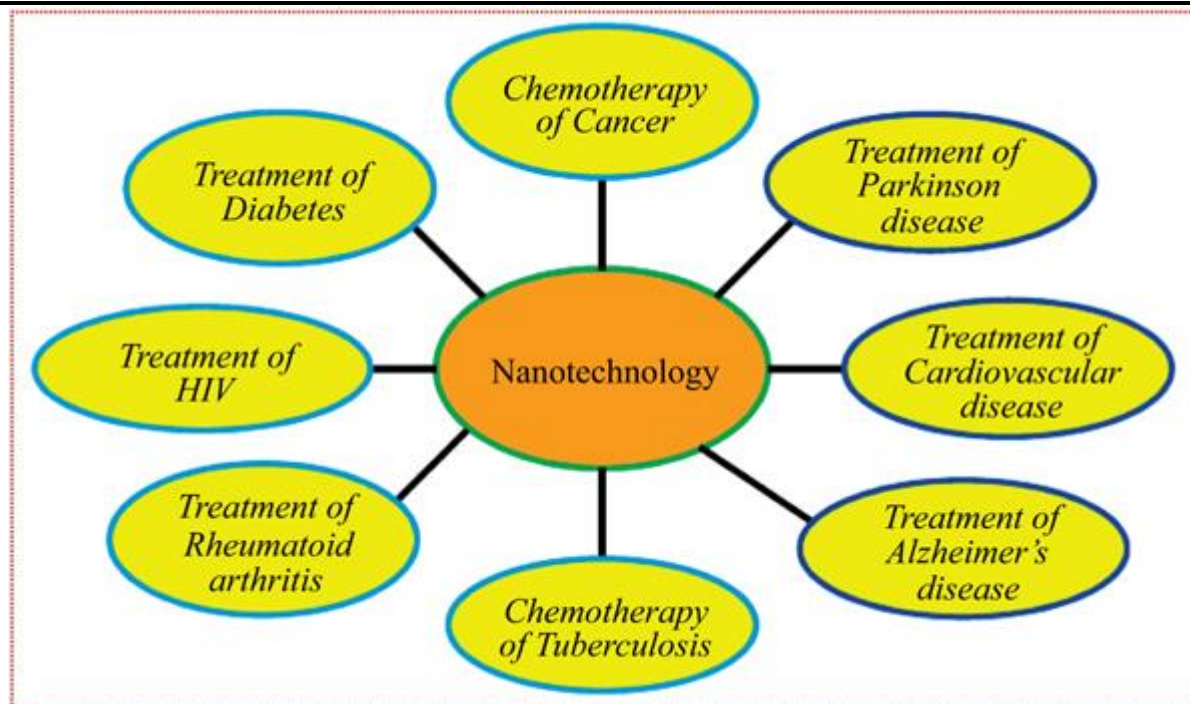
Figure: Nanotechnology [44]

1. NANOPARTICLES-

Nanoparticles are solid, colloidal particles of size ranging from 10nm to <1000nm. In nanomedical science, the size used is <200nm [10]. They acts as a potential carrier, as they are capable of passing through smallest capillary vessels due to their extremely small size, they can perforate cells and tissues cracks to target organs like liver, lung, lymph and spinal cord, due to their biodegradable nature, they show controlled release properties, they are also useful in minimizing harmful side effects and enhancing the efficacy of drugs [4]. The uses of nanoparticles have shown how innovatively drugs are transported and developed in the blood flow [2]. In a drug delivery, they used to trap the biomolecules or drugs into their interior surface [4]. Its best use has been seen in biomedical fields.

TYPES OF NANOPARTICLES-

1.1 Polymeric nanoparticles-

Polymeric nanoparticles are submicronic colloidal carriers of size <1µm. As compared to other colloidal carriers polymeric nanoparticles have great advancement in treating diseases and disorders. Due to their physiochemical properties like size, surface potential, hydrophilic-hydrophobic balance they have been recognized as potential drug carriers for bioactive ingredients such as anticancer drugs, vaccines, peptides, oligonucleotides etc [4].
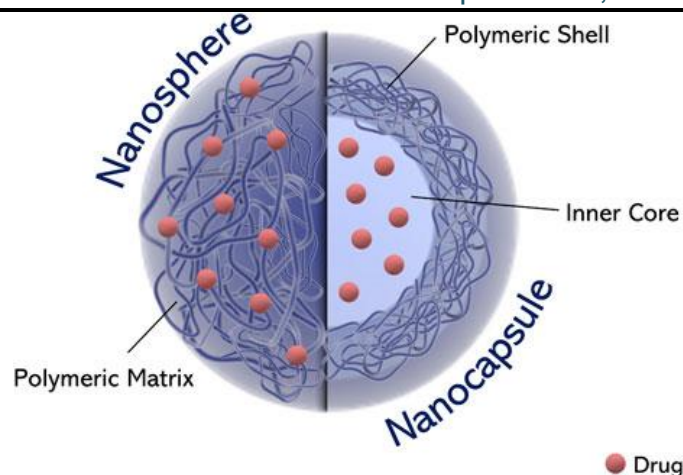
Figure- Structure of polymeric nanoparticle [46]

1.2 Solid lipid Nanoparticles

Solid lipid nanoparticles are the particles made up of solid lipids having mean diameters range between 50-1000nm[4]. They are used as carrier system for water dissolvable medication. They are new potential colloidal transporter system and preferable alternative materials to polymer which is discernible to oil in water emulsion for parenteral nourishment.
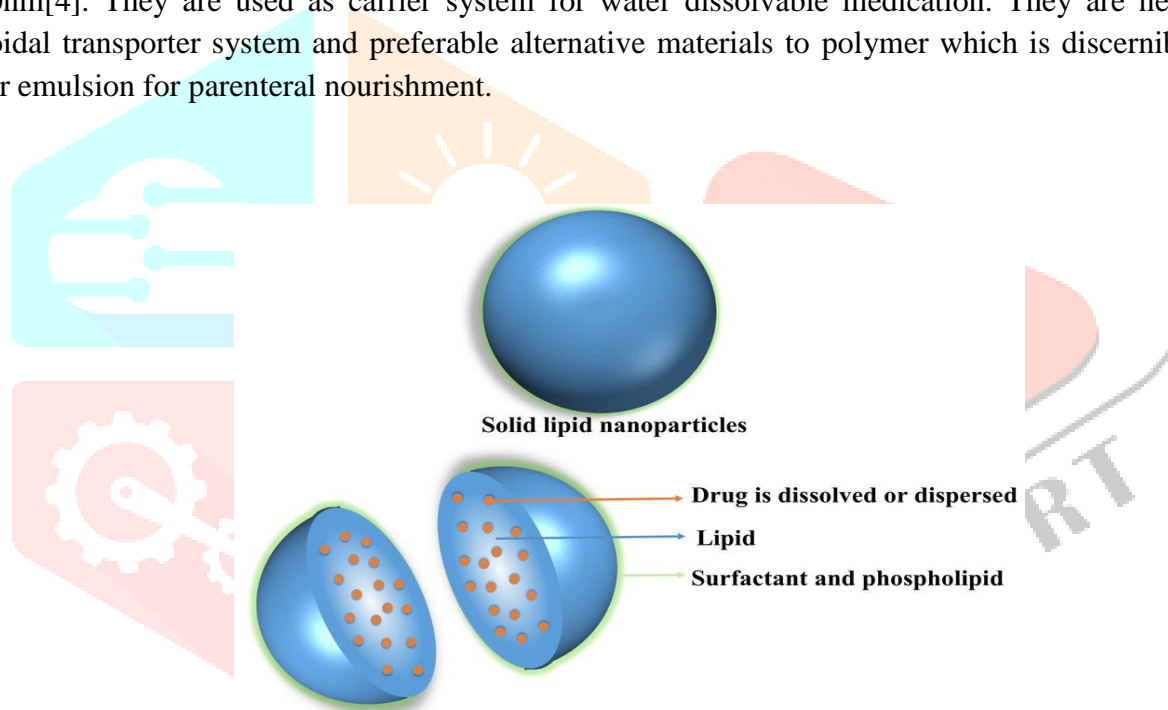
Figure – Structure of Solid Lipid Nanoparticle [43]

1.3 Metal Nanoparticles

Metal nanoparticles are made up of pure metals like platinum, silver, titanium, iron, etc. or their compounds. They are covered with a shell that is made up of organic or inorganic material or metal oxide.Metallic nanoparticles in present days are widely utilized in biomedical sciences and engineering. They show a huge potential in nanotechnology as they can be easily synthesized and modified which allow them to conjugate\bind up with antibodies and various drugs. "Sohail Nadeem and Shagufta Ijaz in 2015 discussed about the mathematical model of blood flow through a tapered elastic artery with overlapping stenosis. Equations of impedance resistance to blood flow and wall shear stress are computed. The effect of different flow parameters like pressure gradient, temperature and velocity profiles are discussed with the help of graph and they concluded that contribution of metallic nanoparticles disclosed that it is important to reduce consequences of wall shear stress and resistance impedance to flow [11].
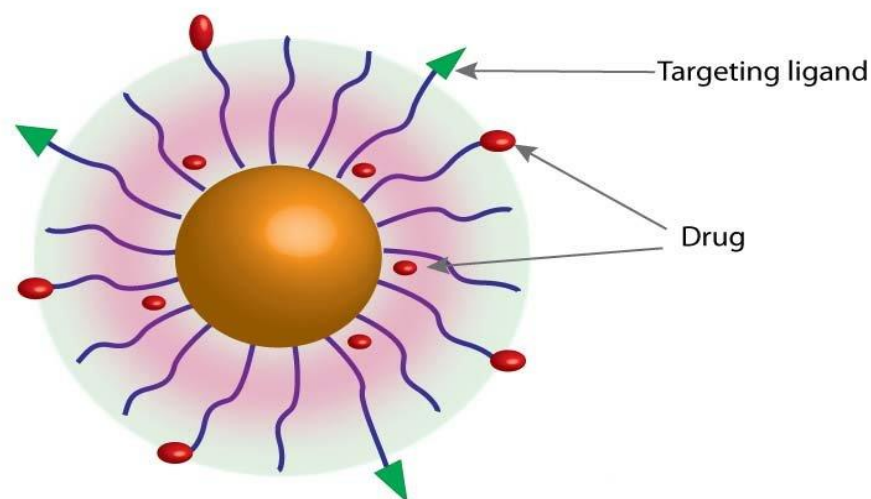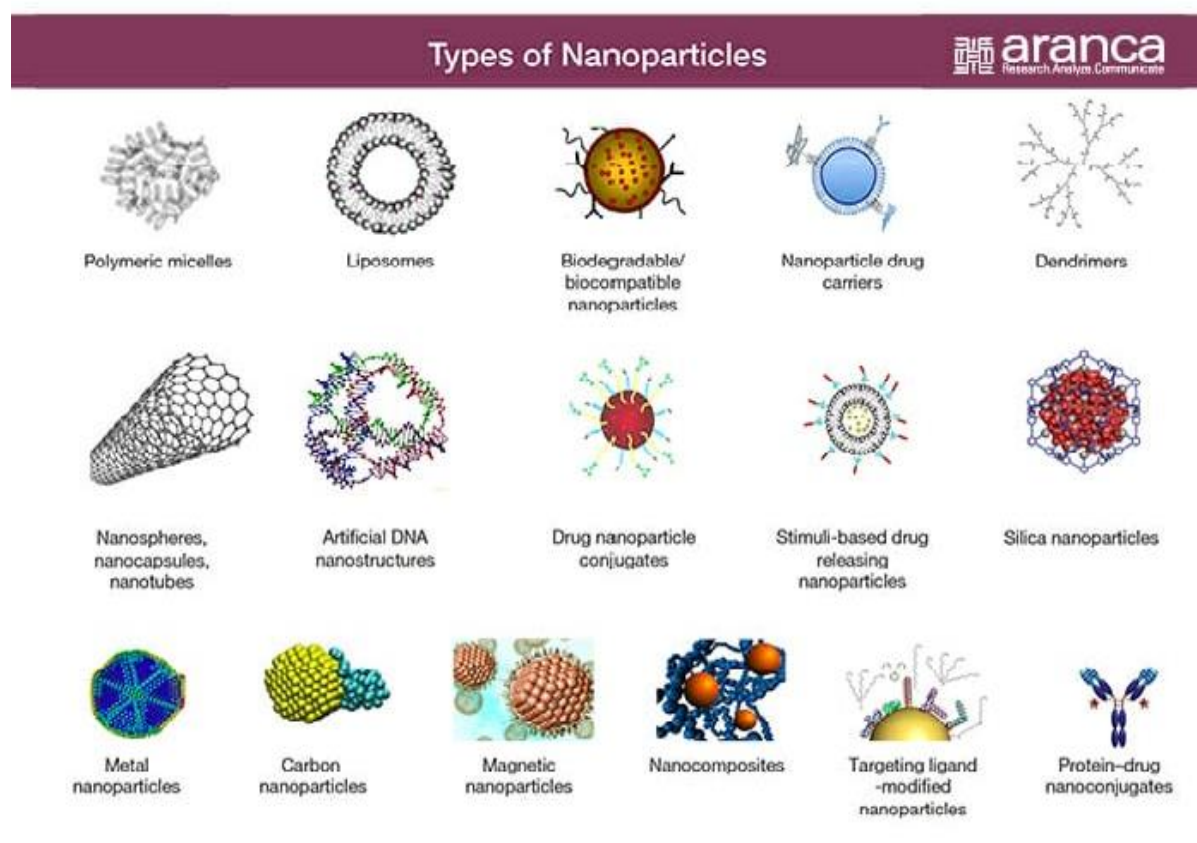
Figure: Structure of Metal Nanoparticle [43]

2. BLOOD

Blood is non-Newtonian fluids consist of plasma, formed elements. Plasma accounts for 55% of blood fluid. It contains proteins, glucose, minerals, hormones, CO2 and blood cells. Blood constitutes 7% of human body weight. Average adult has a blood volume of approximately of 5 litres comprise of plasma, red blood cells, white blood cells, and platelets. RBC constitutes approx. 45% of whole blood, plasma roughly 54.3% and WBC of 0.75%. Blood performs various function within body like supply and exchange of oxygen and carbon dioxide, supply of nutrients like glucose, amino acids etc., removal of waste materials, immunological and messenger functions etc.

2.1 Blood circulatory system-

Blood circulatory system, also known as cardiovascular system or vascular system. It is an organ system which allows blood to circulate and transport nutrients, oxygen, carbon dioxide, hormones etc. from one cell to another. It helps in the nourishment of the body and better immunization, maintains pH and temperature of the body.

Figure: Circulatory System [16]

2.2 Blood flow and Blood Flow Rate-

Blood is circulated by heart through the vertebrate vascular system that carries oxygen and nutrients to the blood tissues and waste materials away from it. Blood circulatory system consist two components - systematic circulation and pulmonary circulation. Blood circulatory system also known as cardiovascular system or vascular system, it is an organ system which allows blood to circulate and transport nutrients, oxygen, carbon dioxide, hormones etc from one cell to another. It helps in the nourishment of the body and be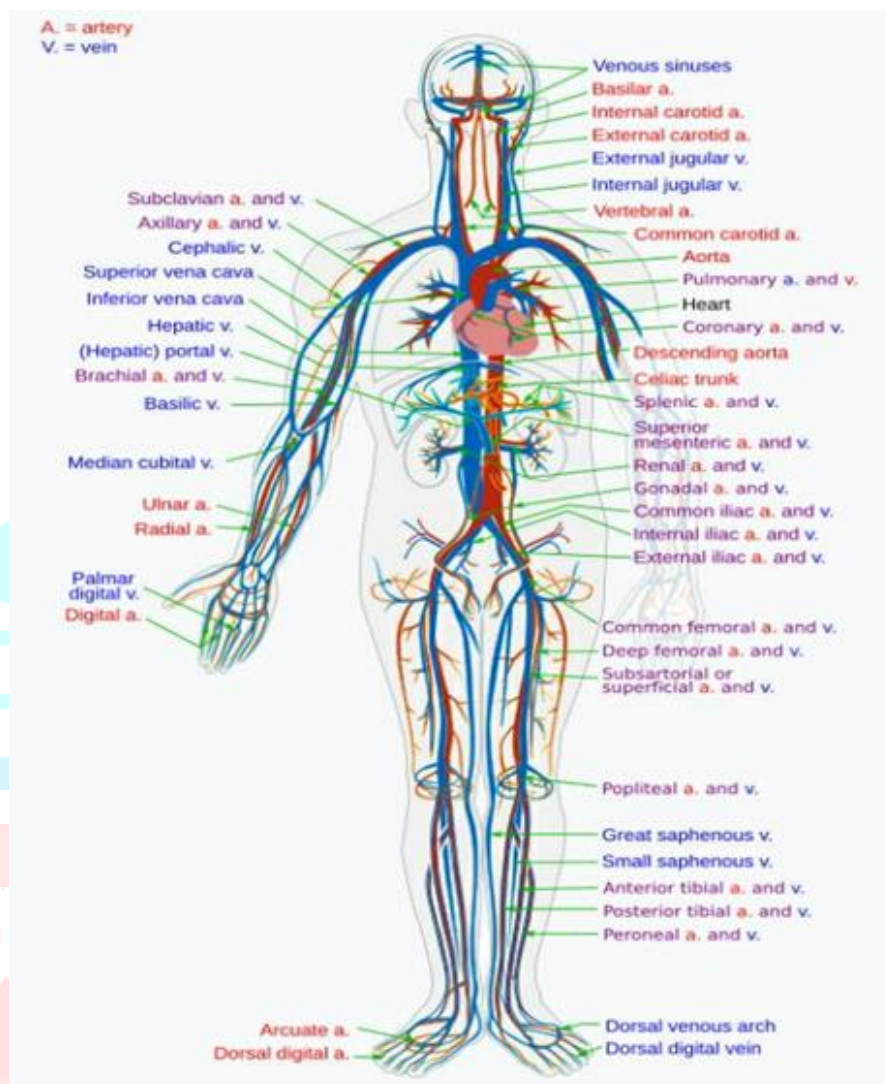tter immunization, maintains pH and temperature of the body. Many diseases harm circulatory system like cardiovascular disease which harms the cardiovascular system and lymphatic diseases that harms the lymphatic system. The volume of blood that flows through any tissue in a given period of time is called as local blood flow and it is generally expressed in ml/min.

Blood flow rate through different organs[17]-

	Percent of Cardiac Output	ml/min	ml/min/100g of Tissue Weight
Brain	14	700	50
Heart	4	200	70
Bronchi	2	100	25
Kidneys	22	1100	360
Liver	27	1350	95
Portal	(21)	1050	
Arterial	(6)	300	
Muscle (inactive state)	15	750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid gland	1	50	160
Adrenal glands	0.5	25	300
Other tissues	3.5	175	1.3
Total	100.0	5000	

3. CHARACTERIZATION OF NANOPARTICLES:

Nanoparticles are generally characterized by their size, morphology and surface charge with the help of some advanced microscopic techniques like SEM (scanning electron microscopy), TEM (transmission electronmicroscopy), AFM (atomic force microscopy). The average particle diameter, their size distribution and charge has a great effect on physical stability and in vivo distribution of the nanoparticles [2].

3.1 Size effect:

Nanoparticle size distribution and morphology plays an important role in the characterization of nanoparticles. Its major application has been in the drug release and drug targeting. From the various studies, it has been found that particles smaller in size offer large surface area, which will result in transportation the drugs to the particles surface, which will lead to the fast drug release. As a result drawback, there is an aggregation of smaller particles during storage and transportation of nanoparticle dispersion. To avoid the leakage into blood capillaries, the size used must be large enough but not too large to0 get affected by macrophage clearance [1].

3.2 Shape Effect:

The nanoparticles shape is an important factor in determining blood circulation time and vessel wall adhesion [19, 20]. Non-spherical nanoparticles shows greater resistance to microparticle sequestration in the blood flow [21]. Non-spherical nanoparticles marginate more readily than the spherical nanoparticles and result in establishing firm adhesion to vessel wall [22]. Gentile et.al [22] shown that disc-shaped and hemispherical nanoparticles outperformed their spherical counterparts in near-wall margination. Toy et.al [23] given the experimental evidence that gold nanorods display higher margination propensity than nanospheres [24]. Vahidkhah and Bagchi computationally investigated the effect of shape on drug carriers at different stages in the margination-adhesion cascade [24]. Non-spherical nanoparticles can flow through capillaries in much better way, causing other biological consequences. (Le at al.2009 and Verma at el. 2012)

3.3 Stiffness Effect:

In comparison to the rigid particles like WBCs and platelets, deformable particles shows more complex behaviour in blood flow, due to their transverse motion [24]. Various therapeutic particles are considered as deformable particles, like polymer particles and liposomes [25]. The behaviour of deformable particles to drift away from the wall to the centre of the vessel, extend their circulation time in blood flow [24]. The stiffness of nanoparticles receives relatively less attention as compared to the size, shape, and surface functionalization [24]. On the nanoscale, Anselmo et al. [26] shown that the softer nanoparticles (10kpa) were better than softer nanoparticles (3000kpa) in blood circulation time and targeting specific sites both in vivo and vitro which also showed that tuning nanoparticles stiffness helps in extending circulation time, reducing macrophage uptake and improving targeting. Hence, in conclusion there is a decrease in the margination probability with the increase in Ca (inversely proportional to stiffness), which also showed that rigid particles are more readily to marginate than the soft particles [24].

3.4 Surface Charge:

Surface charge of nanoparticles has remarkable role in the biological systems as it determines many of their interactions [41, 42].

3.5 Other factors:

Moreover, surface coating and nanoparticle structure also influence its biocompatibility and toxicity. The concentration of nanoparticles is a major factor that contributes to the toxicity of large particles.

4. Nanoparticles in the treatment of different diseases-

4.1 Cancer therapy-

Over the past years, several efforts have been made in the development of nanomedicines such as nanoparticles, micelles, dendrimers, or liposomes, for the specific delivery of anticancer drugs to the tumour sites [28]. The journey of nanoparticles to the tumour sites for the cancer therapy follows some key steps [29, 30]

(1) Transport and circulation in a complex vascular network with RBC, WBC and many others.
(2) Movement from central stream of the blood flow to the vessel wall region and firm adhesion to the endothelium near the tumour site
(3) Through leaky vasculatures, diffusion into tumour tissues
(4) Recognition and internalization by tumour cells

Due to the margination behaviour of nanoparticles, the journey of encapsulated drug molecules becomes easy and can be more proficiently delivered to the targeted tissue, which will help in the interaction of nanoparticles with the vascular wall. This will ultimately result the nanoparticles to better recognize the biophysical and biological abnormalities, such as the presence of fenestrations or the expression of specific receptors on the surface of endothelial cells. The margination property of nanoparticles and their subsequent adhesion to the endothelium helps the nanoparticles in transmigrating across endothelial walls and in entering a targeted area of tissue. Finally resulting in delivering the encapsulated drug molecules to the tumour sites. The various dispersion characteristics of nanoparticles(size, shape, surface property and stiffness) are responsible for their margination tendency[24].

Studies about their intrinsic properties, including experimental [31-33], theoretical [30] and numerical [34,35], for the margination behaviour of nanoparticles, have revealed the physical mechanism. There are various studies which have shown that the nanoparticles which are larger in size easily marginate into the near vessel wall region, while the one smaller in size are trapped between RBCs and circulate through blood flow [24].
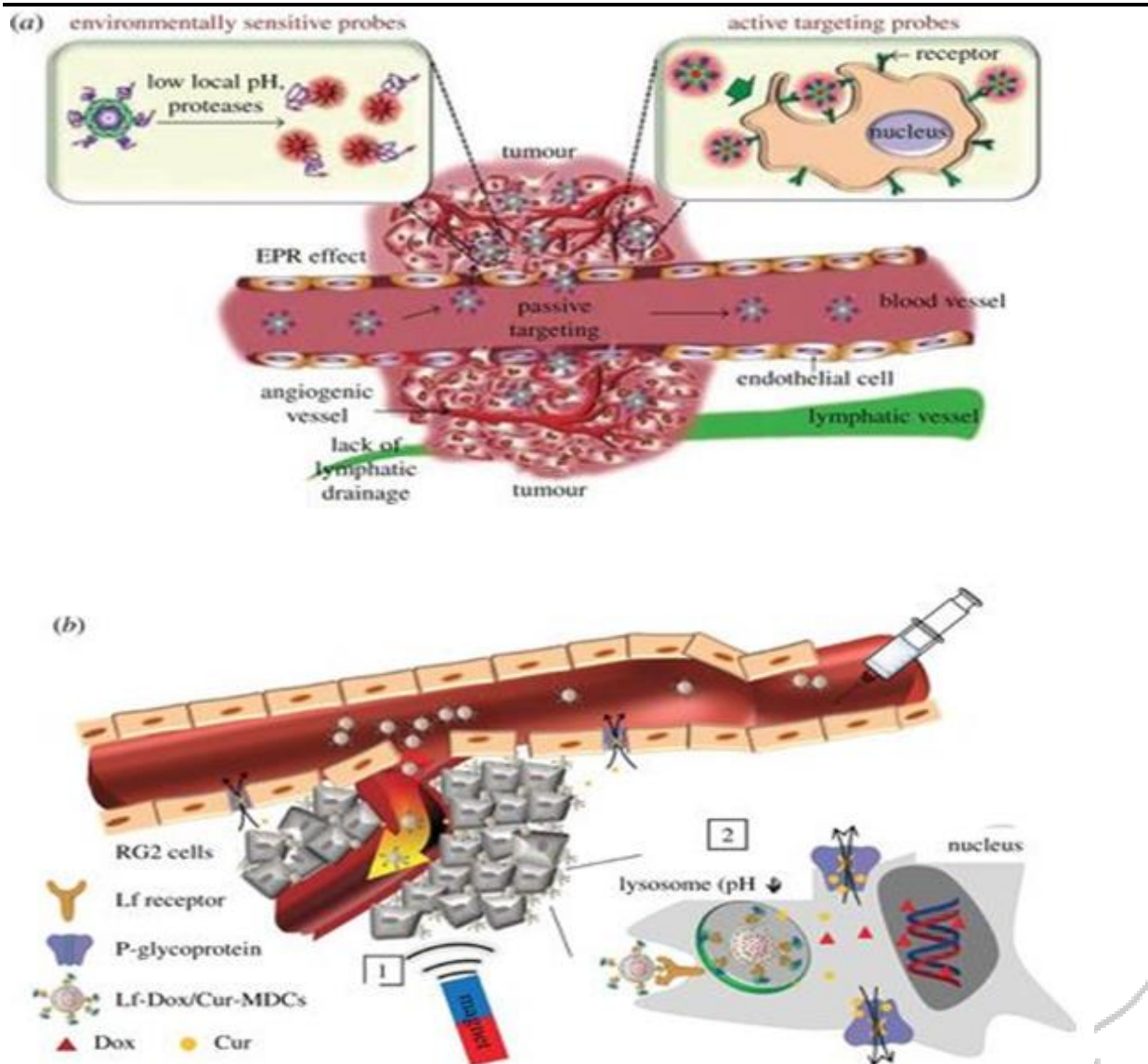
Figure: Representation of NP-based drug delivery for cancer treatment [24]

4.2 Cardiovascular diseases-

Cardiovascular System consists of the heart and its blood vessels. These diseases are the leading causes of millions of deaths globally. Cardiovascular diseases are the group of heart and blood vessel disorders. It is actually related with the growth of fatty deposits inside the arteries that is also known as Atherosclerosis and it increase the risk of formation of blood clots. Nanoparticles are designed as a drug carrier to provide a sustained curative stimulus at the injured tissue. Nanotechnology helps in the early detection and the better treatment of cardiovascular diseases. The remarkable role off nanoparticles in cardiovascular diseases is superior medical imaging, targeted delivery of drugs and targeted delivery of nanoparticle to kill ailing cells. Nanoparticle based drug delivery system evade the problems linked with traditional drug delivery systems like their non-specificity, severe side effects, and damage to the normal blood cell. By modifying the size, shape and surface modifications can better change its in-vivo pharmacokinetic and pharmacodynamic data and help in better therapeutic strategy [36,37,38].
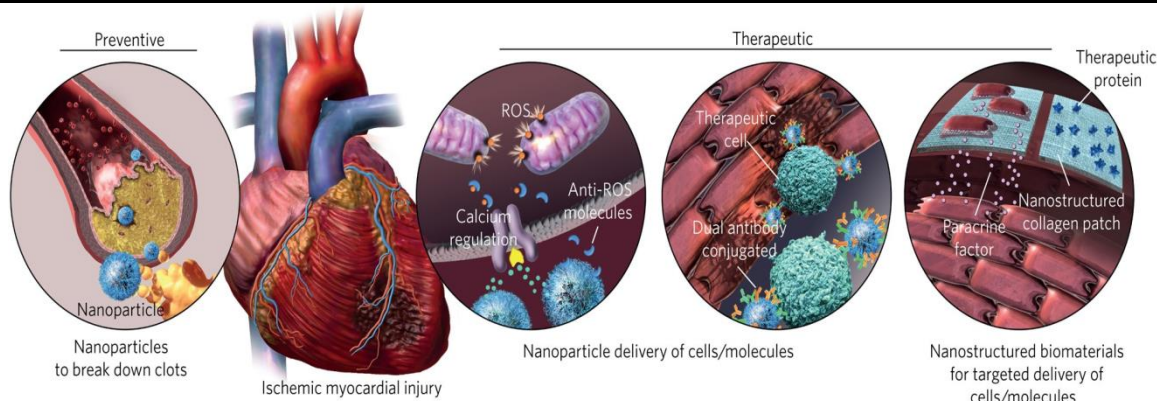
Figure: Application of various nano platforms in the prevention and   treatment of cardiovascular disease [45].

Yuting Sun, Yuexin Lu et al. in 2020 discussed about the roles of nanoparticles in stem-based cell therapy for cardiovascular diseases. In cardiac diseases nanoparticles can easily deliver gene in stem cell and track the stem cells for long-term monitoring and intensify retention after transplantation. They found that nanoparticles in peripheral vascular disease treatment facilitates stem cell therapy, copying the extra cellular matrix and acting as soft non-viral gene delivery tool.

Types of nanoparticles used in treatment of cardiovascular diseases:

1. **Quantum Dots:**

   Quantum dots are nanoscale, low-dimensional semiconductor material in 3-D that do not exceed twice the exciton Bohr radius of semiconductor material. They are spherical and their diameter is between 2 and 20nm. Due to their distinctive optical properties, they emit brighter and stable fluorescence. Rafieerad et al. in 2019 studied about the 0D titanium carbide Mxene quantum dots can be incorporated in the chitosan-based hydrogel to generate 3D platform with better physiochemical properties for stem cell delivery and its repair.

2. **Solid-lipid nanoparticles:**

   Solid lipid NPs are mainly of size ranging from 50nm-1000nm[4]. It is composed of solid lipid core surrounded by layer of surfactant in aqueous solution having different potential combination of lipid and surfactant. Solid lipid NPs have efficiency to overcome several physiological barrier that obstruct drug delivery to tumour and it is also capable to escape multi drug delivery [43].
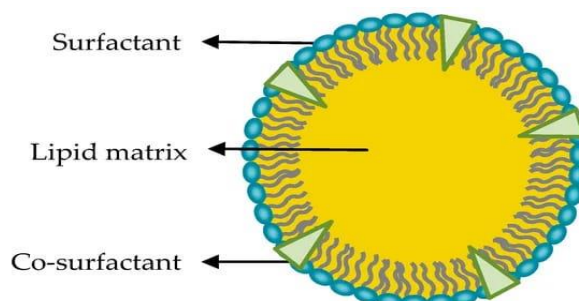

Figure: Structure of solid lipid nanoparticles showing surfactant co-surfactant and lipid matrix [44].

Other types-

Some other types of nanoparticle includes micelles, lipid-calcium-phosphate, protein-based NPs and polymeric nanoparticles [44, 45].

3. Alzheimer-

Neurodegenerative diseases are rapidly increasing with the aging population. Among all the neurodegenerative disorders Alzheimer is the most common among elderly people. Alzheimer occurs to due the deposition of amyloid-fibrils in amyloid peptide and tangles are found as intracellular deposit in brain made up of twisted strains. It is a progressive disease which destroys memory, loss of lexical access, impairment of judgement clinically. Targeted drug delivery to central nervous system for treatment of neurological diseases such as Alzheimer confined due to the limitation possessed by Blood-Brain-Barrier. Commonly used nanoparticles in the treatment of Alzheimer disease are polymeric nanoparticle, gold nanoparticle, gadolinium nanoparticle, selenium nanoparticles, protein based nanoparticles etc [39]. Mustafa, Nazirouglu, Salina et al. in 2017 discussed about the clinical therapeutic of Alzheimer disease by use of selenium nanoparticles and they found that oxidative nanoparticles decreased the activities of reactive oxygen species scavenging enzymes likesuperoxide-dismutase and catalase in the brains of rats. They found that Se-rich nanoparticles have potential to treatneurodegenerative-disorders.
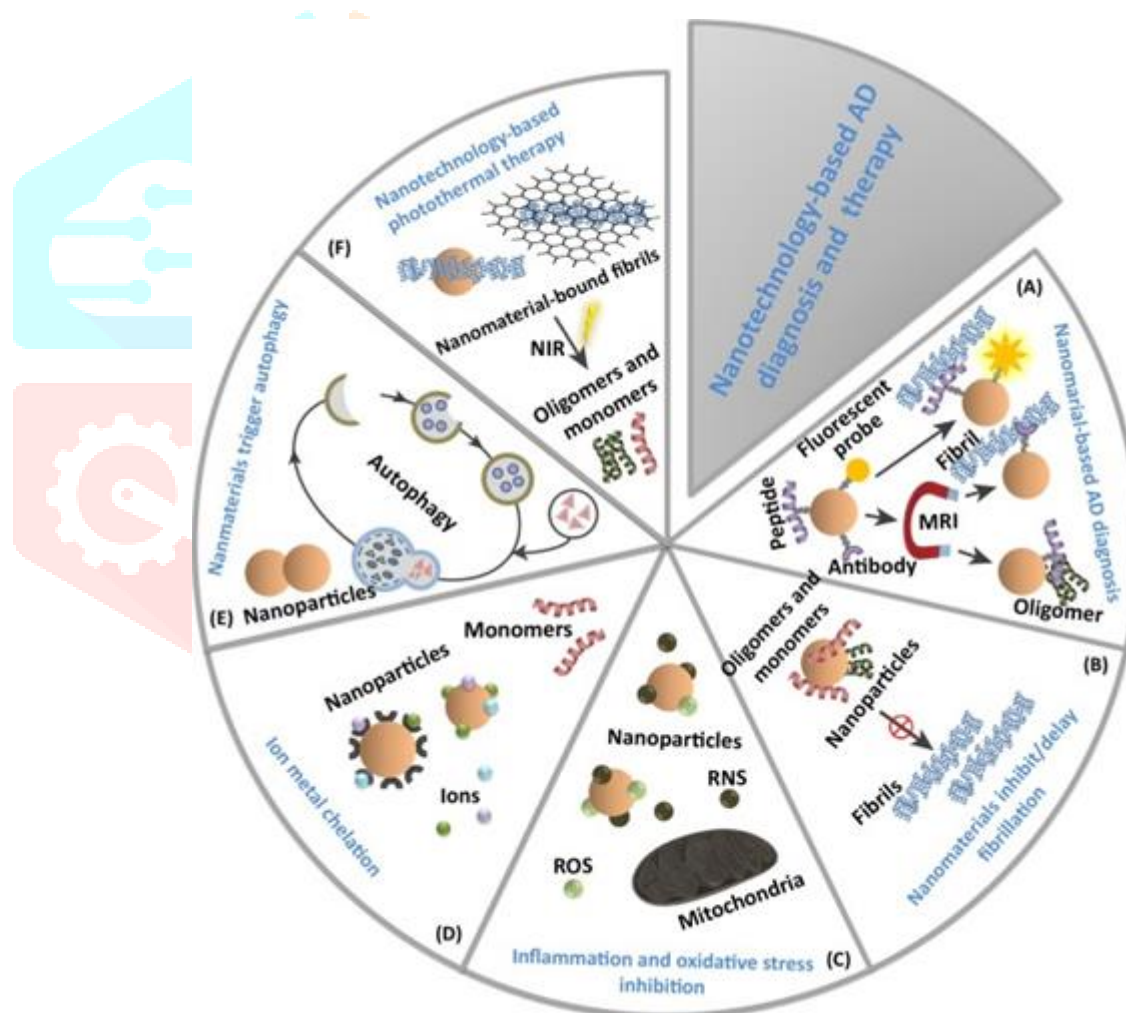

Figure: Advances in Alzheimer's Diagnosis and Therapy [45]

Mathematical modelling-

The representation of our world problems into mathematical problems, solving the mathematical problems and interpreting these solutions in the language of the real world are termed as 'Mathematical Modelling'. This representation helps in understanding the significant properties of the real world and which may allow

some form of prediction of future events. In fact every branch of knowledge has two aspects, one of which is theoretical, mathematical, statistical and computer based and other of which is empirical, experimental and observational. Mathematical modelling is essential to the first of these two aspects.

It is assumed that the flow of blood in the right coronary artery, governed by the Navier-Stokes equations:

$$\rho(\partial v/\partial t \ + \ v.\nabla v) = -\ \nabla.\tau - \nabla P$$

And the continuity equation for an incompressible fluid

$$\nabla.v = 0$$

In these equations, v is the three dimensional velocity vector, t time. P pressure, ρ density. Writing the Navier-Stokes equations during this form allows the pliability to use an arbitrary non-Newtonian blood model.

Gentile et al. (2008) discussed about the transport of nanoparticles in blood vessels under the effect of vessel permeability and blood rheology. Tan et al. (2012) studied the impact of red blood cells os nanoparticles transport and dispersion.
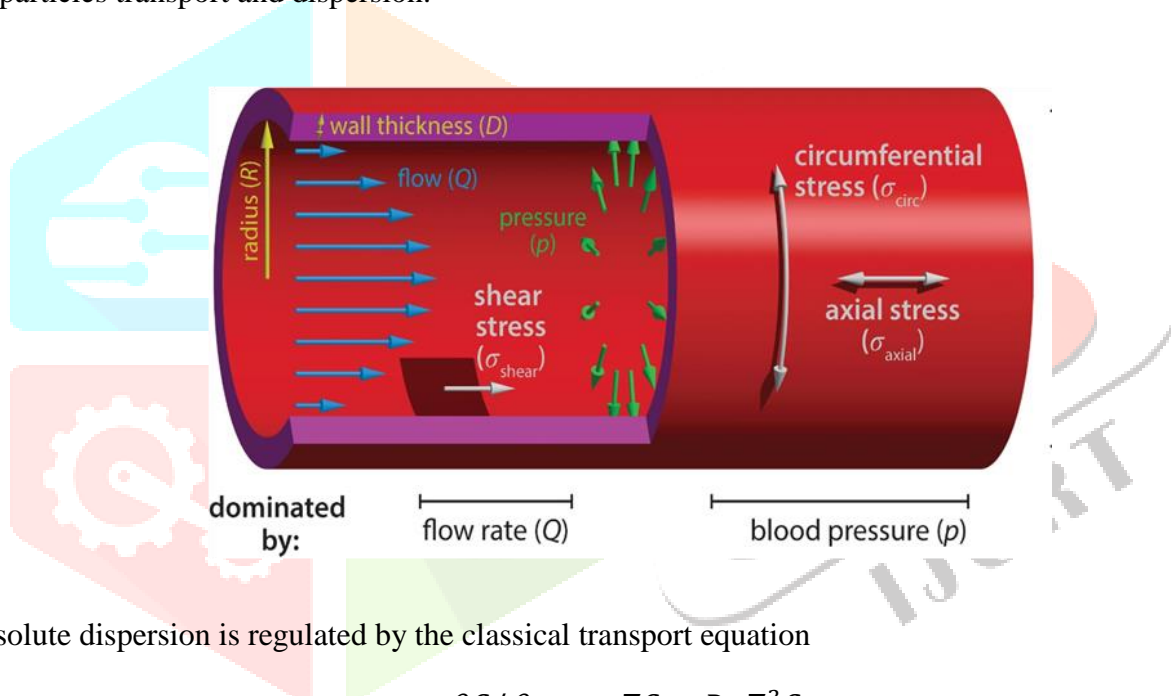
The solute dispersion is regulated by the classical transport equation

$$\partial C/\ \partial t \ + u.\nabla C = D_m \nabla^2 C$$

Where C, the local solute concentration, u is the fluid velocity field and D_m is the solute Brownian diffusion coefficient in a quiescent fluid. The transport equation emphasizes that the solute dispersion is governed by pure convection ($u.\nabla C$) and pure diffusion ($D_m\nabla^2 C$) Taylor and Aris introduced the idea of an effective longitudinal diffusion coefficient Deff for both the diffusive and convective contributions.

To study the longitudinal diffusion and dispersion authors have considered the circular capillary of finite length, where the blood flow is described by non- Newtonian fluids.

Blood flow-derived forces, Schematic representation of the mechanical forces experienced by endothelial cells due to blood circulation inside the vessels. The blood flow, measured by the volume flow rate Q, causes a shear stress σ on the wall.

Conclusion –

Nanoparticles play an important role in biomedical sciences for the treatment of many challenging and incurable diseases but at the same time it has also some potential limitations. From this review we have concluded that by manipulating the characteristics of nanoparticles (shape, size, surface charge, and stiffness) we can enhance the drug delivery to the targeted or infected sites. Nanoparticles are small in size and are uniquely suited to create system that can better deliver drugs to tiny areas within the body and its qualities like biodegradability, biocompatibility, readily availability and low toxicity provides a better future for drug delivery.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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