IJPSR (2023), Volume 14, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 December 2022; received in revised form, 20 March 2023; accepted 30 May 2023; published 01 September 2023

OPSONIZATION AS A LONG CIRCULATORY APPROACH: A CHALLENGE IN DRUG DELIVERY

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Keywords:

Phagocytes, Antibodies, Opsonin, Immunodeficiency, Antigenicity

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ABSTRACT: Opsonisation is the process of coating infections with antibodies to make them more receptive to phagocyte ingestion. Opsonization is a crucial step in host defence that prepares particles or complexes for easy ingestion by phagocytic cells. It has been acknowledged that activated macrophages could proactively capture opsonized nanoparticles in the bloodstream and then accumulate in the reticuloendothelial system (RES) organs. Based on this fact, a trapping strategy is proposed, transforming a normal nanoparticle into an opsonized attractant to target and regulate macrophage polarization. Developing an effective therapeutic approach against systemic infections linked to chronic immunodeficiency illness presents a significant problem for medical practitioners. Long circulatory carrier systems provide a practical substitute for dealing with the problems caused by systemic infections. The pathophysiology of opsonization is when the process is not occurring. Opsonization fights off foreign invaders like bacteria and viruses, supports self-tolerance, and inhibits autoimmunity. Self-tolerance is the ability of the immune system to recognize its self-antigens without mounting a response. However, the extent to which the carrier system has obscured the operationalization process will determine whether the above technique is clinically effective. Molecular weight, lipophilicity, antigenicity, size, shape, biochemical nature, and other factors have all been found to have a significant impact on the opsonization process. This examination links the opsonization method and the carrier system formulation strategy.

INTRODUCTION: We have seen a dramatic increase in the creation of long-circulating vehicles in the last few decades, particularly at the nanoscale. Opsonization is an immune process that uses opsonin to tag foreign pathogens for elimination by phagocytes. Without an opsonin, such as an antibody, the negatively-charged cell walls of the pathogen and phagocyte repel each other.

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DOI: 10.13040/IJPSR.0975-8232.14(9).4317-30

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(9).4317-30

The pathogen can then avoid destruction and replicate inside the human body. It is especially helpful in administering powerful and anticancer treatments since retaining the carrier system in the bloodstream for a long enough time enhances therapeutic results and reduces undesirable side effects of medications.

However, the long circulation of the carrier system is strongly hindered by opsonization, the body's natural defence response against invaders, which goes through the SER (reticulo-endothelial cells). Opsonin's' adhesion to nanoparticle surfaces, which facilitates their phagocytosis clearance, triggers the immune response cascade. Opsonin's are particular immune system-related proteins, like complement or immunoglobulins.

Without opsonin proteins adsorbed to the surface [1]. Because hydrophobic surfaces absorb blood serum proteins more easily, opsonin proteins can recognize hydrophobic particles more quickly than hydrophilic particles [2, 3]. Adsorption-mediated endocytosis is another method by which intravenously delivered nanoparticles can be removed from systemic circulation. The interaction between the positively charged nano transporter and the negatively charged cell membrane leads to adsorption-mediated endocytosis [4].

Long circulatory nanoparticles are made by coating them with PEG (polyethylene glycol), dextran sulphate, combined PEG and water-soluble chitosan, biomimetic long-circulating entities like RBC membrane coated nanoparticles, heparin or dextran surface bearing poly (methyl methacrylate), or biomimetic mucin modified PLGA nanoparticles, among other materials [5-9]. PEG, which surrounds the particles with a hydrophilic layer and hinders detection by the mononuclear phagocyte system, is currently the gold standard for adding long-circulating characteristics. Red blood cells (RBCs), the body's own long-circulating organisms, have recently inspired a new method for creating biomimetic nanoparticles [10]. Many of these systems use hydrophilic polymers or biomolecules to modify surfaces. However, product stability, scaling, and feasibility of applications are key concerns for these strategies to be realistic and enforceable.

Understanding the variables that affect blood circulation duration and nanoparticle biodistribution is crucial for effectively creating long-circulatory nanoparticles. Here, the important variables influencing the retention period in blood circulation and organ distribution of nanoparticles have been identified as particle size, shape, surface charge, hydrophilicity, and surface modification. Suppose these elements are kept at an optimum level. In that case, they can help nanoparticles circulate for a longer period of time by delaying opsonization and allowing them to escape the reticuloendothelial system.

Opsonization Process: One of the main challenges for polymeric nanoparticles delivered intravenously is the opsonization process. When nanoparticles are administered intravenously (I.V.), the opsonization process begins with the adsorption of opsonin proteins from the blood serum to the surface of the nanoparticles. This enables mononuclear phagocytic system (MPS) macrophages to quickly identify and remove these polymeric nanoparticles before they can carry out their intended therapeutic function. Together, these two procedures make up the primary clearance mechanism for the blood's removal of unwanted substances greater than the renal threshold limit. When MPS organs are sequestered by biodegradable polymer nanoparticles that the phagocytosis process cannot remove, it often results in poisoning and other adverse effects [11-13].

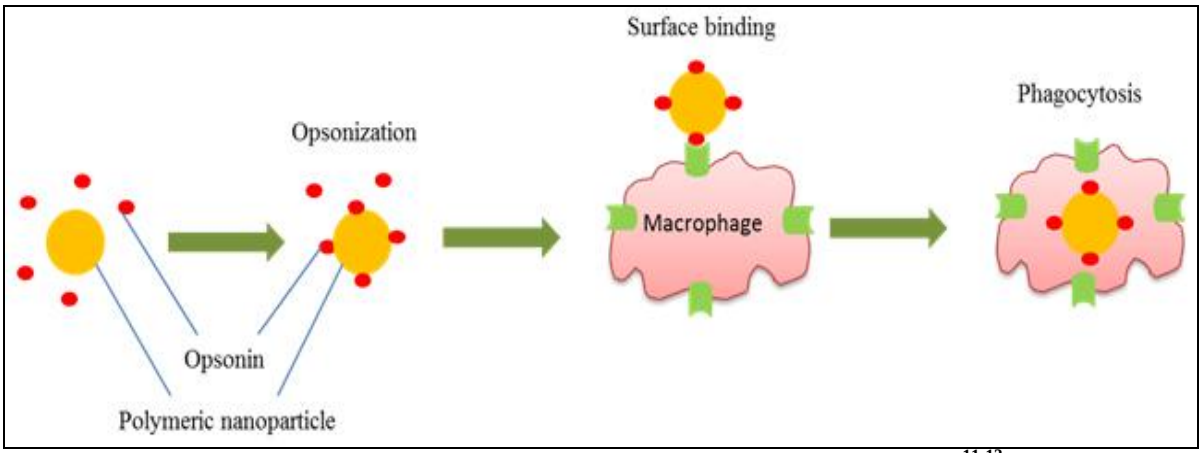

FIG. 1: PROCESS OF OPSONIZATION AND PHAGOCYTOSIS [11-13]

Physical interactions with certain blood components called opsonin significantly impact the lifespan of polymeric nano-carriers in circulation. Complement proteins C3, C4 and C5, known to be prevalent opsonin, and additional blood serum proteins laminin, fibronectin, C-reactive protein, type I collagen, and immunoglobulin are among these components [14-16]. Numerous *in-vivo* animal

investigations using hereditary and artificially generated C3 deficient animal models have indirectly demonstrated that opsonin plays a significant role in clearing foreign particles. For instance, studies have shown that these animal models are frequently more susceptible to certain diseases that may be easily managed by phagocytosis in animal models who do not have a C3 deficiency [17].

Opsonin binds to polymeric nanoparticle surfaces through a variety of mechanisms, including van der wall, electrostatic, ionic, hydrophobic/hydrophilic, and other attractive forces. Following opsonin binding, opsonized particles are attached to the macrophage using opsonin that has been surface-bound. Macrophages will normally be unable to distinguish foreign particles without surface-bound opsonin proteins. Macrophages may follow a specific, non-specific or supplement-enabled approach. Specialized receptors found in phagocytic cells can interact with particular opsonin proteins. The second way of attachment involves phagocytes' non-specific binding to blood serum proteins adsorbed on their surfaces, which may also stimulate phagocytosis [18]. The third important technique of phagocytic attachment is complement activation. One of several mechanisms can activate the complement system, including the classic, alternative and lectin track.

Antibodies are necessary for the classical complement pathway, either in the form of immunoglobulin (IgG or IgM) linked to cell surface antigen (Ag) or as an Ag-Ab immune complex. The antibody binds to the serum protein C1, which causes the activation of the proteins C4, C2 and C3 and the production of the proteins C5, C6, C7, C8 and C9. The C5-C9 membrane attack complex (MAC), which finally forms as a result, lyses and kills the cell. The alternative pathway is naturally activated by binding C3 fragments to the pathogen's surface and can be started even in the absence of antibodies. The mannose-binding lectin binds to the mannose present on the surface corona of bacteria, activating the lectin pathway. Although some hypotheses have been put forward to elucidate the presence of additional activation pathways, they have not been fully explained. Regardless of the activation mechanism, the complement activation's enzymatic cascade results in the creation of the enzyme C3 convertase, which cleaves the third component of the complement system, the central protein [18]. The essential active component that causes the cleavage of several complement proteins is the fragment C3b of C3 (C5–C9). These proteins form the membrane attack complex (MAC), which can disrupt microorganisms, viruses, and drug-delivery nanocarriers.

The third and final step of the clean-up process is phagocyte consumption of foreign substances. This procedure stage normally entails a phagocyte endocytosing the particle or foreign substance. The phagocytes will start to secrete enzymes and other oxidative-reactive chemical substances, such as superoxide, oxyhalide molecules, nitric oxide, and hydrogen peroxide, to break down the phagocytosed material after the particle has been endocytosed [19].

Although opsonization is intended to protect the body's natural defences against foreign invaders like bacteria, viruses and other disease-causing microorganisms or particulates, it also encourages the removal of circulating drug carriers, which is essential for achieving the proper systemic therapeutic drug concentration.

Physical and Chemical Properties Affecting the Longevity of The Blood Circulation:

Size: Nanoparticles' *in-vivo* fate is determined by their size. The retention of smaller particles in the blood stream, which range in size from 70 to 200 nm [20, 21], is known to be inversely related to particle size. Renal clearance typically removes nanoparticles smaller than 5 nm in diameter from the blood circulation [22, 23], which causes short blood half-lives. Most often, the optimal size of nanocarriers used in nanomedicine falls between 20 and 200 nm, as NCs smaller than 100 nm would escape from blood vessels through fenestrations in the endothelial lining, and NCs larger than 200 nm would be more effectively captured by the RES and may cause embolization in the liver and lung [20]. Due to the heterogeneity in size, it is hard to identify a specific threshold for NCs to adapt to the long circulatory effect. Another plausible explanation for the relationship between size and biodistribution is that it may simply be a matter of a filtering process, whereby the spleen and liver

swiftly clear larger particles. In comparison, smaller particles are concentrated in the bone marrow [24].

In addition, the curvature and size of the surface are linked, as smaller spherical particles have a greater surface curvature than larger spherical particles. It was discovered that the surface curvature of tiny particles decreases protein adsorption. When examining the pattern of proteins present on 70 versus 200 nm particles, it is feasible that the surface curvature of the 70 nm particles reduces the quantity of linked proteins as compared to the 200 nm particle.

Shape: The form of intravenously injected nanocarriers is a largely overlooked property yet is thought to have a significant impact on blood circulation time [25-27]. Biconcave, disk-like particles may be more effective than spherical ones at reducing cellular and phagocytic uptake. According to research, the particle's local form at the point of attachment, rather than its overall shape, determines when a macrophage starts to internalise [28]. For instance, an elliptical particle may internalise quickly if it attaches to a macrophage at its pointed end, but particles adhering to its flat section may persist for a longer time. A particle's shape, contact area, volume, local curvature at the contact site, and orientation are crucial to the nature of interaction with blood components and blood vessel wall.

A recent study compared pegylated gold nanorods to pegylated gold nanoparticles (spherical-shaped particles). It was discovered that the gold nanorods had less liver absorption and longer bloodstream circulation times [29]. Hypothesized in 2009 that the mechanobiological mimicry of RBCs could boost the flexibility and blood circulation time of intravenously administered nanocarriers by creating biconcave-shaped microparticles [30]. Recently, the tumour dispersion kinetics of nanorods with a size of 44 nm and those of nanospheres with a hydrodynamic radius of 35 nm were examined [31]. Despite having similar blood flow patterns, it was found that nanorods extravasated to the interstitial 4 times faster and diffused deeper in the tumour than nanospheres.

Surface Charge: One surface property that can affect how nanocarriers behave *in-vivo* after intravenous administration is surface loading. The presence of charge on the surface of the particles can change the overall plasma circulation profile as well as the opsonization profile and identification of the intravenously delivered particles by MPS organs [32, 33].

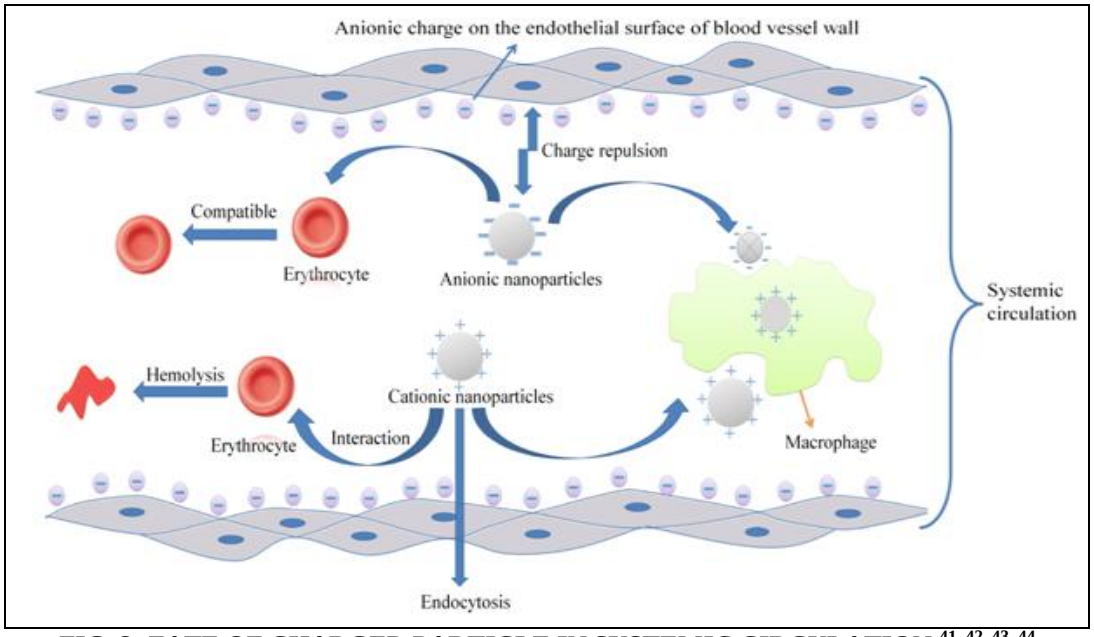

FIG. 2: FATE OF CHARGED PARTICLE IN SYSTEMIC CIRCULATION [41, 42, 43, 44]

Depending on the polymer employed to create the nanocarriers, the surface charge of the nanocarriers may be anionic, cationic, or neutral. In their research, Rosser *et al.* in 1998 showed that neutrally charged particles are phagocytized by the mononuclear phagocytic system (MPS) after the

charged particles have been easily detected by opsonin proteins [34]. Increasing or decreasing the clearance of nanocarriers by MPS with a negative surface charge that can be increased, decreased, or have no influence [35-37]; nonetheless, plasma proteins often detect particles with positive charges and quickly remove them from the systemic circulation [38-40]. Additionally, when positively charged particles interact with negatively charged blood vessel wall luminal surfaces, the blood circulation is quickly cleared [41]. Additionally, cationic nanocarriers are more likely than anionic nanocarriers to have harmful consequences [42]. For instance, on carbosilane, polyamidoamine, poly-lysine and polypropylene imine surfaces, haemolysis was observed in the presence of specific amounts of unshielded primary amines (positive charge) [43-48].

Hemocompatibility of Nanocarriers: It is generally known that the physical and chemical characteristics of intravenously delivered particles, such as size, shape, and surface chemistry, as well as the physiological environment it came into touch with, determine their biocompatibility [49-51]. The term "biocompatibility" is used by Kohane and Langer in 2010 to describe how benign a material's relationship with its biological environment is [52]. However, given the significance of the appropriate functionality of biomaterial in a physiological environment, several researchers have adjusted this concept in the delivery system context. In other words, a substance has reached a high degree of biocompatibility when it interacts with the body without causing any negative effects, such as poisonous, immunogenic, carcinogenic, or thrombogenic effects. Therefore, it is crucial to do the following when characterizing the intravenously given particles to evaluate hemocompatibility. The internationally recognized ISO-10993 standard recommends using in-vitro tests for hemolysis, thrombogenicity (including platelet effects), and complementary activation to assess the hemocompatibility of nano-drugs administered intravenously.

Hemolysis: Nonimmunogenic (e.g., through direct drug-erythrocyte membrane contacts) and immune-mediated (*e.g.*, by a drug-specific antibody) haemolysis are two types of drug-mediated haemolysis. Compared to other blood components, red blood cells (erythrocytes) occupy a larger volume percentage in the bloodstream, increasing the likelihood of interacting with an intravenously delivered particle. This interaction ultimately results in undesirable physiological effects (severe haemolysis may result in life-threatening conditions, such as anaemia), necessitating the examination of haemolytic activity, which is still a crucial component of the preclinical characterization of nanoparticles. Since, many of the research was done using blood to see the early harmful effects of nanoparticles, especially cationic charged particles, numerous writers mentioned haemolytic effects of various nanoparticles in the literature [43-48]. For instance, it was discovered that the haemolytic tendency increased proportionally with the quantity of cationic surface groups (positive surface charge) in a set of similar-sized fullerenes (C60- derivatives) while the anionic surface groups were determined to be safe [46].

Thrombogenicity: Some intravenously delivered nanocarriers frequently require surface engineering to lengthen the systemic circulation period to obtain the intended therapeutic outcome. The contact with the coagulation system's components will increase as the circulation time increases (i.e., a mixture of red blood cells, aggregated platelets, fibrin, and other cellular elements). By interacting with these components, the administered nanocarriers activate the coagulation cascade, which in turn causes thrombus to partially or completely block the blood vessel. Incubation of nanoparticles with platelet-rich plasma derived from freshly collected whole human blood is one step in *in-vitro* analyses of platelet aggregation and plasma coagulation time.

Complement Activation: A particle count and size analyzer is used to examine the plasma to determine the number of active platelets. Finally, the active platelets linked with the nanoparticles sample will be compared to control plasma to calculate the % platelet aggregation [54]. Although extensive information about the impact of nanocarrier surface properties on thrombogenicity is not yet available, thrombogenicity exhibits the same charge dependence as haemolysis. In particular, Koziara et al. demonstrated that the PEG coating reduces platelet aggregation and activation while increasing particle surface loading does so [55].

The activation of the complement induced by the nano vectors may impact the biodistribution of the intravenously injected nano vectors by causing a rapid clearance of the systemic circulation by phagocytosis by reticuloendothelial. Complement activation has been shown to play a critical role in removing non-specific pathogens and supporting cell-mediated immunity by enhancing B-cell responses to an antigen and increasing the stimulation of dendritic cells (DC) and T-cells [56]. Anaphylaxis, a disease that poses a life-threatening hazard and hypersensitivity (allergic) reactions are both caused by Complement activation in response to systemically delivered medicines. The propensity to activate the complement system should be checked for in nanoparticulate carriers intended for systemic delivery. If the nano transporter succeeds in significantly activating the complement, its surface properties should be able to minimize these interactions to a tolerable level.

Long-Circulation Nano-Carriers:

Pegylating: Increased systemic circulation time is a popular tactic to lengthen the nanoparticles' retention period (NPs). Polyethylene glycol (PEG) surface modification gives nanoparticles (NPs) a stealthy property that prevents opsonin binding and reticulo-endothelial cell absorption. NCs' protein-resistant surfaces typically exhibit the following molecular peculiarities: They have hydrophilicity I They contain hydrogen-bond acceptors (ii). They exclude hydrogen-bond donors (iii). (iv) They have a neutral electrical charge overall [57].

Mechanism of Action of the Peg Coating: The hydrophilic PEG-based coatings greatly lengthen the nanocarriers' duration in the bloodstream. The Food and Drug Administration (FDA) considered PEG non-toxic and approved human ingestion [58]. The hydrophilicity of the PEG coating, which is based on the formation of a sterile hydrophilic coating, is what causes the blood half-life of the coating to be prolonged. Besides hydrophilicity the other factors that play a major role in opsonisation process is chain flexibility [59, 61], polymer corona thickness [20, 24], molecular weight of PEG derivatives [63], density on the carrier surface and configuration [64-66].

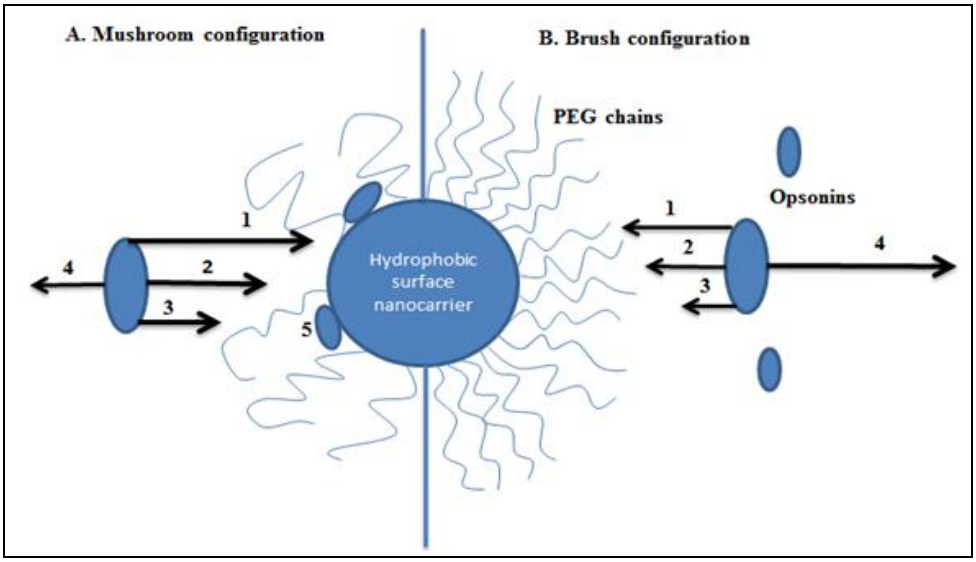

Fig. 3: OPSONINS AND PEGYLATED HYDROPHOBIC SURFACE NANOCARRIER INTERACTION MECHANISM, IN BOTH BRUSH AND MUSHROOM CONFIGURATION OF PEG CHAINS 1: HYDROPHOBIC ATTRACTION FORCE BETWEEN THE OPSONIN AND HYDROPHOBIC SURFACE NANOCARRIER, 2: VANDER WAALS ATTRACTION BETWEEN THE OPSONIN AND HYDROPHOBIC SURFACE NANOCARRIER, 3: VAN DER WALLS ATTRACTION BETWEEN THE OPSONIN AND PEG CHAINS,4: STERIC REPULSION RESULTING FROM PEG CHAINS, 5: MINIMUM DENSITY OF PEG CHAINS RESULTS IN OPSONIN ADSORPTION ON THE HYDROPHOBIC SURFACED NANOCARRIER

Chain Flexibility: In addition to hydrophilia, chain flexibility is a crucial element of PEG-coated layers that contributes to the stealthy nature of the injected particles [59, 61]. Opsonin had trouble identifying the surface for adsorption because of the transitory, flexible, and quickly changing structure of PEG chains [67]. In order to repel proteins from polymer chains on particle surfaces and produce stealth

nanocarriers, hydrophilicity, and chain flexibility serve as effective coating protectors for intravenously administered particles against opsonization [61]. Hydrophilicity creates a sterically hindered hydrodynamic surface [68]. Accordingly, the flexible structure of PEG molecules may account for the decreased complement activation of PEG relative to dextran [62].

Polymer Layer Thickness and Molecular Weight: To prevent interactions between plasma proteins (opsonin) and the hydrophobic surface of particles, the PEG layer thickness must be optimal. The smallest coating layer thickness needed to ensure effective particle coating relies on a variety of variables, including the size of the nanocarrier and any potential adsorbable proteins [69]. According to studies, the particle diameter is roughly 5% of the thickness of the minimum effective hydrodynamic layer [20]. In order to shield 60-200 nm polystyrene particles from complement activation and subsequent mono nuclear phagocytic absorption by macrophages, Moghimi *et al.* showed that 4 kDa PEG provides a coating thickness of 5 nm [70]. Additionally, multiple investigations showed that the blood half-life of PEG-coated nanocarriers rose according to the molecular weight of PEG [12, 63].

Density on the Supporting Area and Configuration: Recent research looked at the circumstances that cause proteins to repel from hydrophobic plane surfaces where PEG chains were connected to one end in a "brush" shape [64]. Long PEG chains and a high surface density with a brush structure were discovered to be the ideal circumstances for protein repulsion [71]. The mushroom-like shape is caused by low surface densities of PEG molecules covering the nanocarrier's surface [65, 66]. In contrast, at higher densities, the PEG molecules extend to avoid overlapping with other PEG molecules, resulting in brush configuration [65, 72]. It is believed that there is a cloud of potential chain confirmation that is dense enough to prevent opsonin interaction with the PEG protective layer. A huge water cloud can be created by associating two to three water molecules with each PEG molecule, creating a brush-like or mushroom-like structure. The PEG segments connected to the surface of the nanoparticles can sterically reject the deposition of big proteins [73]. Many methods, including small-angle neutron scattering [74], ultrasonic velocity measurement, and surface sorbed protein measurement, can be used to characterize the surface.

Alternative Approaches for Stealth Nanoparticles:

Poloxamine and Poloxamer: As it imparts a hydration layer on the surface of nanocarriers, surface modification employing poloxamer and poloxamine has been used as one of the main techniques to limit phagocytic absorption by the reticuloendothelial system after intravenous delivery for several decades. These are hydrophilic blocks of ethylene oxide (EO) and hydrophobic blocks of propylene oxide (PO) monomer units, which are combined to form amphiphilic block copolymers. Poloxamines are PEO-PPO tetra block copolymers linked by ethylenediamine bridges, while poloxamers' are triblock copolymers type a-b-a (PEO-PPO-PEO) [76-78].

Due to the hydrophobic fraction of PPO, these polymers can be physically adsorbed to the nanoholder's surface. The hydrophilic fraction is physically exposed to the surface after the hydrophobic PPO portion physically adsorbs on the hydrophobic surface of the nanocarrier. According to several studies, the coating produced by poloxamine and poloxamer bestows a hydrophilic coating and lengthens the retention period in the systemic circulation. Susan *et al.* showed that the surface-modified PLGA nanoparticles with sizes ranging from 80 to 150 nm with polypropylene oxide-polyethylene oxide (PPO-PEO) block copolymers of the poloxamer and poloxamine series (poloxamer 407, poloxamine 904 and poloxamine 908) shows that poloxamer 407 or poloxamine 908 surface-modified PLGA nanoparticles display prolonged blood 39% and 28% of the injected dose of PLGA nanospheres coated with poloxamer 407 and poloxamine 908 respectively are still present in the blood circulation three hours after intravenous administration [79].

Polysaccharides: Polysaccharides are suitable for supplying nanocarriers in the bloodstream with a stealthy coating because of their hydrophilic nature. Several research groups created A surface-protected hydrophilic layer on the nanoparticle surface using derivatives of chitosan [80, 81], dextran

[82, 83], hyaluronic acid 84 and heparin [85–87,] which improved the circulation half-life. Additionally, polysaccharides possess multifunctional groups that are effective for ligand attachment and drug conjugation, are biodegradable, biocompatible, and less immunogenic and toxic [85, 88, 89].

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Zwitterionic Polymers: In 2012, Xio *et al*. created a new long-circulation contrast medium in the blood by adding a zwitterionic structure to the surface of magnetite nanoparticles coated with polyacrylic acid [92].

3-(Diethylamino) propylamine created the zwitterionic structure (DEAPA). EDC/NHS [N-(3-dimethylaminopropyl) -N'-ethylcarbo-diamides hydrochloride/N-hydroxy succinimide] coupling chemistry was used to perform DEAPA grafting. Compared to uncoated particles, these particles exhibit five times less macrophage cell absorption, a longer circulation period, and less cell toxicity [92].

It has been demonstrated that additional zwitterionic phospholipid derivatives reduce the complement activation brought on by liposomes.[93] The rate of opsonin adsorption in the bloodstream is decreased by zwitterionic polymers, which, like PEG, bind water molecules strongly and produce an electrostatically induced hydration layer by binding to them. Sulfobetaine and carboxylesterase are zwitterionic compounds that connect water molecules *via* electrostatic interactions more strongly than other betaines that rely on hydrogen bonding, such as PEG [95, 96]. As a result of the aforementioned data, zwitterionic polymers were determined to be similar to regularly used poly (ethylene glycol) (PEG) to give intravenously given nanocarriers a stealthy quality.

Polyglycerols: Polyglycerols (PGs) or polyglycerols are hydrophilic aliphatic polyether polyols that can be structured in branched or linear forms and are biocompatible, flexible, and have an antifouling effect similar to PEG [97-99]. Furthermore, polyglycerols have numerous hydroxyl groups and are hyper-branched, allowing additional functionalization [97]. Long circulation half-lives of hyperbranched polyglycerols (33 hours for 106 kDa and 57 hours for 540 kDa) indicate their potential as stealth polymers [100].

The blood circulation period is prolonged, and there is minimal protein adsorption in PG-decorated liposomes.[97,101] In 2009, Wyszogrodzka *et al*. investigated the interactions between a variety of hyperbranched polyglycerol dendrons modified by alkanethiols and a number of biofouling-relevant proteins, including fibrinogen, lysozyme, albumin, and pepsin. The findings showed that all polyglycerol dendrons have exceptional resistance to test proteins for the whole 24-hour study period [102].Hyperbranched polyglycerols resist the non-specific adsorption of proteins on magnetic nanoparticles. When it comes to preventing the adsorption of proteins, hyperbranched polyglycerols perform favourably on par with methoxy poly (ethylene glycol), a linear MPEG with a molecular weight of 750 [103]. Additionally, PGs are more heat and oxidative stress resistant than PEG, making them suitable candidates for biomedical applications [97].

Polyoxazolines: In amphiphilic block-co-polymers, polyoxazoline (POx) has been widely employed as a hydrophilic segment. To create polymeric micelles, poly (2-ethyl-2-oxazoline) must be connected with a hydrophobic block polymer, such as poly (epsilon-caprolactone) [104), poly (1,3-trimethylene carbonate) or poly (aspartic acid) [106].

Additionally, compared to PEG grafted poly (L-lysine), poly (2-ethyl-2-oxazoline) grafted with poly (L-lysine) was found to be a potential carrier for the delivery of non-viral therapeutic DNA.[107]Additionally, POx was demonstrated in a study to be equivalent to PEG in lengthening circulation time when used to graft liposomes [108]. Recent research on the cytotoxicity of poly(2-oxazoline) amphiphiles shows that, in general,

these polymers are not harmful, even at high concentrations [109].

Poly (Amino Acids): Poly (hydroxyethyl l-glutamine) or poly (hydroxyethyl-l-asparagine) (PHEA) are two examples of poly (amino acids) that have been developed as a substitute for PEG. These poly (amino acids) act as potential stealth polymers [101] and gets degraded without difficulty, reducing the risk of accumulation and toxicity [102]. Also, these polymers prolong the blood circulation of NPs at par with PEG. Additionally, PHEA coated liposomes proved to be more effective than PEGylated liposomes in maintaining the stealth effect of ABC at low lipid doses [103].

Biomimetic Approaches: Kopecek *et al.* [104] first described HPMA, which have a variety of features, including biocompatibility, hydrophilicity, and the capacity to adapt structural alterations, ushering in a new era in macromolecular drug delivery. Low molecular weight medicines with HPMA conjugations [105, 106] and targeting molecules [107-110] have longer circulation times, which promote EPR-mediated tumour accumulation. Drug conjugates facilitate drug release within cells with peptide linkers that are cleavable by enzymes (e.g., GFLG). In the last few decades, interest is growing towards biomimetic coating for imparting stealth character to intravenously administered nanocarriers so that they will remain in systemic circulation for a prolonged period.

RBC-Based Nanocarriers: Recently, a new approach for producing biomimetic nanoparticles has been motivated by body's own long circulatory entities, red blood cells (RBCs). RBCs are natural oxygen carriers, having a highly flexible structure with a circulation half-life of 120 days, representing an ideal system for prolonging the circulation time of intravenously injected nanocarriers beyond that of pegylated nanocarriers [8]. Doshi *et al.* and Markel *et al.* developed highly concave nanoparticles and showed that mechanobiological mimicry of RBCs can increase particle elasticity and extend their circulation time [27, 30]. Hu *et al.* have developed a new drug delivery platform that couples RBC membrane-derived vesicles with polymeric nanoparticles prepared from Poly (lactic-co-glycolic acid) (PLGA) polymer [110].

The discovery of RBC membrane proteins also showed that RBC surface-bound proteins prevent macrophage absorption. For instance, the RBC surface protein CD47 has been found to block macrophages from consuming RBCs [111]. Along with CD47, additional proteins have been found on the surface of RBCs, such as C8-binding proteins (C8bp), [112] homologous restriction proteins (HRP), [113] decay accelerating factor (DAF), membrane cofactor protein (MCP), complement receptor 1 (CR1) and CD59, [114] which prevent the complement system from recognizing them and thereby limit their uptake. In 2010, Tsai et al. created polystyrene beads with a CD47 surface and profiled them for macrophage uptake. It was discovered that polystyrene beads coated with CD47 block macrophage absorption [115].

Thus, the above findings gave the concept that if the delivery system possesses autologous surface characteristics to RBCs, then such a system might be able to make the delivery system long circulatory.

Biomimetic Mucin: With long sections of densely clustered serine and threonine residues containing O-linked glycans coupled with N-acetyl galactosyl amine found in the mucus of the epithelium, machines, a major family of large and heavily glycosylated proteins are known [116, 117]. Due to its amphiphilic nature, the machine behaves like a natural surfactant similar to Pluronic's [118]. The machine may have use as biocompatible coverings for synthetic materials because of its natural origin, protective role against pathogens, and anti-fouling properties that promote favourable host reactions, compatibility, and controlled cellular contact [119].

When these processes are used to change a nanoparticle's surface, surface epitopes are covered, resulting in a long-lasting, non-immunogenic nanoparticle. In 2013, Tasneem *et al.* created mucin-functionalized Poly lactic-co-glycolic acid (PLGA) nanoparticles by conjugating the mucin's amino group to the PLGA's terminal carboxylic acid groups, followed by the solvent evaporation method for synthesis. According to the findings, mucin-modified PLGA nanoparticles showed promise in preventing plasma protein (opsonin) adsorption, which then prevents complement and platelet activation.

TABLE 1: SOURCES OF LITERATURE

S. no.	Journal	Remark	Reference
1.	Journal of colloid and interface science	Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles	Thasneem Y *et al*. 2013
2.	Expert Opinion on Biological Therapy	Nanoparticles disguised as red blood cells to evade the immune system	Fang RH *et al*. 2012
3.	Journalof microencapsulation	Long circulating PEGylated PLGA nanoparticles of cytarabine for targeting leukemia.	Yadav KS *et al*. 2011
4.	Journal of controlled release	Endocytosis of nanomedicines. Journal of controlled release	Sahay G *et al*. 2010
5.	Journal of controlled release 2010	Polymer particle shape independently influences binding and internalization by macrophages	Sharma G *et al*. 2010
6.	Biomaterials.	Long-circulating polymeric nanoparticles bearing a combinatorial coating of PEG and water-soluble chitosan	Sheng Y *et al*. 2009
7.	Molecular pharmaceutics.	Factors affecting the clearance and biodistribution of polymeric nanoparticles	Alexis F *et al*. 2008
8.	Proceedings of the National Academy of Sciences of the United States of America	Role of target geometry in phagocytosis	Champion JA *et al*. 2006
9.	International journal of pharmaceutics	Opsonization, biodistribution and pharmacokinetics of polymeric nanoparticles	Peppas NA *et al*. 2006
10.	Biomaterials Science: An Introduction to Materials in Medicine Elsevier Academic Press, Amsterdam	Innate and adaptive immunity: the immune response to foreign materials. Biomaterials Science:	Mitchell R *et al*. 2004
11.	Advanced Drug Delivery Reviews	Nanosized cationic hydrogels for drug delivery: preparation, properties and interactions with cells	Vinogradov SV *et al*. 2002
12.	European journal of pharmaceutics and biopharmaceutics	Surface-modified biodegradable albumin nano-and microspheres. II: effect of surface charges on in vitro phagocytosis and biodistribution in rats	Roser M *et al*. 1998
13.	Biomaterials	Human serum albumin as a probe for surface conditioning (opsonization) of block copolymer-coated microsphere	Norman M *et al*. 1992

CONCLUSION: An excellent therapeutic approach against systemic infections is provided by long-circulating carrier systems. Among the different approaches used so far in this subject, pegylation and bio-molecular approaches appear to have a better therapeutic potential.

However, a thorough acute and chronic toxicological profiling of the system in blood is necessary to determine the therapeutic success of these techniques. The development of a suitable defence mechanism against systemic infections is aided by our improved understanding of the molecular effects of the opsonization process thanks to advances in molecular pharmacology and pharmaceutical technology.

ACKNOWLEDGEMENT: All authors thank the management and director of the Himalayan Institute of Pharmacy and Research, Rajawala, Dehradun, Uttarakhand, for providing the academic environment and scientific facilities for conducting the study.

CONFLICTS OF INTEREST: Author(s) has no conflict of interest

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How to cite this article:
Rawat M, Jaswal S, Bisht AS and Joshi R: Opsonization as a long circulatory approaches: a challenge in drug delivery. Int J Pharm Sci & Res 2023; 14(9): 4317-30. doi: 10.13040/IJPSR.0975-8232.14(9).4317-30.