WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 5, 165-175. Review Article ISSN 2277– 7105

IMPORTANCE OF NATURAL POLYMERS AS NANOPARTICLES FOR DRUG DELIVERY SYSTEM

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Article Received on
14 March 2022,
Revised on 03 April 2022,
Accepted on 24 April 2022
DOI: 10.20959/wjpr20225-22235

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ABSTRACT

Currently, natural and synthetic polymers are typically used as a drug delivery vectors in the form of nanoparticles and size should be within the range of 1-1000 nm. Nanoparticles improved bioavailability of water insoluble drugs, carry large payloads, protect the therapeutic agents from physiological barriers, as well as enable development of novel classes of bioactive macromolecules. Nanoparticles could be fabricated in many different shape and size using a wide range of organic and inorganic materials with polymer of natural or synthetic origin. The use of nanoparticles in the drug delivery systems and nanomedicine invariably requires parenteral administration, there has been a continues to be a major need for the use of polymeric carriers that are both biocompatible and biodegradable. The objective of the review focuses the application of nanotechnology to deliver therapeutic or diagnostic agents using biodegradable polymers.

KEYWORDS: Nanoparticles, Natural Polymer, Synthetic Polymer, Biodegradeable Polymer, Chitosan.

INTRODUCTION

Owing to their high surface area to volume ratio, it is possible to achieve high ligand density on the surface for targeting purposes.[1] Nanocarriers could be used to increase local drug concentration by carrying the drug within and control releasing it when bound to the targets.

The natural, synthetic and lipids polymers are typically used as drug delivery vectors.[2] Nanoparticles improved bioavailability of water insoluble drug, carry large payloads, protect therapeutic agents from physiological barriers as well as enable the development of novel classes of bioactive macromolecules. Materials at the nanometer scale often have different physical and biochemical properties from those of the same materials at bulk volume properties that make nanostructures attractive for diagnostic and therapy applications. Since the size of the nanoparticles is significantly smaller than a cell, they can deliver a large payload of drugs, contrast agents or fluorescent probe onto the surface or interior of the cell, without disrupting its function. These particles are able to deep penetrate tissues, going through the fenestration of the small blood vessel epithelial tissue. They can enter the systemic blood circulation without forming blood platelet aggregates.[2, 3]

The reduced particle size entails high surface area and hence a strategy for faster drug release. Drug delivery rates and particle integrity can be modulated and controlled by engineering carriers in such a way that they can be activated by changes in the environmental pH, chemical stimuli by the application of a rapidly oscillating magnetic field, or by application of an external heat source. Among the engineered constructs investigated and developed for this specific target are: polymeric micelles, dendrimers, polymeric and ceramic nanoparticles, protein cage architectures, viral-derived capsid nanoparticles, polyplexes and liposomes. There are several techniques for producing polymeric nanocarriers, such as soft lithography, nanoimprinting and injection molding, which are capable of fabricating nanostructures with complicated patterns and other easier processing methods for producing polymer membranes with nanopores, nanofibers, nanotubes and multiple nanofilms/layers.[3] Nanoparticles offered a number of advantages over free drugs as likes; Protect drug from premature degradation; Prevent drugs from prematurely interacting with the biological environment; Enhance absorption of the drugs into a selected tissue (for example, solid tumor); Control the pharmacokinetic and drug tissue distribution profile and Improve intracellular penetration.

For a rapid and effective clinical translation, nanocarrier should be made from a material that biocompatible, well characterized and easily functionalized, exhibit high differential uptake efficiency in the target cells over normal cells (or tissue), soluble or colloidal under aqueous conditions for increased effectiveness, extended circulating half-life, a low rate of aggregation and a long shelf life.

MATERIALS AND METHODS

Different materials have been used for nano carrier systems like albumin, gelatin, starch, ethyl cellulose and synthetic polymers such as poly lactic acid, poly cyanoacrylates and poly hydroxybutyrate. Routes of administration are by injection, i.e. intravenous, intramuscular and intraarticular or by the nasal route. Natural polymers can also be used to manufacture nanocarriers for drug delivery. Among them the most utilized polymers are gelatin, dextran and chitosan. In general nanoparticles have high encapsulation efficiency like;

1) Nanoscale drug carriers can enter into the capillaries, and freely flow in the blood circulation. It also can go through cells, be absorbed though pinocytosis by histiocyte and enhance bio-availability of drug.

2) Because the specific surface area of nano-drug carriers is very high, solubility of poor water-soluble drugs in the nano-carrier is relative enhanced and overcome the problems preparation with conventional methods.

3) Nano-carriers can be made to targeted position system, decrease the dose of drug and reduce the side effects with special processing.

Release Mechanism of Biodegradable Polymers: Biodegradable polymers release drug in one of the two ways: erosion and diffusion. Release from biodegradable polymers *in-vivo* is governed by a combination of both mechanisms, which depends on the relative rates of erosion and diffusion. Erosion is defined as the physical dissolution of a polymer as a result of its degradation.[3, 4] Most biodegradable polymers used for drug delivery are degraded by hydrolysis. Hydrolysis is a reaction between water molecules and bonds in the polymer backbone, typically ester bonds, which repeatedly cuts the polymer chain until it is returned to monomers. Other biodegradable polymers are enzymatically degradable, which is also a type of chain scission. As water molecules break chemical bonds along the polymer chain, the physical integrity of the polymer degrades and allows drug to be released. There are two possible mechanisms of erosion. When water is confined to the surface of the matrix, as in the case of a hydrophobic polymer, chain scission will occur only on the surface and the drug will be released as the surface of the polymer matrix erodes. If the water penetrates the polymer matrix faster than it hydrolyzes the bonds on the surface, then erosion will occur throughout the entire material called as bulk erosion. In many cases, the erosion of a polymer matrix *in-vivo* is some combination of these mechanisms. Degradation by surface erosion alone may be preferred, because the degradation rate can be controlled through the surface area of the matrix.[4] In the case of diffusion controlled release, the drug's concentration

gradient in the polymer matrix is the driving force for the molecules to diffuse into the surrounding medium. The diffusion of a drug molecule through the polymer matrix is dependent upon the solubility of the drug in the polymer matrix and the surrounding medium, the diffusion coefficient of the drug molecule, the molecular weight of the drug, its concentration throughout the polymer matrix, and the distance necessary for diffusion. Drugs can be either distributed evenly throughout the matrix or encapsulated as a reservoir.[5] The release rate for the reservoir system factors in the membrane thickness and area. Practically, reservoir systems often have a lag period after placement *in-vivo*, as opposed to the burst release present for most other systems. However, these systems need to be carefully engineered to prevent premature membrane rupture that might release a toxic amount of drug into the body.

When a drug dissolved in the matrix and the mechanism for delivery is diffusion, then the driving force for release is the concentration gradient and release predictions can be made based on Fick's laws of diffusion. Cumulative release from diffusion-controlled matrix devices is inversely proportional to the square root of time. This presents an engineering challenge because surface area becomes smaller due to degradation, with a resulting decrement in the release rate.

4) By controlling the degradable speed of polymers *in-vivo*, nano-carriers can extend biological half-life of drug, improve the efficacy of the short-half-life drugs and reduce side effects of medication.

5) Because of eliminating the limit of specific barriers such as blood brain barrier, blood ocular barrier and cell membrane barrier to the drug, nano-particulate drug carriers can pass through these barriers to treat scathing sites.

The central principle of nano drug carrier is to realize drugs delivery effective, safe and controllable. Therefore, targeting, controlled release and safety of drugs an important and topical issues in pharmacy research area. The emergence of nano delivery system make feasible to realize targeting and controlling release of drug.

Polymer Molecular Weight: Polymer molecular weight, being an important determinant of mechanical strength, is a key factor in determining the degradation rate of biodegradable polymers. Low molecular weight polymers degrade faster than high molecular weight

polymers thereby losing their structural integrity more quickly. As chain scission occurs over time, the small polymer chains that result become more soluble in the aqueous environment of the body. This introduces holes into the polymer matrix. Consequently, lower molecular weight polymers release drug molecules more quickly. This can be used to further engineer a system to control the release rate. A combination of molecular weights might be used to tailor a system to meet the demands of specific release profiles.

Preparation of Nanoparticles: Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials dependent upon the following parameters like; size of nanoparticles required, inherent properties of the drug, e.g., aqueous solubility and stability, surface characteristics such as charge and permeability, degree of biodegradability, biocompatibility and toxicity, drug release profile desired and antigenicity of the final product.

Nanoparticles have been prepared most frequently by three methods as dispersion of preformed polymers, polymerization of monomers and ionic gelation or coacervation of hydrophilic polymers. However, other methods such as supercritical fluid technology and particle replication in non wetting templates (PRINT) have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry.[6,7] Various methods which can be used to study the *in-vitro* release of the drug like, side by side diffusion cells with artificial or biological membranes, dialysis bag diffusion technique, reverse dialysis bag technique, agitation followed by ultracentrifugation/centrifugation, Ultra-filtration or centrifugal ultra-filtration techniques. Usually the release study is carried out by controlled agitation followed by centrifugation.[7] Due to the time consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred. There are following a number of the advantages of natural plant based materials using natural polymers in the preparation of nanoparticles as polymers. ***Local availability;*** Developing countries governments promote the production of plant because of the wide application in a variety of industries. ***Biocompatible and non-toxic;*** Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (mono saccharides) units. Hence, they are non- toxic. ***Low cost;*** It is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many

developing countries are dependent on agriculture. ***Biodegradable;*** Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health (*e.g.*, skin and eye irritation).

Passive Targeting and Active Targeting Using Nanoparticles: Drug targeting strategies have frequently been divided into categories of passive and active. These terms, however, do not represent what is really occurring *in-vivo* and tend to cause misunderstandings in defining a specific drug targeting strategy called as passive targeting and based on drug accumulation in the areas around the tumors with leaky vasculature; commonly referred to as the enhanced permeation and retention (EPR) effect (more on the EPR effect below). Passive targeting happens to almost all drug carriers whether such distribution is intended or not. While the EPR effect may be in effect for i.v. administered nanoparticles, the majority (N 95%) of administered nanoparticles are known to accumulate in other organs, in particular the liver, spleen and lungs. Does this mean there a passive targeting to these unintended? If N 95% of an administered dose ends up at unintended sites of the body, the outcome can hardly be described as selective. The bottom line is that passive targeting is a misnomer. Rather there is simply distribution of drug or drug delivery system by blood circulation. The term passive targeting needs to be replaced with blood circulation and extravasations, which is not limited to drug delivery to tumors. Successful therapeutic application of blood circulation and extravasations can be achieved through technologies, such as locally activated delivery, where drug release and/or drug actions are limited to selective sites within the body such as a tumor but not the liver. Active targeting is used to describe specific interactions between drug/drug carrier and the target cells, usually through specific ligand-receptor interactions. The ligand-receptor interactions are possible only when the two components are in close proximity. The term active targeting has a flavor of guiding a drug/drug carrier to a target site like a cruise missile does. Current drug delivery systems, however, do not have the ability to guide a drug/drug carrier to a target site like a cruise missile does. Current drug systems, however, do not have the ability to guide themselves to a target. They reach the target area as a result of blood circulation and extravasations followed by intratumoral retention and distribution.[8] The term active targeting simply means a specific ligand-receptor type interaction for intracellular localization which occurs only after blood circulation and extravasations. This is why increasing blood circulation time by PEGylation (i.e., modifying the surface of nanoparticles with poly (ethylene glycol)) and improving the EPR effect is

expected to enhance delivery to the tumor site. Previous studies have shown that the presence of the tumor-targeting ligand does not always result in increased accumulation of the nanoparticles in tumors, suggesting that active targeting does not automatically translate into effective delivery to the entire tumor.

Classification of the current targeted drug delivery processes default pathway delivery to the following;

1. Systemic targeting based on blood circulation and extravasations;

a. Ligand-receptor interaction mediated

b. Locally-activated delivery

i. Self-triggered release of the drug at the target cells

ii. Externally-activated release of the drug at the target cells

2. Intracellular targeting;

a. Low-pH activation technologies that use lysosomes

b. Mechanisms that avoid (default) lysosomal delivery

Biodegradable Polymers Used in the Preparation of Nanoparticles

Gelatin: Gelatin is obtained by either alkaline or acidic hydrolysis of collagen. It has a triple helical structure with a high content of glycine, proline and hydroxyproline residues. Gelatin that is formed from alkaline treatment of collagen has more carboxyl groups and a lower isoelectric point than that derived from acidic hydrolysis. The physicochemical properties of gelatin depend on the method of extraction and the extent of thermal denaturation that occurs during the purification. Gelatin nanoparticles can be prepared by various methods, including chemical cross linking, water in oil (w/o) emulsification and desolvation. Gelatin is cross linked with agents such as glutaraldehyde. Efficient cross linking usually results in decreased rate of drug release. Water in oil emulsification involves extruding a preheated aqueous solution of gelatin into vegetable oils such as corn or olive oil.[6] The two step desolvation method involves the drop wise addition of water miscible non solvent such as acetone and ethanol. While the use of collagen, the parent compound of gelatin, in drug delivery is rare, collagen nanoparticles have been used to deliver genes by exploiting the electrostatic interaction between the positively charged polymer and negatively charged deoxyribonucleic acid.[7]

Chitosan: Chitosan is a modified natural carbohydrate polymer prepared by the partial N-deacetylation of chitin, a natural biopolymer derived from crustacean shells such as crabs,

shrimps and lobsters. Chitosan found in some microorganisms, yeast and fungi. The primary unit of chitin polymer is 2-deoxy-2-(acetylamino)glucose. These units combined by glycosidic linkages, forming a long chain linear polymer.[7] Although chitin is insoluble in the most solvents but soluble in most organic acidic solutions at pH less than 6.5 including formic, acetic, tartaric acid it is insoluble in phosphoric and sulfuric acid. Chitosan can be described in general by the following parameters; degree of deacetylation in %, dry matter in %, ash in %, protein in %, viscosity in Centipoise, intrinsic viscosity in ml/g, molecular weight in g/mol, turbidity in NTU units. All of these parameters can be adjusted to the application for which chitosan is being used. The deacetylation is very important to get a soluble product. In general, the solubility of heteroglucans influenced by the distribution of the acetyl groups, the polarity and size of the monomers, distribution of the monomers along the chain, the flexibility of the chain, branching, charge density and molecular weight (50,000-2,000,000 Da) of the polymer. Viscosity (10-5000 cp) can be adjusted to each application by controlling the process parameters.

Applications of Chitosan Nanoparticles as Parenteral Administration; Nano sized particles can be administered intravenously because the diameter of the smallest blood capillary is approximately 4 μm. Particles greater than 100 nm in diameter are rapidly taken up by the reticuloendothelial system (RES) in the liver, spleen, lung and bone marrow, while smaller-sized particles tend to have a prolonged circulation time. Negatively-charged particles are eliminated faster than positively-charged or neutral particles. In general, opsonins (serum proteins that bind to substrates leading to their being taken up by the RES) prefer to adsorb on hydrophobic rather than hydrophilic surfaces. The creation of a hydrophilic coating (such as polyethylene glycol (PEG) or a nonionic surfactant) on hydrophobic carriers significantly improves their circulation time. Together, these data suggest that generating nanoparticles with a hydrophlilic but neutral surface charge is a viable approach to reduce macrophage phagocytosis and thereby improve the therapeutic efficacy of loaded drug particles. The most promising drugs that have been extensively studied for delivery by this route are anticancer agents. Following intravenous injection, many nanoparticle systems including chitosan NP exhibited a marked tendency to accumulate in a number of tumors. One possible reason for the phenomenon may involve the leakiness of tumor vasculature. Doxorubicin loaded chitosan NP showed regression in tumor growth and enhance survival rate of tumor-implanted rats after IV administration.[8] In addition, chitosan NP less than 100 nm in size have been developed which showed to be RES evading and circulate in the blood for

considerable amount of time. Delivery of anti-infectives such as antibacterial, antiviral, antifungal and antiparasitic, is another common use of nanoparticles. The low therapeutic index of antifungal drugs, short half-life of antivirals and limited ability of antibiotics to penetrate infected cells in intracellular compartments make them ideal candidates for nanoparticle delivery. Thus, it has been suggested that nanoparticles should improve the therapeutic efficacy while decreasing the toxic side effects of these drugs. In theory, chitosan NP are very attractive carrier system for these drugs as they offer many advantages such as hydrophilic surface particles, nano-size of less than 100 nm.[9]

Applications of Chitosan Nanoparticles as Ocular Administration: Among mucoadhesive polymers explored now, chitosan has attracted a great deal of attention as an ophthalmic drug delivery carrier because of its absorption promoting effect. Chitosan not only enhance cornea contact time through its mucoadhesion mediated by electrostatic interaction between its positively charged and mucin negatively charged, its ability to transient opening tight junction is believed to improve drug bioavailability. It was found that chitosan solutions prolonged the cornea resident time of antibiotic in rabbits. The same effects were also observed employing chitosan NP as demonstrated by that chitosan NP remained attached to the rabbits cornea and conjunctiva for at least 24 hr.[9] In addition, found that after ocular administration of chitosan NP in rabbits most of drug were found in extra ocular tissue, cornea and conjunctiva, while negligible drug were found in intraocular tissues, iris or ciliary body and aqueous humor. Together, these results suggested that chitosan NP showed to be attractive material for ocular drug delivery vehicle with potential application at extra ocular level.

Fibrin: Fibrin and fibrinogen have a well established application in research in tissue engineering due to their innate ability to induce improved cellular interaction and subsequent scaffold remodelling compared to synthetic scaffolds. Furthermore, due to its biochemical characteristics, mainly in cellular interactions, fibrin-based materials also found applications in the field of drug delivery with special focus in cell delivery. Fibrin is a protein matrix produced from fibrinogen, which can be autologously harvested from the patient, providing an immunocompatible carrier for delivery of active biomolecules, especially cells. Polymerized fibrin is a major component of blood clots and plays a vital role in the subsequent wound healing response. *In-vivo*, formation of fibrin clots is initiated by vascular injury, which causes the release of the enzyme thrombin, a serine protease that activates

many constituents of the coagulation cascade. Thrombin cleaves peptide fragments from the soluble plasma protein fibrinogen, yielding insoluble fibrin peptides that aggregate to form fibrils. A fibrin meshwork formed, which entraps platelets and other blood-borne components to create a clot that is stabilized through cross linking by the transglutaminase Factor XIII. In addition, fibrin naturally contains sites for cell, and therefore has been investigated as a substrate for cell adhesion, spreading, migration and proliferation. Fibrin glue is a biological adhesives also used in surgery (abdominal, thoracic, vascular, oral, endoscopic) due to its haemostatic, chemotactic and mitogenic properties.[10] Fibrin glue mimics the last step of the in vivo coagulation cascade through activation of fibrinogen by thrombin, resulting in a clot of fibrin with adhesive properties.

Alginate*:* Alginate is a polysaccharide derived from brown seaweed. Like chitosan, alginate can be processed easily in water and has been found to be fairly non-toxic and non-inflammatory, enough so that it has been approved in some countries for wound dressing and for use in food products. Alginate is biodegradable has controllable porosity, and may be linked to other biologically active molecules.[11] Alginate forms a solid gel under mild processing conditions, which allows it to be used for entrapping cells into beads and other shapes. Interestingly, encapsulation of certain cell types into alginate beads may actually enhance cell survival and growth. In addition, alginate has been explored for use in liver, nerve, heart and cartilage tissue engineering. Unfortunately, some drawbacks to alginate include mechanical weakness and poor cell adhesion. Again, to overcome these limitations, the strength and cell behavior of alginate have been enhanced by mixtures with other materials, including the natural polymers agarose and chitosan. Collagen, chitosan, and alginate are just a few of the many natural polymers that are currently being studied as biomaterials. Their natural biological compatibility and activity make them attractive candidates for a variety of biomedical applications. Exploring how these polymers work and how they are designed by nature can help us better engineer synthetic materials to mimic these successful natural scaffolds.

CONCLUSION

Natural origin polymers have received considerable interest for drug delivery and tissue engineering applications. However, the combination of both applications into a single material has proven to be very challenging. From the points of review, we can conclude that the properties of natural origin materials that render them attractive for applications where the

combination of a scaffold material and a carrier for an active biomolecules desirable. Because of Nano drug a new type of drug, the development of Nano drug will cause the revolution of the diagnosis and treatment. Recently, Nano-technology has been applied in the traditional Chinese medicine and it gave birth to the new concept 'Nano Chinese Medicine'. Among the activity of Chinese medicine, effective site, the original drug, compound and new agents using Nano-technology has made some progress. However, at present, the basic theory of Nano-technology applied in medicine and preparation of nano drugs are still incomplete, especially the safety of nano medicines has many problems remain to be explored in depth. Therefore, the research in the field of Nano-technology applied in medicine has a great deal with the work which needs to be done.

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