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RESEARCH ARTICLE

A REVIEW ON MATHEMATICAL MODELS FOR NANOPARTICLE DELIVERY IN THE BLOOD

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Abstract

One of the ubiquitous causes of deaths are the Cardio Vascular Diseases or CVDs. The implementation of nanotechnology in the treatment of CVDs has evinced better bio-compatibility and enhanced cell interactions. This provides a strong potential for their mathematical modeling with the diseased blood vessels. In our current study we have reported various mathematical models used for the treatment of CVDs employing nanotechnology. Mathematical modeling provides a tool to comprehend the type, shape and size of the nanoparticles that can be employed as possible drug delivery systems. Mathematical models help to predict how nano-drugs have many improvements like expanded drug loading capacity and programmable pharmo-kinetic properties over the conventional drugs. The amalgamation of mathematical models with clinical data provides for designing these optimal therapies. This review encapsulates the current state of mathematical modeling approaches to treat CVDs using nanoparticle targeted drug delivery.

Introduction:-

Mathematical modelssimulate a few hundred blood vessels and generate information in a suave format for the whole circulatory system. The mathematical models take into account nanoparticle circulation, endocytosis and drug release. Therefore, these theoretical models outstrip the curbs foisted by experimental data in-availability. Thus, it may be used to predict drug solubility and diffusion coefficient more convincingly before clinical trials.

Nanodrugs are a revolution. They offer a robust mechanism for providing the remedies of cardiovascular diseases due to their capability of interacting with cellular processes and guiding their functions. The pharmaceutical use of nanotechnology offers persistent and controlled delivery. Mathematical modelling of nanoparticles in the blood flow offers proper functioning and designing of nanoparticles through complex vasculature that consists of blood vessels of different diameters, fluctuating from centimeters to microns. Mathematical models predict pressure, velocity, temperature etc. to examine the nanoparticles interactions in a systematic way. Models of ordinary differential equations, partial differential equations, matrices, linear programming and algebraic equations are used for scheming the nanoparticle targeted drug delivery models. These theoretical screenings are relatively easy in computer simulations. The models help in accomplishing smarter clinical designs because they replicate the drug delivery procedure covering all lengths and time dimensions.

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The promising ability of nanotechnology still lies unexplored. Through this review article we have made an attempt to give a gist of the mathematical models for nanoparticle delivery in the blood. We have considered a number of research papers and review articles with prime focus on the mathematical models. We have categorized various features of nanoparticles and numerous mathematical models on diffusion, dispersion, Newtonian and non-Newtonian flows, magnetic effect, heating effect, size and shape dependency of nanoparticles to outline the relevant mathematical principles and perspective to develop and design the mathematical models.

Diffusion And Dispersion Models

Researchers, over the past few years, have been working on the approaches to escalate the effective quantity of nanoparticles directed at the diseased site whilst simultaneously reducing their dispersion in the vessels. Nanoparticles must reach the diseased site by convective or diffusive transport in the cardiovascular system.

The noteworthiness of permeability of blood vessel walls and the rheology of blood on the transfer of nanoparticles in the blood is of fundamental understanding for nanoparticle delivery via diffusion. The effective dispersion of the nanoparticles is treated with due attention given to their size and volume fraction that is critical for designing nanomedicine-based drugs.

The notion of effective diffusion coefficient D_{eff} was proposed by Aris [5]

$$D_{eff} = D_m + \frac{{r_e}^2 U^2}{48 D_m} \quad (1)$$

Where r_e is radius of the tube, U is mean flow velocity

$$\frac{r_e U}{D_m} = Pe \quad (2)$$

is the Peclet number.The longitudinal dispersion of nanoparticles in the blood vessel is of vital importance in the delivery of nanodrugs. Decuzzi et al. [6]obtained a common expression for D_{eff} in a Newtonian fluid model in a permeable capillary :-

$$D_{eff} = D_m \left[1 + \frac{Pe^2}{192} f(\Omega, \Pi, z')\right] \quad (3)$$

Where π is the permeability parameter, Ω is the pressure parameter, z' is the longitudinal non-dimensional coordinate along the capillary. They studied the effective diffusion of nanoparticles in permeable and non-permeable capillaries. They showed that for a specified capillary size and under suitable hemodynamic conditions, there exists a critical radius for which effective diffusion through the capillary is lowest. They also proposed that the size of nanoparticle should be chosen depending upon the mass of tumor, its malignancy and state.

Gentile et al. [7] considered blood in character of Casson fluid and perused the outcome of permeability and rheology of blood for the longitudinal transport of nanoparticles in blood vessels. They showed that an enhancement in value of rheological parameter and permeability the effective diffusion is reduced. Gentile and Decuzzi[8] presented a more precise model to outturn the diffusion of nanoparticles in blood vessels by studying the time dependence on dispersion of nanoparticles in blood. They showed that since the steady state is achieved, the effective diffusion did not depend on the plug radius and wall permeability.

Shaw et al. [9] studied the ascendancy of nanoparticle volume fraction, pressure distribution, permeability of blood vessels and yield stress on the productive nanoparticle dispersion. They employed two-layered model of blood considering a core region of aggregated red blood cells surrounded by a cell-free layer of plasma. They showed that the effective diffusion of the nanoparticles in the blood decreased with an amplification in volume fraction of nanoparticles.

Bali et al. [10]investigated the effect of rheological parameters, permeability parameters and pressure drop in the blood vessel for the controlled longitudinal nanoparticle diffusion, administered in the intravascular system. The dispersion of nanoparticle loaded drug depends on the type of the diseased site. The effective longitudinal diffusion of nanodrugs can be used for designing and developing nanomedicine for curbing the comparative dosage.

Reddy et al. [11] analyzed the dispersion of nanofluid in tapered artery with stenosis. They considered a suspension of silver nanoparticles in a couple stress fluid model involving a catheter. They observed that concentration dispersion is higher for stenotic region, thus nanoparticles are suitable for the treatment of CVDs.

Catering to the practical needs of temperature dependence of the nanoparticles for the development of nanodrugs, Srikanth et al. [12] developed a model so that the optimum temperature in the deliverance of drug is served by the catheter. The mathematical formulations involved the coupled non-linear momentum, temperature and concentration equations wereanswered by Homotopy Perturbation Method. The evolved physical model has immense applications in the biomedical field to curb the thickening of stenosis in the arteries.

While designing a controlled drug- release system, it is important to discern and realize the kinetic behavior of nanoparticles. The effects of osmosis, ion exchange, swelling or eroding of polymers determine the controlled diffusion of drugs Yahya et al. [13] modelled the diffusion control mechanism of nanoparticles for drug release in cylindrical geometries. They used MATLAB for obtaining the exact solution of drug release profile for different concentrations of polymeric nanoparticles. Reddy and Srikanth [14]analysed the thermal dispersion of nanofluid in stenotic tapered blood vessel. They modelled blood like a couple stress fluid under the effect of catheter. They reported high intense vortex regions at the stenosis.

In order to achieve the desired medication responses, nanocarrier design has a presiding role. Eltayeb et al. [15] inspected the consequence of nanoparticles' shapes in drug delivery system. They employed COMSOL multi-physics fluid flow module and showed that multiply twinned shape has the highest drug concentration contrary to the oval shape which has the lowest.

Nanoparticle Transportation Models

The anomalous, aberrant and atypical growth in the thickness of the arterial wall at various sites in the cardio vascular system is known as stenosis. When it induces a thrombus inside the blood vessel, it may cause perilous consequences like enlargedimpedance to blood flow or in some serious cases complete obstruction.

Stenosis may be an outcome of hypertrophy or stiffening of a sphincter muscle or unbridled maturing of fibrous tissue, embryonic mal development. Stenosis may also lead to the wayward cell growth in the regions which might result in major tissue damage.

Stenosis can evolve in series or may be abstract. Numerous studies have been conducted to comprehend the dynamics of blood flow with arteries through obstructions. They can be classified broadly according to the type of blood flow model used which is Newtonian and non-Newtonian fluid models.

Newtonian Fluid Models

The placing of a catheter in the blood vessels to dissolve the stenosis is one of the most common methods of treatment. A catheter is made of pharmaceutical brand polyvinyl, polyester-based thermoplastic, polyurethane etc. The introduction of a catheter causes an annular region between the vessel wall and the catheter. Catheter thus alters the hemodynamic condition in the blood vessel under consideration. Ijaz and Nadeem [16] examined the impact of the catheter on the flow of blood in a tapered artery having overlapping stenosis. They developed mathematical equations in response to mild stenosis conditions and answered by using homotopy perturbation method.

It has been reported that nanoparticles effectively cut back the coagulation effects of the stenosis. Ijaz and Nadeem [17]analyzed the copper nanoparticle in a composite stenosed artery with a catheter and connoted the usefulness of nanoparticles as drug carriers. They presented a theoretical analysis of catheter injection and related permeability effects in the vertical stenosed artery. They demonstrated that the composite stenosis can be effectively treated by the use of copper nanoparticles.

When a stenosis is created in a blood vessel, the motion of the blood can be described as a peristaltic motion. When the cross section of a vessel is contracted or expanded periodically, peristaltic motion transpires. The effect of peristalsis on a nanofluid flow in an artery under mild stenosis situation was systematically inspected by Venkateshwarlu et al. [18]. The mathematical equations were solved by the use of long wave length assumption. They concluded that nanoparticles should be brick shaped so that the nanofluid flow is favorable in the reduction of stenosis.

Physiological systems have tubes which may be elastic, movable or permeable. Due to the complexity of the cardiovascular system, amodel for nanofluid flow in a bifurcated artery with mild stenosis in its root artery was

studied by Srinivasacharya and Rao [19]. They validated that the flow rate and impedance change suddenly on both the sides of the apex due to the back flow at the junction and secondary flow at the apex.

Kawab et al. [20]evolved a mathematical model for nanofluid steady flow in an inclined tube with overlapping stenosis and permeable walls. The non-linear coupled equations were resolved by homotopy perturbation method. The non-invasive approach to deal with CVDs developed in this model is highly relevant.

Non-Newtonian Fluid Models

Profusely, blood is modeled as a Newtonian fluid. But in blood vessels with very small diameter and large shear rate, blood reveals its non-Newtonian fluid properties. When the shear rate exceeds $100s^{-1}$, blood can be modeled as a non-Newtonian fluid. In ailing conditions, it has been experimentally proven that blood shows rheology of non-Newtonian fluids. Vinoth et al. [21]studied the dissimilarity between non-Newtonian and Newtonian blood flow models in large blood vessels and showed that non-Newtonian blood flow model should be assumed for imitation.

Jeffrey fluid is a class of non-Newtonian fluid which exhibits shear thinning characteristic which means that the viscosity of blood elevates with the shear stress. Ellahi et al. [22] discussed the nanoparticle influences in the tapered artery with stenosis along with a catheter considering blood as a Jeffrey fluid. Heat and mass transfer effects were attended. Ellahi et al. [23] inspected the impacts of nanoparticles for Jeffrey fluid flow in tapered artery with stenosis. This model has an enhanced approach because the permeable nature of the arterial walls with the slip effect was considered for designing the mathematical formulations.

The longitudinal transfer of nanoparticles has also been examined with blood modeled using a Casson fluid. Casson fluid is an example of a non-Newtonian fluid having the property of yield stress. Casson rheological model describes the flow of a visco-elastic fluid. It is used for modeling the blood flow in narrow arteries with diameter 130-1000 μm at low shear rates. Gentile et al. modeled the longitudinal transfer of nanoparticles in blood vessels with blood as a Casson fluid. With the use implementation of Taylor and Aris theory, they showed that an increase in rheological parameter and permeability of the vessels can cause resistance to nanoparticle delivery.

Blood is a heterogeneous fluid. Due to the presence of plasma and blood cells, blood cannot be regarded as a single-phase viscous fluid in vessels of diameter less than 100μm. It has been pointed out that the behavior of blood in tubes with shear rates less than 20 s^{-1} can be effectively traced by the power law fluid model. Blood has been regarded as Newtonian fluid in plasma and non-Newtonian power law fluid in the core region which has the suspension of RBCs. Bali et al. [24] assessed the effect of peripheral layer and slip condition on nanoparticle transportation in the capillaries presuming blood as a power law fluid. They regarded the capillary walls as impermeable and non-absorbent to the nanoparticles.

To describe the shear thinning nature of blood for a wider shear rate, K-L model is used. It has two parameters – yield stress and plasma viscosity which is an advantage over Casson model. Bali and Gupta [25] investigated the transportation of nanoparticles with K-L model through bell shaped stenosed micro-vessels. For the effective diffusion of nanoparticles, the rheological parameters, micro-vessel permeability, shape and geometry has been taken into account. They inferred that the total diffusion of nanoparticles is greatest at the vessel wall and lowest at the axis of symmetry.

Table 1:-

Bingham plastic fluid	$\tau = \mu e + \tau_0 \ (\tau \geq \tau_0)$ $e = 0 \ \ (\tau \leq \tau_0)$
Herschel-Bulkley fluid	$\tau = \mu e^n + \tau_0 \ (\tau \geq \tau_0)$ $e = 0 \ \ (\tau \leq \tau_0)$
Casson fluid	$\tau = \mu e^{1/2} + {\tau_0}^{1/2} \ (\tau \geq \tau_0)$ $e = 0 \ \ (\tau \leq \tau_0)$
Prandtl fluid	$\tau = A \sin^{-1} e/c$
Prandtl- Eyring fluid	$\tau = Ae + B \sin^{-1}(e/c)$
Ellis fluid	$e = A\tau + B\tau^n$
Reiner- Philliphoff fluid	$\tau = \mu_\infty + e[\frac{\mu_0 - \mu_\infty}{1 + (\frac{\tau}{\tau_0})^2}]$

Rabinoswitch fluid	$e = \frac{\tau}{\mu_0} + \sum_q s_q \tau^{2q+1}$

Table 1 summarizes the some of the non-Newtonian fluids along with theequation of stress (τ) and strain (e) relation where μ is the coefficient of viscosity. These models describe the behavior of fluid at varying shear rates. The mechanics of these fluids combined with the nanodrug behaviour is a salient feature for developing any mathematical model.

Unsteady Flow Models

For designing a complex model that takes into consideration numerous physiological phenomena, some practical problems need to be considered. For instance, a notable difference in time scale arises in the drug transport in the blood vessels. The drug may take some time to release which would involve a number of cardiac cycles. This arises the need for unsteady flow models. Also, realistic diseased arterial segments have shown that the presence of stenosis potentially contributes to the blood flow behavior. Multiple sites of narrowed blood vessels have an unsteady blood flow. The insertion of a catheter significantly effects the blood flow and its characteristics. In such a case cross model is used for describing the unsteady blood flow. Cross models are in compliance with the experimental results obtained for the blood dynamics for unsteady blood flow.

Zaman et al. [26] took into account the nanoparticle diffusion in unsteady blood flow in catheterized stenosed blood vessel. Explicit finite difference method was employed to solve the equations under mild stenotic conditions with the use of momentum and temperature formulations. They showed that the nanoparticle concentrationmaximizes with the rise in thermophoresis parameter in the arterial cross section.

In the case of multiple stenosis at different locations in an arterial segment, Bingham Plastic fluid represents approximately the flow characteristics of blood. The vessel walls are almost rigid due to plaque formation and the blood represents the properties of viscous incompressible fluid, described by the Bingham Plastic fluid model. Jamil et al. [27] gave a mathematical model for unsteady blood flow with nanoparticles through stenosed arteries under the influence of periodic body acceleration. They concluded that the blood flow velocity can be controlled using nanoparticles in the stenosed arteries.

Magnetic Field Effect Models

Magnetic nanoparticles are an important outcome of nanotechnology. They work through magnetic absorption of specific tissue for targeted delivery of drugs. Tissues are almost pellucid to magnetic energy; thus, magnetic fields can traverse the tissues. This provides for the use of magnetic responsive nanoparticles in drug delivery. The pharmo-kinetic properties of these particles can be controlled and eventually their interactions with the cells or the bio-compatibility can be monitored. The ease of surface modification under the influence of magnetic field is the key feature that enables the drug to be attached to the nanoparticles.

Magnetic targeting is used to hoard the drug carrier at the desired target site under the effect of external magnetic field. In 1996, Lubbe et al. [28] showed the responsiveness of magnetic drug targeting in phase I and II clinical trials to concentrateepirubicin-conjugated nanoparticles. Pouponneau et al. [29] employed a catheter-based method to disperse magnetic particles around a tumor in blood vessel. Similarly, catheter methods have been used for particle up to 1-5mm in size because they cannot pass through pulmonary circulation just by injecting.

Haghdel et al. [30] gave the mathematical model for nanoparticle targeted drug delivery system in magnetic field. They considered various non-Newtonian blood flow models and their numerical simulations showed that Herschel-Bulkeley or power law models are best suited for magnetic nanoparticle targeted drug delivery.

Ardahaie et al. [31]analyzed the arterial blood flow containing nanoparticles in magnetic field. Numerical simulations were used to solve the equation. They assumed a conductive field and used ohm's law.The result showed that magnetic field accelerated the nanoparticle movement in the blood.

Abu-Hamdeh et al [32] showed that the magnetic field intensity and the magnetic field permeability effect the controlled drug delivery of nanoparticle in magnetic field. The equations were examined numerically while applying the magnetic field at right angles to the decree of the flow. They emphasized that magnetic field helps to precisely

control the particle settlement in the blood vessels that can cure the blockages and the clots without involving any surgeries.

Ndenda et al. [33] gave a magnetic drug targeting model to capture the effective dispersion of drug-coated nanoparticles through a microvessel. The effects of various parameters like magnetization and magnet-tumor distance on the dispersion of drug was discussed. They assumed that the magnetic nanoparticles experience a force that relies on the magnetic field and its gradient. The qualitative aspects of this mathematical model depicted that higher the volume fraction of magnetic particles and higher the magnetization led to higher targeted delivery of nanodrugs.

Lee et al. [34]asserted on the effectiveness of magnetic drug delivery in arterioles and capillaries. They considered the magnetic field generated by a magnetic diploe and a bar magnet. They studied the influence of different dipole moment and the location of magnet from the blood vessel which significantly effects the nanoparticle diffusion rates.

Heating Effect Models

Nanofluids are defined as nanoscale colloidal suspensions of nanomaterials in a base fluid. Nanofluids possess enhanced thermal properties like thermal conductivity, thermal diffusivity and viscosity. Researchers have been using Maxwell's models to describe the heating effects of nanofluids. But they do not offer a good application. Mathematical modeling of nanofluids helps to determine the thermophysical properties like thermal conductivity and viscosity etc. Various models have been put forward to determine the thermal properties of nanofluids.

Effective medium theory

Effective medium theory is a static model to model the thermal conductivity of nanofluids. It does not take into consideration the random motion in the mixture. This theory is valid for dilute nanofluids containing nanoparticles within micrometer and millimeter range. Maxwell gave this theory which is the foundation behind most of the models used for predicting the thermal conductivity of nanofluids. It states that nanoparticles are not moving in the fluid and there is no interaction in-between the fluid particles and nanoparticles. This first model evolved from for a system of spherical particles in solid-liquid mixtures. The thermal conductivity k_{nf} of nanofluids, is stated as-

$$k_{nf} = \frac{k_p + 2k_f + 2\emptyset_p (k_p - k_f) k_f}{k_p + 2k_f - \emptyset_p (k_p - k_f)} \quad (4)$$

where k_{nf} is nanofluid conductivity, k_p is the nanoparticle conductivity, k_f is the base fluid conductivity and $\emptyset_p$ is the volume fraction.

Maxwell's model wasdeveloped to a great extent by Hamilton and Crosser [35]. They regarded a shape factor for the geometry of the nanoparticle in the nanofluid. The shape of nanoparticle significantly contributes to the thermal conductivity of the nanofluid if it is comparatively larger than the thermal conductivity of the base fluid. Hamilton-Maxwell model for non-spherical shaped particles is given as-

$$k_{nf} = \frac{k_p + (m-1)k_f + (m-1)\emptyset_p (k_p - k_f) k_f}{k_p + (m-1)k_f - \emptyset_p (k_p - k_f)} \quad (5)$$

where m is the shape factor.

Layering model

Yu and Choi [36] worked on the Maxwell model and included an interfacial layer. The interfacial layer formed on the nanoparticle as it is dispersed in the base fluid, promotes a thermal bridge in the nanoparticle and the base fluid. The interfacial layer is thus combined with the size of the original nanoparticle to give an equivalent nanoparticle. It was assumed there are no collisions among the particles and also no clusters are formed.

$$k_{nf} = \frac{k_p + 2k_f + 2\emptyset_p (k_p - k_f)(1+\beta)^3 \emptyset_p k_f}{k_p + 2k_f - \emptyset_p (k_p - k_f)(1+\beta)^3 \emptyset_p} \quad (6)$$

where β is the thickness of the nanolayer formed.

Aggregation model

Clustering nanoparticles in the base fluid causes their aggregation. These aggregates of nanoparticles reduce the particle velocity of the nanofluid. More significantly, they reduce the stability of the nanofluid. Many researchers considered different nanoparticles shapes and clusters for dilute and homogeneous nanofluids. Since this model was oversimplified, a second model was developed that considered formation of complex structures. This model was

more accurate. Wang et al. [37]created another aggregation and clustering model that reduces to effective medium theory at lower concentrations and changes to Bruggerman model at higher concentrations.

Brownian model

Brownian motion or the random and chaotic movement of nanoparticles within the nanofluid is caused by the persistent collisions of nanoparticles with the molecules of the base fluid. Brownian motion prominently effects the heat transfer in nanoparticles and also causes increased aggregation. The effects of Brownian motion in nanofluids can be observed as convection. Bhattacharya et al. [38] designed a thermal model combining these effects that not only do the nanoparticles mix but also break free from the clusters. They validated the Maxwell's model for large sized particles; but when the size of the particle decreased, the Brownian motion dominated. Similarly, Kumar et al. [39] gave a model on Fourier's law of diffusion through the nanofluids. Parsher et al. [40]reported that convection due to the Brownian motion is the major factor for the increase in thermal conductivity of nanofluids. They observed that heat transfer in the nanofluid occurred via oscillations of atoms which was aided by the formation of interfacial layer.

Li et al. [41] reported that thermal conductivity of nanofluid was not only elevated by Brownian motion but also due to increase in the nanofluid temperature which simultaneously decreased the viscosity causing in les agglomeration and more Brownian motion.

Jang and Choi [42]studied the heat transfer in nanofluid and concluded that heat transfer occurring by Brownian motion is negligible. The heat transfer in nanofluid rather occurred through particle-to-particle conduction.

$$k_{nf} = k_f(1 - \emptyset_p) + k_p\emptyset_p + 3C\frac{r_f}{r_p}k_f {Re_r}^2 Pr\emptyset_p \quad (7)$$

where r_f denotes the diameter of the base fluid molecule, r_p is the diameter of the nanoparticles, Re is the Reynolds number, Pr is the Prandlt number and C is an empirical constant.

Xuan et al. [43] combined the Brownian motion and aggregation in their model. They gave the importance of radius of gyration of the nanoparticle clusters formed. With reduced radius of gyration or cluster size, the nanoparticles moved faster that increased the effective thermal conductivity.

$$\frac{k_{nf}}{k_f} = \frac{k_p + 2k_f - 2\emptyset_p(k_f\emptyset_p)}{k_p + 2k_f + \emptyset_p(k_f\emptyset_p)} + \frac{\rho_p\emptyset_p c_p}{2k_f}\sqrt{\frac{2k_BT}{3\pi r_c\mu}} \quad (8)$$

where ρ_p is the density of the nanoparticles, $c_p$is the specific heat capacity of the nanoparticles, r_c is the apparent diameter of nanoparticles cluster, k_B is the Boltzmann constant and μ is the dynamic viscosity of the base fluid.

Molecular dynamics model

The inherent complexities of the nanofluids make it difficult to anticipate sthe thermal conductivity of the nanofluids. Some researchers modelled how the base fluid's molecules intercommunicate with the nanoparticles. He used molecular dynamics to simulate the interfacial layer interactions. They reported that interfacial layer increased the nanofluid thermal conductivity.

Viscosity Models

Viscosity of a fluid depends on the fluid temperature. Viscosity holds a direct effect in the equations governing fluid flow. Various parameters like pressure drop and skin friction depend on viscosity or μ. Many experimental works and simulations approaches have been made to analyse the effect of various parameters on viscosity.

The first model for nanofluid viscosity was given by Einstein [44]. In this model spherical nanoparticles with a volume fraction of less than 2% has been considered.

$$\mu_{nf} = (1 + 2.5\,\phi)\mu_f \quad (9)$$

Brinkman[45] proposed a model for higher concentration of nanoparticles as:

$$\mu_{nf} = \mu_f\,/(1 - \phi)^{2.5} \quad (10)$$

Batchelor [46] gave a new model for nanoparticle viscosity considering the Brownian motion of the nanoparticles.

$$\mu_{nf} = (1 + A\phi + K_H\phi^2)\mu_f \quad (11)$$

Where A is the coefficient of Einstein's model and K_H is Huggins coefficient that reports the immediate effect of Brownian motion on nanoparticles.

Frankel and Acrivos[47] derived a model for evenly distributed nanoparticles with maximum concentration.

$$\mu_{nf} = \frac{9(\frac{\phi}{\phi_{max}})^{1/3}}{8(1-(\frac{\phi}{\phi_{max}})^{\frac{1}{3}})}\mu_f \quad (12)$$

Hosseini et al. [48] gave an expression to predict the viscosity of nanofluids.

$$\frac{\mu_{nf}}{\mu_f} = \exp\left[a + c_1\frac{T}{T_0} + c_2\phi + c_3\left(\frac{r_p}{1+d_{nf}}\right)\right] \quad (13)$$

Where a depends on the properties of nanofluids, $c_1, c_2 and c_3$ is experimentally determined, $T and T_0$ are the real and reference temperatures of the nanofluid and d_{nf} is the thickness of the nanolayer.

The above-mentioned models are suitable to predict the viscosity of the nanofluids.

Specific Heat Capacity Models

Most of the researches on nanofluids focus only on k_{nf} or thermal conductivity. But specific heat capacity or c_p is a vital parameter to describe the thermal properties of nanofluids.

Pak et al. [49] gave the first model to predict specific heat capacity of nanofluids.

$$c_{p_{nf}} = (1-\phi)c_{p_f} + \phi c_{p_p} \quad (14)$$

where c_{p_f} is the specific heat capacity of the base fluid and c_{p_p} is the specific heat capacity of the nanoparticles.

An enhanced model considering the thermal equilibrium for nanoparticles and the base fluid was given by Xuan et al. [50]

$$c_{p_{nf}} = \frac{(1-\phi)(\rho c_p)_f + \phi(\rho c_p)_p}{(1-\phi)\rho_f + \phi\rho_p} \quad (15)$$

The study of specific heat capacity accounts for only 5% of studies. More attention is needed on this aspect of nanofluid parameter for the successful designing of the targeted drug delivery systems.

Size And Shape Dependency Models

Nanomaterials have shown various physical properties that are dissimilar to their bulk materials. This happens due to a change in area-to-volume ratio that results in size and shape governing properties of nanoparticles. The various mathematical models are presented here for understanding the shape and size dependency of nanoparticles.

Size Dependency Models

For the purpose of understanding the thermal and mechanical properties of nanoparticles for their transportation in the circulatory system, it is necessary to understand their heat and mass transfer applications. The study of physical properties of nanomaterial behavior has become an inductive path of research. The small measurements of nanoparticles lead them to exhibit various properties corresponding to the bulk form of the same material. The major criterion that affects the conduction of nanoparticles is the size of nanoparticles.

Qi and Wang [51] developed a model to reckon with the size and shape dependency of nanoparticles. Basically, metallic nanoparticles were taken into account. They used a continuous media model for nanoparticles of size greater than 1 nm. They showed that lattice parameters decreased with the decrease in particle size.

Morris [52] in his chapter on the properties of nanoparticles discussed the surface properties like electrical, optical, thermal and mechanical properties. Andrievski[53] pointed out five principal features that effect the size of nanoparticles. They can be stated as-

1. The reduction of any crystal to nanometer size causes in a major rise in the role of interfacial defects.
2. These interfacial properties are different at nanoscale levels.
3. The characteristics physical lengths of the crystal structure like mean free path and Frank-Read loop size change for nanoscale objects.
4. The nanocrystals can show quantum nature.
5. The nanometer particles show residual stresses, pores, interface segregations etc that are not seen in conventional crystals.

Singh et al. [54] proposed a theory to study the size dependent specific heat, melting entropy and enthalpy of nanoparticles. They delineated that specific heat increases with the lessening of particle size whereas the melting entropy and enthalpy show an opposite trend.

Pandey [55] showed that lattice parameters not only depended on size of nanoparticles but also on surface energy. Achhal et al. [56] gave the importance of particle size of nanoparticles to improve the efficiency of nanofluids. They used molecular dynamics instead of analytical methods and the results showed that they were closer to the experimental values.

The thermodynamic properties of nanoparticles rely mostly on the ratio of its surface area to the volume of the material. Jalal and Mawlood[57] used cohesive energy as a thermodynamic parameter to relate the size dependent properties of nanoparticles with various physical properties. The effect of size has a major role in studying nanoparticles behavior.

Melting temperature

The melting temperature of a nanoparticle in a size dependent formula is given as-

$$T_{np} = T_{bs}\left(1 - \frac{N}{2n}\right) \quad (16)$$

where T_{bs} is the melting point of the bulk state and $\frac{N}{2n}$ depends on the size of nanoparticles.

Debye temperature

Debye temperature is the measure of the highest temperature due to single normal vibration. It has been reported that Debye temperature for nanomaterials decreases with the reduction in size. The relationship of nanomaterial Debye temperature as a function of particle size is given as-

$$\theta_{Dnp} = \theta_{Dbs}(1 - \frac{2d}{D})^{1/2} \quad (17)$$

where θ_{Dbs} is the Debye temperature for bulk material, d is the atomic diameter and D is the diameter of the nanoparticles.

Melting entropy

The size dependent melting point T_{np} is directly linked to the melting entropy of nanomaterials.

$$S_{mnp} = S_{mbs} + \frac{3R}{2}\ln\frac{T_{np}}{T_{bs}} \quad (18)$$

where S_{mnp} is the melting entropy of the nanoparticles and S_{mbs} is the melting entropy of the bulk material.

Specific heat capacity

The size dependency of the specific heat capacity of the nanomaterial is given as-

$$C_{pnm} = C_{pbs}(1 - \frac{2d}{D})^{-1} \quad (19)$$

where C_{pbs} is the specific heat capacity of the bulk material.

Shape Dependency Models

In most of the studies, the physical performance of the nanoparticles is analyzed either by considering the nature of the base fluid or different nanoparticles. Usually in many investigations, spherical shape of nanoparticles is considered. But practically there are limited applications and significance of spherical shaped nanoparticles. Non-spherical shaped nanoparticles are utilized in drug delivery, cancer therapy, clinical diagnosis etc. [58].

Timofeeva et al. [59] discussed the shape effects of nanoparticles. They showed that the thermal conductivity and viscosity of nanoparticles depends on the shapes of particles. They used four major shapes namely spherical, platelet, cylinder and bricks. Devaki et al. [60]studied the MHD peristaltic flow of copper-water nanofluid in an artery with mild stenosis for different shapes of nanoparticles. The results showed that brick shaped nanoparticles increased the velocity, temperature and pressure gradient.

Ahmed and Nadeem [61] studied the arterial flow of copper nanofluid comprising different shapes of nanoparticles such as bricks, platelets and cylinders. The problem was modeled in a toroidal coordinate system and solved using perturbation approximation. The difference in the behavior of different shapes of nanoparticles in a catheterized curved artery has been highlighted in this study.

Nanoparticle Penetration Across Cells And Tissues Models

Agent based modelling combined with CFD approaches has a great potential. When blood cells and capillary diameters are comparable, the reduced number of white blood cells and platelets with respect to the red blood cells make red blood cells as the major driver for nanodrug delivery. Thus, the study of nanoparticle in a blood vessel has a relative importance of RBC enhanced diffusion and Brownian diffusion. They both are comparatively important for nanodrug delivery.

Hossain et al. [62]in their work on the mathematical modeling of coupled drug and drug-encapsulated nanoparticle transport in patient specific coronary artery walls have devised a catheter-based nanoparticle drug delivery system. This computational tool framework can be used to diffuse plaques. Riveting on spherical shaped nanoparticle of size 20-500 nm; Hossain et al. have studied the properties like viscosity and miscibility of nanoparticles in the blood. Navier-stokes equation conjoined with advection-diffusion equation has been used to ascertain the concentration of nanoparticles at the arterial wall. Nanoparticle accumulate near the bifurcation area of the arteries which has a pronounced effect on the spatial distribution of nanoparticles. Once the nanoparticles invade the arterial walls, they diffuse more with uniform distribution. It was reported that nanoparticle deposition and plaque site harmonized well which rendered an excellent opportunity to study the local behavior of nanoparticle.

Aidun et al. [63] have systematically probed the nanoparticle response to the cellular blood flow. Since the nanoparticles have size of order 10 nm and RBCs have size of order 10 μm , therefore the analysis of the transport of nanoparticles is affected by labyrinthine dynamics. The dynamics predominantly depend on the Brownian effect and nanoparticle and RBC interaction. Tan et al. [64] studied a paraphrased Brownian motion effect for nanoparticles for RBC deformation and fluid flow. Tan et al. [65] put to use 2-D simulations to determine the behavior of nanoparticle transport in cellular blood flow. Nanoparticle dynamics and mesoscale 3-D model was used for examining the nanoparticle transfer in cellular blood flow.

Aidun et al. [66] captured the critical nanoparticle size (~1μm) which prevents greater retention of nanoparticles in the region near the wall which is cell free. The RBC driven shear induced diffusivity dominates over Brownian diffusivity which is grounds for high radial diffusion rates.

The more effective transport of nanoparticles relies on the critical shear rate. The characterized nanoparticle diffusion tensor was analyzed by Aidun et al. [67]. Nanoparticle diffusion tensor manifests high anisotropy. A critical shear rate (~$100s^{-1}$) exists about which the diffusion tensor switches from linear and non-linear. This proposed empirical formulation offers to reinforce effective continuum models for in vivo nanoparticle drug delivery.

Owing to the physiological applicability, geometry and flow patterns, a multiscale framework for nanoparticle distribution in microvascular bifurcations was also studied by Aidun et al. [68]. The segregation of solutes at microvascular bifurcations has been studied in response to the Zweifaen Fung (ZF) effect. Nanoparticles segregation at the bifurcation, which is stirred by the RBC motion depends on the ratio of flow rates between the daughter branches. The results showed that the presence of a driving force is responsible for the heterogeneity of the nanoparticle at the bifurcations. This model would help in fabricating a nanodrug delivery mode for full vasculature.

Sabourian et al. [69]summarized the investigations of active and passive transport of nanoparticles across the cell. They reviewed the various factors for designing nanoparticle so that they can be internalized more efficiently into the diseased cells and also increase their rate of cellular uptake. They discussed that size of nanoparticles is the prime factor to be considered while designing the models for cellular uptake of nanoparticles at the diseased site. The size range from 10 to 60 nm is the optimum size for cellular uptake of nanoparticles.

Ismael et al. [70]discussed a mathematical model for nanoparticle transport in the tissue in the presence of a vertical vessel. The nanoparticles push through from the blood vessel into the tissue bed. They emphasized that nanoparticle transport depended on the thermophoresis parameter. This model has interesting applications in the nanoparticle drug delivery in deep tissues.

Conclusions:-

A comprehensive review on mathematical models for nanoparticle delivery in the blood is presented here. The utilization of mathematical models is a significant tool to describe the pharmokinetics of nanodrugs. The mathematical equations reveal the transportation rate of nanoparticles in the blood stream.

Dispersion and diffusion of drugs is the rudimentary mechanism for the transport of nanoparticles in the blood vessels. The foundation of effective diffusion was laid by Taylor and Aris that followed a huge revolution. Researchers have worked on the time dependent models, different non-Newtonian models of blood and different geometries of nanoparticles to ascertain the controlled release of nanodrugs in the blood.

The blood vessels under diseased conditions develop stenosis that increases the impedance to flow. Such abnormal state is answered by non-Newtonian fluid models for blood. The rheological parameters, permeability and the geometry of stenosis with nanoparticles in the blood are convincingly studied by these mathematical models.

When a drug is injected or given orally as a dosage, there is a time lapse before it reaches the circulation. To account for such time differences, unsteady blood flow models are designed. The cases of multiple stenosis are productively described by these unsteady blood flow mathematical models.

The nanoparticle diffusion rates are greatly improved by the utilization of magnetic field. Lube et al. [28] provided a breakthrough in magnetic drug targeting. These mathematical models have depicted high volume fraction of nanoparticles under magnetization.

The thermophysical properties of nanoparticles in blood is studied using various models like effective medium theory, layering model, aggregation model, Brownian model and molecular dynamics model.Viscosity is a direct effect of the thermal properties of the fluid. Einstein gave the first model to study the viscosity of nanofluids. The viscosity models are governed by the volume fraction of nanoparticles. Another property that is the direct outcome of heat is the specific heat capacity. Specific heat capacity models are again controlled by volume fraction of nanoparticles in the blood.

Nanoparticles evolve from their bulk materials. Thus, their properties are dominated by their size and shape. The size of nanoparticles establishes the melting temperature, Debye temperature, melting entropy and specific heat capacity. On the other hand, various shapes of nanoparticles like blades, platelets, cylinders and bricks are prominently used to study the velocity, temperature and pressure gradient of nanofluids.

The potency of nanoparticles to target the diseased site is regulated by their behavior under the blood flow. The capillaries with very small diameters have only red bloods cells as the major driver for nanodrug delivery. The RBC enhanced diffusion models are used to study the nanoparticle penetration across cells and tissues. Different physiological applications and flow patterns are effectively answered by these mathematical models.

Scientists have been working to produce cell-specific targeting ligands to enhance drug delivery of nanoparticles. Efforts are being made to develop bio-compatible nanoparticles to allow for greater cellular uptake and limited toxicity. More efforts should be made to improve drug-capacity of nanoparticles. For the characterization of the thermophysical properties of the nanoparticles, only thermal conductivity and viscosity are considered. But these parameters are governed by various factors like temperature, concentration, shape and size of the nanoparticle as well as their aggregation. These factors also need to be fully explored for the enhancement of nanoparticle delivery in the blood.

Further, due attention should be given to the surfactants and pH adjustments for the better transportation of nanoparticles in stenosis of various geometries. The study of nanomaterials like carbon nanotube and graphene still needs more exploitation. In order to refurbish new models and correlations the effect of micro convections, clustering and Brownian motion of the nanoparticles also need to be taken into account. These gaps and challenges will provide significance developments in the study of transportation of nanoparticles. These researches will fuel some unprecedented discoveries in the field of nanomedicine.

The focus of this review article is to describe the use of mathematical modeling to determine optimal nanoparticle transportation rates in the blood vessels. Indispensably, mathematical modeling can harness the best use of nanotechnology in the cure of cardiovascular diseases.

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

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