FABAD J.Pharm. Sci., 38,2, 107-118, 2013

RESEARCH ARTICLE

Biodegradable Polymeric Nanoparticles are effective Systems for Controlled Drug Delivery

Hazal Ezgi GÜLTEKİN[*], Zelihagül DEĞİM[*o]

Biodegradable polymeric nanoparticles are effective systems for controlled drug delivery

SUMMARY

Biodegradable polymeric nanoparticles are drawing attention in the use of controlled drug delivery systems recently. These nanoparticles are biodegradable/biocompatible systems and they provide specific delivery for many molecules such as drugs, vaccines, peptide/proteins and genes. Because of having various advantages, biodegradable polymeric nanoparticles are widely used in many areas. In this article; the general properties, preparation methods, specific application areas and drug release characteristics of biodegradable polymeric nanoparticles have been reviewed.

Key Words: *Biocompatible, biodegradable, nanoparticles.*

Biyoparçalanabilir polimerik nanopartiküller kontrollü ilaç taşıyıcılar için etkili sistemlerdir

ÖZET

Biyoparçalanabilir polimerik nanopartiküllerin kontrollü ilaç taşıyıcı sistemlerde kullanımı son zamanlarda dikkat çekmektedir. Bu nanopartiküller biyoparçalanabilir/biyouyumlu sistemlerdir ve ilaç, aşı, peptit/proteinler ve genler gibi birçok molekülün spesifik taşınmasını sağlar. Biyoparçalanabilir polimerik nanopartiküller, çeşitli avantajlara sahip olmaları nedeniyle birçok alanda yaygın kullanılırlar. Bu makalede; biyoparçalanabilir polimerik nanopartiküllerin genel özellikleri, hazırlama metotları, spesifik uygulama alanları ve ilaç salım karakteristikleri derlenmiştir.

Anahtar kelimeler: *Biyouyumlu, biyoparçalanabilir, nanopartiküller*

Received: 22.04.2016
Revised: 30.05.2016
Accepted: 01.07.2016

[*] Department of Pharmaceutical Technology, Gazi University Faculty of Pharmacy, 06330 Ankara, Turkey

[o] Corresponding Author Address:
E-mail: zdegim@gazi.edu.tr

INTRODUCTION

Nanotechnology has gained importance in many areas recently. Nanostructured materials are materials having size of 1-100 nm range, which have certain properties and functions because of their ‘’size effect”. Biological systems such as viruses, membranes and protein complexes are natural nanostructures. Therefore, nano-sized materials have the capacity of being utilized with biomedical devices (1). In recent years, nanotechnology is used for the purpose of drug and vaccine delivery (2).

Nanoparticles with variable structure and properties have been formulated for various therapeutic applications (3). Also they allow the delivery of small moleculer weight drugs as well as macromolecules like proteins, peptides and genes in the body via various administration routes. This provides delivery of the macromolecules to specific targeted tissue or organ (2). In this article preparation of biodegradable polymeric nanoparticles and their applications in the area of medicine has been reviewed (2).

Polymeric nanoparticles are submicron-sized colloidal particles, which a therapeutic agent can be encapsulated within their polymeric matrix or adsorbed to the surface (2). Natural or synthetic polymers are used to prepare polymeric nanoparticles. Natural polymers such as proteins and polysaccharides have not been widely used because of their problems in preparation. Therefore, synthetic polymers are more preferable in this field. The most widely used synthetic polymers for nanoparticles are poly(lactic acid) (PLA) , poly(glycolic acid) (PGA) and their copolymers, poly(lactide-co-glycolide (PLGA). These polymers are biocompatible and resorbable in natural conditions (4). The choice of the polymer depends on the properties of the system such as therapeutic application of the formulation, targeted drug release profile, biocompatibility, etc. (3).

Biodegradable polymers are widely used in many fields such as tissue engineering, regenerative medicine, gene therapy, novel drug delivery systems and implantable devices (5). Controlled drug delivery systems are one of the most common areas in which biodegradable polymers are applied. Biodegradable polymers have long been used in controlled release technology because of their reabsorbing ability by the body (6). Biodegradable polymers can be natural or synthetic. However, synthetic polymers are more advantageous than natural ones (7). Synthetic biodegradable polymers are biologically inert, in general. Their more predictable properties, batch-to-batch uniformity, suitable profiles for specific applications and being deprived of many disadvantages of natural polymers make them more preferable (8). The biodegradation mechanisms of biodegradable polymers are shown in Figure 1.

Biodegradable nanoparticles deliver the drug to a target site effectively increasing the therapeutic benefit and minimizing side effects. On the other hand, they provide controlled release of pharmacologically active agents to the spesific site with optimal rate and dose regimen (9).

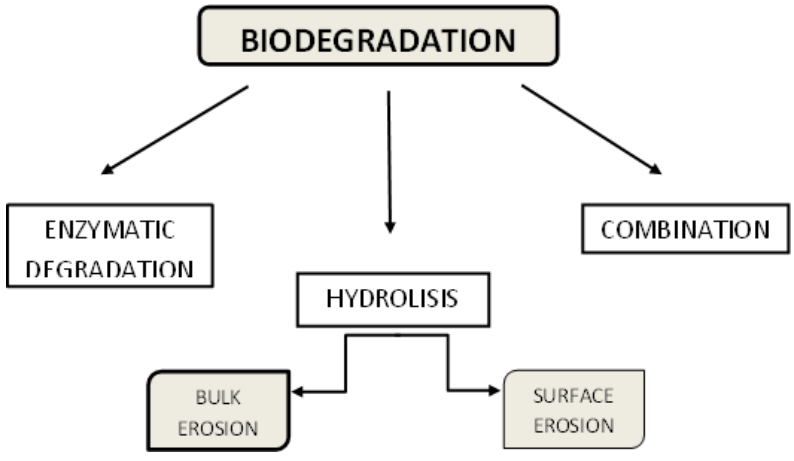

Figure 1. Biodegradation Mechanisms of Biodegradable Polymers

Preparation of biodegradable nanoparticles

Many methods are used for the preparation of biodegradable polymeric nanoparticles. The nanoparticle formulation can require a polymerization reaction or can be achieved directly from a macromolecule or preformed polymer(10). According to various designs and final application factors the base polymer is selected. There are many effective factors like size of the target nanoparticles, characteristics of the active agent(solubility, stability,etc.) to be encapsulated in the polymer, surface properties and functionality, state of biodegradability-biocompatibility and drug release profile of the gained product. According to these criteria the methods can be classified into three basic methods such as *(i)*dispersion of preformed polymers, *(ii)*polymerization of monomers and *(iii)*ionic gelation method (2).

Polymerization of Monomers

It is also possible that nanoparticles are prepared by polymerization of monomers (10). Vaccines or drugs are encapsulated in the nanoparticles by two techniques such as dissolving the drug in the polymerization medium and adsorption/conjugation of the therapeutic agent onto the polymerizated and formed nanoparticles. The gained nanoparticle suspension is purified via removing stabilizers. The surfactants used, can be recycled for following polymerization (2). This is a simple and effective method to prepare biodegradable polymeric nanoparticles (11).In this technique the effect of variables such as organic solvent concentration, type of surfactant and amount of monomer used in polymerization must be evaluated (12).

Dispersion of Preformed Polymers

Many monomers are suitable for a micellar polymerization in aqueous phase and they can compose slowly biodegradable or nonbiodegradable polymers but the residuel molecules in the polymerization medium can be toxic. Because of these problems, methods using preformed polymers are more preferable than monomer polymerization methods (10).

Emulsification/solvent evaporation method

Emulsification/solvent evaporation method has two steps. In the first step, the polymer solution is emulsificated into an aqueous phase and in the second step, polymer solvent is evaporated to induce polymer precipitation as nanospheres (10).

In this technique, the polymer is dissolved in an organic solvent like dichloromethane, chloroform or ethyl acetate. The drug is dissolved or dispersed into the preformed polymer solution, after that the obtained mixture is emulsified into an aqueous solution to attain an oil in water (O/W) emulsion using various surfactant/ emulsifying agents. After having a stable emulsion, the organic solvent is evaporated via increasing temperature or continuous stirring (9). Figure 2 shows a schematic representation of emulsification/solvent evaporation method (10). Frequently used biodegradable polymers in this technique are PLA and PLGA.

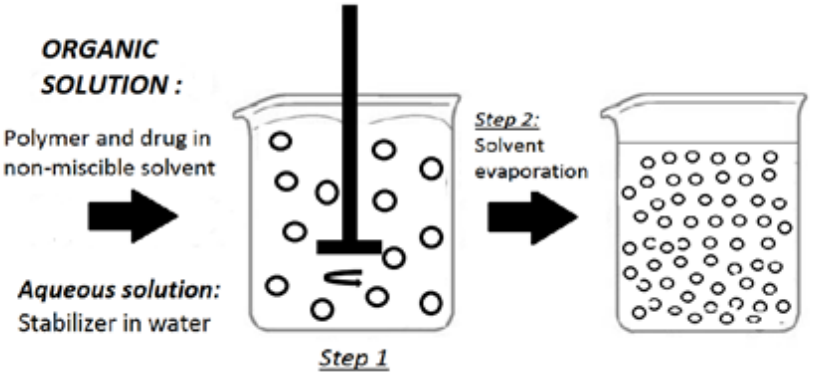

Figure 2. Schematic represantation of the emulsification/solvent evaporation method

Emulsification/Solvent Diffusion Method

Emulsification/solvent diffusion method was suggested in the literature as an organic solvent using based procedure, and then it was adapted to the salting-out technique(mentioned below). It includes dissolution of the encapsulating polymer in a partially water soluble solvent such as propylene carbonate and saturation with water. Gained polymer-water saturated solvent phase is emulsified in an aqueous solution, which contains stabilizer, to induce solvent diffusion to the external phase and to form biodegradable nanoparticles. After that, the solvent is removed by evaporation or filtration (10).

Nanoprecipitation method

Nanoprecipitation method is simple, reproducible and and has been used widespread (13). The main principle of this method is the interfacial deposition of a polymer(synthetic, semi synthetic and natural) after diplacement of a semipolar solvent, which is miscible with water, from a lipophilic solution. After the rapid diffusion of the solvent(i.e. ethanol, acetone, hexane, methylene chloride or dioxane) into non-solvent phase, the decrease of interfacial tension among the two phases becomes. It leads to the formation of small droplets of organic solvent by increasing the surface area (14).

Salting out method

The methods mentioned above require the use of organic solvents, which are hazardous to the environment and to the physiological system. In order to meet the requirements (about the residual amount of organic solvents in colloidal systems) which were specified by US FDA, the salting out method has been developed (9).

In salting out method, the polymer is dissolved in a water-miscible organic solvent such as acetone or tetrahydrofuran (THF). After that, the organic phase is emulsified in an aqueous phase. The required aqueous phase should contain the emulsifier and a high concentration of salts which are not soluble in the organic phase (2).

Ionic gelation

Various natural macromolecules have been used to preapare biodegradable polymeric nanoparticles such as gelatin, alginate, chitosan and agarose. These hydrophilic natural macromolecules are suitable polymers to prepare nanoparticles by the ionic gelation method (2).

The ionic gelation method includes a complexation between the negative and positive charges of a cross-linking agent and the hydrophilic polymer in a determined pH value (15). The ionic interaction between different charges at room temperature leads to the transition of materials from liquid to gel. Preparing chitosan nanoparticles by ionic gelation with tripolyphosphate (TPP) is a commonly used method (16). Diop et al. prepared insulin-loaded chitosan nanoparticles by ionic gelation method. They used sodium tripolyphosphate as cross-linking agent. The study demonstrated the bioefficiency of the polymeric nanoparticles on diabetic rats (17).

Surface modification of biodegradable polymeric nanoparticles

After intravenous administration of polymeric nanoparticles, the body immune systems recognize them easily and eliminate from the circulation. Not only size of nanoparticles, their surface properties also determine the amount of adsorbed blood components, mostly opsonins named proteins. Opsonization is the process of binding opsonins to the surface of nanoparticles and renders them a target for phagocytes (9). This process decreases the circulating time of the nanoparticles in blood. Because of that, a surface modification is necessary to design long-circulating nanoparticles (9).

Surface modification increases the stability of nanoparticles in blood. Surface of the biodegradable nanoparticles can be coated with biocompatible hydrophilic polymers, surfactants or copolymers with hydrophilic properties (18).

The desired surface characteristics can be achieved by coating nanoparticles with hydrophilic polymers (19). Poly-(ethylen glycol) (PEG) polimers are one of the most popular materials to modify nanoparticles(20).

PEG is a nonionic, nontoxic, hydrophilic polymer. It is also an effective stabilizer because of its high hydrophilicity, chain flexibility, electrical neutrality and absence of functional groups (19).PEG causes a steric, hydrated barrier on nanoparticles and protect them from opsonization (2).

Except PEG, there are many polymers used in surface modification. These polymers are also soluble and hydrophilic. Synthetic polymers of the vinyl series, such as poly(acryl amide) (PAA) and poly(vinyl pyrrolidone) (PVP) can be used to modificate particular systems (21).

In a study by Gaumet et al. PLGA nanoparticles were prepared and coated with chitosan to increase surface hydrophilicity. The in vitro studies showed that the surface modified nanoparticles were more effectively interact with Caco-2 cells (an human intestinal cell model for particle uptake studies) than uncoated PLGA nanoparticles. In brief, the hydrophilic characteristics of chitosan provided enhancing the interaction of the nanoparticles with intestinal cells (22).

Drug loading of biodegradable polymeric nanoparticles

Drug loading efficiency is an important property for nanoparticles. The therapeutic agents can be loaded into the biodegradable polymeric nanoparticles by two methods: firstly, by encapsulating of drug molecule at the same time of nanoparticle production or secondly, by adsorbing/conjugating the drug to the formed nanoparticles by incubating them in the drug solution. The drug entrapment efficiency can be higher by using the firstly mentioned method (9).

Drug release from biodegradable poylmeric nanoparticles

Drug release from nanoparticles and following biodegradation steps are significant for developing a successful formulation. The release rates of nanoparticles are associated with;

desorption of the conjugated/adsorbed drug, diffusion through the nanoparticle matrix, nanoparticle matrix erosion and the combination of erosion-diffusion process. Therefore, diffusion and biodegradation mechanisms control the process of drug release (9).

Methods to determine in vitro release profile of the nanoparticles are (a) side-by side diffusion cells with artifical or biological membranes; (b) dialysis bag diffusion method; (c) reverse dialysis sac method; (d) ultracentrifugation; (e) ultrafiltration; (f) centrifugal ultrafiltration method (9).

Biodegradable Polymers for Preparation of Biodegradable Polymeric Nanoparticles

Many polymers can be utilized to prepare biodegradable nanoparticles. These polymers must be biodegradable and biocompatible in particular.

Poly (lactic acid) (PLA)

PLA is a thermoplastic biodegradable polymer (23). It is an aliphatic polyester which degrades into a natural product : L-lactic acid (24). PLA has many applications in biomedicine area; such as sutures, stents, dialysis media and drug delivery systems (23). The nanoparticles prepared with PLA allow the encapsulation of hydrophobic molecules (25). PLA is a biodegradable and biocompatible polymer. Therefore, use of PLA nanoparticles as drug delivery system is safe. In general, PLA nanoparticles are prepared by solvent evaporation, solvent displacement methods (2).

Poly(lactide-co-glycolide) (PLGA)

Poly(lactide-co-glycolide)(PLGA), shown in Figure 3, is a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA)(3,26). It is a widely used polyester and it is in the class of biodegradable polymers for pharmaceutical use because of its biodegradability and biocompatibility (13).

PLGA has US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approval in humans (27). Thus, PLGA and its different derivatives have been used in controlled delivery systems. It is capable of carrying a large number of therapeutic molecules. PLGA-based biodegradable nanoparticles are also suitable for oral drug delivery (28).

PLGA produces biodegradable metabolite monomers (lactic acide and glycolic acid) after degradation in the body. Because of these two monomers there is no systemic toxicity related by using PLGA for drug delivery applications (29).

PLGA and its modified polymers have been also used to form nanoparticles by overcoming the dissolution and bioavailability problems of poorly water soluble drugs. Their low intrinsic toxicity, form of encapsulating matrices and degradation at a optimal rate into harmless byproducts make these polymers useful in controlled drug delivery systems (30).

Poly(caprolactone) (PCL)

Poly(caprolactone) (PCL) (Figure 4) is exposed to ester hydrolysis in physiological conditions. It can be used in long-term implantable systems because of its slow degradation rate. Its high permeability to various drugs and low toxicity properties make PCL suitable for colloidal drug delivery (3,31). The methods for preparing PCL nanoparticles are: nanoprecipitation, solvent displacement and solvent evaporation (29).

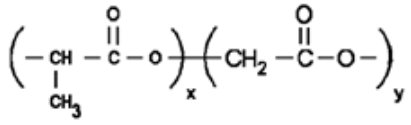

Figure 3. Structure of PLGA, x and y indicate the number of times each unit repeats

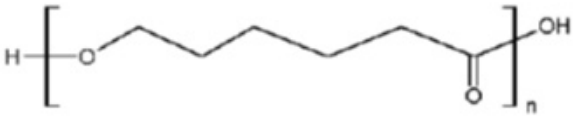

Figure 4. Structure of poly (caprolactone) (PCL)

Chitosan

Chitosan is a biodegradable and biocompatible polymer obtained by the deacetylation of chitin which presents in crustacean shells, in insect exoskeletons and in fungal cell walls. Chitosan has a wide range of applications such as tissue engineering, food science, micro and nano structured drug delivery systems (16).

There is an electrostatic interaction between positively charged chitosan and negatively charged mucosal tissue and this makes chitosan mucoadhesive (32). One of the most preferable techniques used to prepare chitosan nanoparticles is ionotropic gelation with tripolyphosphate(TPP) (16). Chitosan-TPP nanoparticles have a cationic surface and it provides a quick and unselective celluler uptake in all phagocytic cells. Therefore, for the preferential uptake of the nanoparticles in spesific cell types, chemical modification of chitosan can be required (16).

Poly-alkyl-cyano-acrylates (PAC)

Poly-alkyl-cyano-acrylates (PAC) are biodegradable and biocompatible polymers. But their degradation products are toxic for santral nervous system. Therefore, application of this polymer in humans is not approved. PAC nanoparticles can be prepared by emulsion polymerization, interfacial polymerization and nanoprecipitation methods (29).

Gelatin

Gelatin is a widely used polymer in food and medical products (29). It is a denatured protein obtained by partial acid or alkaline hydrolysis of animal collagen and has many advantages such as: being cheap, biodegradable, biocompatible and having relatively low antigenicity. It does not produce toxic products after degradation in the body (33). The mechanical properties, swelling behaviour and thermal sensitivity of gelatin is relates to its crosslinking degree. Because of having nontoxic, biodegradable, bioactive, cost-effective features; it is suitable for controlled release (29).

The extravasculer administration of gelatin has been approved by FDA. It has been also used as a stabilizer in many protein formulations and vaccines (33). Because of their submicron particle size, gelatin nanoparticles exhibit enhanced particle degradation rate and drug release rate (34).

The biodegradability, biocompatibility, chemical modification potential and cross-linking possibility of gelatin nanoparticles make them favourable carrier systems for drug and gene delivery (33).

Specific application areas of biodegradable polymeric nanoparticles

a) Tumor Targeting

Nanoparticles are colloidal carrier systems and this makes them more adventageous over other drug carriers. These advantages are: high drug loading capacity, the suitability of controlling size and permeability of the carrier and the prevention of the encapsulated drug's metabolism (35).

Long circulating 'stealth' nanoparticles such as poly(ethylene glycol)-coated nanoparticles (PEG-NP) provides greatly enhancement of the drug's therapeutic index. Because of their prolonged circulation time they are capable of accumulating in tumors. However, having long circulation time is not a sufficient property for nanoparticles. For active tumor targeting of nanoparticles two main methods can be used: 1)Direct targeting method; 2) Pre-targeting method. In direct targeting, nanoparticles are covalently coupled with the ligand. Therefore, the drug molecule and the ligand are administered together. In the pre-targeting method, the drug molecule is not coupled with the ligand. The ligand is administered initially and then after a time lag the therapeutic molecule is administered. This time lag provides localizing of the ligand molecule in the tumor (35).

Tumor vasculature is leaky and has an enhanced capability for the uptake of particular drug delivery systems contrary to normal blood vessels that have intact and continuous vasculature. According to the studies tumor vasculature has an enhanced permeability to macromolecules and colloidal delivery systems of diameter up to 600 nm. In a study by Chawla et al., biodegradable poly(caprolactone) nanoparticles were prepared for tumor targeted delivery of tamoxifen(a non-steroidal antiestrogen) and a significant uptake of biodegradable nanoparticles was observed in the estrogen receptor (ER) positive human breast cancer cell (MCF-7) line (31).

In another study by Lu et al., paclitaxel loaded gelatin nanoparticles were prepared. paclitaxel is an anti-microtuble agent and it is highly effective against human bladder cancer cells. In vitro biological activity was evaluated in human RT4 bladder cancer cells and in vivo evaluation study of paclitaxel penetration into bladder tissues was conducted in beagle dogs. As a result paclitaxel loaded gelatin nanoparticles showed an important activity against bladder cancer cells and showed high tissue concentrations. The data from this study suggested that paclitaxel loaded biodegradable nanoparticles are promising formulations for the treatment of bladder cancer (34).

b) Oral Delivery of Nanoparticles

Oral delivery of therapeutic peptide and proteins are an important issue and several strategies have been developed to improve oral delivery of some molecules such as drugs and vaccines. Their delivery by polymeric nanoparticles is one of the strategies to enhance these molecules' oral bioavailability.

Polymeric nanoparticles have spesific properties. Their stability in gastrointestinal tract, protection ability for encapsulated drugs, modulated drug release properties and behaviour in physiological conditions make them suitable for oral delivery of many molecules. Because of having submicron size and large specific surface area, nanoparticles are superior to the larger carriers. As a result, polymeric nanoparticles allow the encapsulation of the protein/peptides and protect them against the harsh conditions of the gastrointestinal tract.

Intestinal epithelium is composed of various cells and structures. Peyer's patches are one of the spesicific structures and they have an important role in intestinal absorption. M cells are particular cells which present in Peyer's patches. M cells are targets for some strategies to improve bioavailability of peptide, proteins and vaccines. Developing polymeric nanoparticles is one of these strategies. There are two main approaches to improve transmucosal transport: a)Modifying the surface properties of nanoparticles. b)conjugating/ adsorbing the targeting molecule to the surface of nanoparticle (36). All these applications provide transport of the biodegradable polymeric nanoparticles in intestinal epithelium

A study by Bagre et al. demonstrated that oral delivery of enoxaparin, a protein structured heparin derrivate, by biodegradable polymeric nanoparticles was possible. In the study, surface modificated enoxaparin loaded chitosan nanoparticles administered orally to rats and the effective results were obtained from both in vivo and in vitro studies (37).

Another study by Graves et al. demonstrates the oral delivery of fenretinide by poly lactide-co-glycolide (PLGA) nanoparticles. Fenretinide is a synthetic retinoid and it has been used for the treatment of breast cancer. However oral administration of fenretinide is a challenge because of its low bioavailability. In this study, three different fenretinide loaded nanoparticle formulations were prepared: The acid terminated PLGA nanoparticles, the ester terminated PLGA nanoparticles and the polyethylene glycol (PEG)/PLGA diblock copolimer nanoparticles. The success of an oral administered formulation can be determined by its ability to enhance the absorbtion of the drug in the intestines. Thus, caco-2 cell permeation studies were carried to indicate the intestinal absorption of prepared nanoparticles. As a result all three types of formulations performed better than the free fenretinide. Because of enhancing the bioavailability of nanoparticles, the performance of PEG modified PLGA nanoparticles was the best (30).

c) Nanoparticles for Gene and Vaccine Delivery

In gene therapy there are two categories for the delivery of nucleic acids: viral and non-viral gene delivery systems. The applications of viral vectors are limited because of their safety problems. However, non-viral vectors are more advantageous than viral vectors. The nanoparticles composed of biodegradable, biocompatible and appropriate (for gen delivery) polymers are used as non-viral vectors (38).

Nanoparticles can rapidly escape from the degradative endo-lysosomal compartment and they have a sustained intracelluler retention. The therapeutic efficacy of the nanoparticles is due to the capability of protecting the therapeutic molecule from degradation by lysosomal enzymes. After their intracelluler uptake and endolysosomal escape, nanoparticles release the encapsulated DNA at a sustained rate leading to sustained gene expression (39).

Nanoparticles containing entrapped or adsorbed antigens are used as vaccine antigens because of minimizing the frequency of immunization. Nanoparticles, which encapsulated antigens, are effective vaccine adjuvants and they offer sustained release of the antigen. They are also appropriate carriers for oral immunization to induce systemic and mucosal immunity (39).

Kim et al., prepared biodegradable chitosan nanoparticles as Hepatitis B vaccine delivery system. Licenced Hepatitis B vaccines, which administered intramuscularly, are delivered by needles causing pain and inconvenience. Therefore, a study with a new vaccine delivery route was conducted. In the study the nanoparticle formulation was injected into the nasal mucosa of the rats. Chitosan is a highly bioabsorptive polymer. Thus, it was absorbed into the nasal mucosa and provided a continuous supply of antigens into the body (40).

d) Nanoparticles For Brain Targeting

Human brain is separated from blood circulation by a highly efficient blood brain barrier 'BBB'. Blood brain barrier is mainly composed of relatively impermeable endothelial cells with tight juctions, enzymatic activity and active efflux transport systems. BBB hinders the transport of water-soluble molecules from blood circulation into central nervous system and transport of lipid-soluble molecules is limited by the activity of enzymes or efflux pumps. Consequently, drug delivery to central nervous system is a major problem (41).

Nanoparticles as drug delivery vehicles are utilized to deliver therapeutic molecules to the brain by infiltrating blood brain barrier. The main superiority of nanoparticle carrier system is its ability of protecting the encapsulated drug molecule's original characteristics. Nanoparticles alo decrease drug leaching in the brain (41).

Interaction of nanoparticles with spesific receptor-mediated transport systems in the BBB is the basis of the strategies for targeting nanoparticles to the brain.

Nanoparticle based drug delivery systems are useful for the treatment of brain diseases because of being safe, effective and also cost effective. However, more optimization, standardization and randomization studies are necessary in this area (41).

In a study by Zang et al. H102 peptide, a molecule for the treatment of Alzheimer's disease, loaded biodegradable nanoparticles were prepared and administered to mice by intravenous injection. The study demonstrated that the biodegradable nanoparticles with suitable modification passed the blood brain barrier and delivered the loaded therapeutic molecule to brain's various regions such as cerebrum, cerebellum and hippocampus (42).

Jose et al., demonstrates the brain targeting of biodegradable nanoparticles in their study. They prepared Bacosid-A loaded PLGA nanoparticles and modified them. Bacosid-A is a drug which used for the treatment of neurodegenerative disorders like Alzheimer disease. The prepared nanoparticles were modified with polysorbate 80 (surfactant) to cross the blood brain barrier. Brain targeting study of the nanoparticles was conducted in rats. The nanoparticle formulation was administered to the rats by intraperitoneal route and the high concentrations of Bacosid-A crossed the blood brain barrier with the developed nanoparticle formulation (43).

Advantages of biodegradable polymeric nanoparticles

Biodegradable nanoparticles are practical drug delivery systems owing to their various advantages below (26):

1. Providing controlled/sustained release properties
2. Subcellular size and biocompatibility with tissue and cells
3. Stability in blood and biodegradability
4. Being non-toxic, nonthrombogenic, nonimmunogenic, noninflammatory
5. Avoiding reticuloendothelial system
6. Suitable for the delivery of various molecules such as drugs, proteins, peptides or nucleic acids

Disadvantages of Biodegradable Polymeric Nanoparticles

Biodegradable nanoparticles have some disadvantages. Small size and large surface area of nanoparticle-based drug delivery systems can cause some physical stability problems like aggregation. Nanoparticle-drug conjugates can be exposed to phagocytosis in the body. Low drug loading capacity and low loading efficiency are the other limitations of developing a nanoparticle drug delivery system (44).

CONCLUSION

Biodegradable polymeric nanoparticles are promising drug delivery systems because of their several advantages. They can be applied in many fields such as developing injectable, oral and implantable formulations. They can encapsulate a wide range of drug molecules. Their superiorities over conventional drug delivery systems and their biodegradability/ biocompatibility properties makes them a useful tool for biopharmaceutical industry. They can also provide the delivery of protein/peptide molecules via protecting their structure in physiological conditions. By developing a biodegradable polymeric nanoparticle formulation, a successful controlled delivery system can be achieved. As a result, attaining more stable and effective formulations by biodegradable nanoparticles is possible in the future.

REFERENCES

1. Xu T, Zhang N, Nichols HL, Shi D, Wen X. Modification of nanostructured materials for biomedical applications. *Mater Sci Eng C* 27 (3): 579-594, 2007.
2. Mahapatro A, Singh DK. Biodegradable nanoparticles are excellent vehicle for site directed in-vivo delivery of drugs and vaccines. *J Nanobiotech* 9 (1): 55, 2011.
3. Labhasetwar V, Song C, Levy RJ. Nanoparticle drug delivery system for restenosis. *Adv Drug Deliver Rev* 24: 63-85, 1997.
4. Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery and targeting. *Curr Opin Solid St M* 6 (4): 319-327, 2002.
5. Heller J, Domb AJ. Recent developments with biodegradable polymers. *Adv Drug Deliver Rev* 55 (4): 445-446, 2003.
6. Brannon-Peppas L. Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery. *Int J Pharm* 116: 1-9, 1995.
7. Lu Y, Chen SC. Micro and nano-fabrication of biodegradable polymers for drug delivery. *Adv Drug Del Rev* 56 (11): 1621-1633, 2004.
8. Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. *Prog Polym Sci* 32 (8-9): 762-798, 2007.
9. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. *J Control Release* 70: 1-20, 2001.
10. Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. *Nanomed-Nanotechnol* 2 (1): 8-21, 2006.
11. Zhang Y, Zhuang X, Gu W, Zhao J. Synthesis of polyacrylonitrile nanoparticles at high monomer concentrations by AIBN-initiated semi-continuous emulsion polymerization method. *Eur Polym J* 67: 57-65, 2015.
12. Puglisi G, Fresta M, Giammona G, Ventura CA. Influence of the preparation conditions on poly(ethylcyanoacrylate) nanocapsule formation. *Inter J Pharm* 125: 283-287, 1995.
13. Govender T, Stolnik S, Garnett MC, Illum L, Davis SS. PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. *J Control Rel* 57 (2): 171-185, 1999.
14. Rao JP, Geckeler KE. Polymer nanoparticles: Preparation techniques and size-control parameters. *Prog Polym Sci* 36 (7): 887-913, 2011.
15. Fàbregas A, Minarro M, García-Montoya E, Pérez-Lozano P, Carrillo C, Sarrate R, Sánchez N, Ticó JR, Su´né-Negre JM. Impact of physical parameters on particle size and reaction yield when using the ionic gelation method to obtain cationic polymeric chitosan–tripolyphosphate nanoparticles. *Inter J Pharm* 446 (1-2): 199-204, 2013.
16. Almalik A, Donno R, Cadman CJ, Cellesi F, Day PJ, Tirelli N. Hyaluronic acid-coated chitosan nanoparticles: Molecular weight-dependent effects on morphology and hyaluronic acid presentation. *J Control Rel* 172 (3): 1142-1150, 2013.
17. Diop M, Auberval N, Viciglio A, Langlois A, Bietiger W, Mura C, Peronet C, Bekel A, David DJ, Zhao M, Pinget M, Jeandidier N, Vauthier C, Marchioni E, Frere Y, Sigrist S. Design, characterisation, and bioefficiency of insulin–chitosan nanoparticles after stabilisation by freeze-drying or cross-linking. *Inter J Pharm* 491 (1-2): 402-408, 2015.
18. Amin ML, Joo JY, Yi DK, An SSA. Surface modification and local orientations of surface molecules in nanotherapeutics. *J Control Rel* 207: 131-142, 2015.
19. Palacio J, Agudelo NA, Lopez BL. PEGylation of PLA nanoparticles to improve mucus-penetration and colloidal stability for oral delivery systems. *Current Opin Chem Eng* 11: 14-19, 2016.

20. Gref R, Lück M, Quellec P, Marchand M, Dellacherie E, Harnisch S, Blunk T, Müller RH. 'Stealth' corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. *Colloid surface B* 18 (3-4): 301-313, 2000.

21. Torchilin VP, Trubetskoy VS. Which polymers can make nanoparticulate drug carriers long-circulating?. *Adv Drug Deliver Rev* 16 (2-3): 141-155, 1995.

22. Gaumet M, Gurny R, Delie F. Interaction of biodegradable nanoparticles with intestinal cells: The effect of surface hydrophilicity. *Inter J Pharm*. 390 (1): 45-52, 2010.

23. Gavasane AJ, Pawar HA. Synthetic biodegradable polymers used in controlled drug delivery system: an overview. *Clin Pharmacol Biopharm* 3(2), 2014.

24. Yoshida VMH, Balcão VM, Vila MMDC, Júnior JMO, Aranha N, Chaud MV, Gremião MPD. Zidovudine–Poly(L-Lactic Acid) solid dispersions with improved intestinal permeability prepared by supercritical antisolvent process. *J Pharm Sci* 104 (5): 1691-1700, 2015.

25. Pavot V, Rochereau N, Primard C, Genin C, Perouzel E, Lioux T, Paul S, Verrier B. Encapsulation of Nod1 and Nod2 receptor ligands into poly(lactic acid) nanoparticles potentiates their immune properties. *J Control Rel* 167 (1): 60-67, 2013.

26. Sharma S, Parmar A, Kori S, Sandhir R. PLGA-based nanoparticles: A new paradigm in biomedical applications. *Trends Anal Chem* 80: 30-40, 2016.

27. Jose S, Sowmya S, Cinu TA, Aleykutty NA, Thomas S, Souto EB. Surface modified plga nanoparticles for brain targeting of Bacoside-A. *Eur J Pharm Sci* 63: 29-35, 2014.

28. Akl MA, Kartal-Hodzic A, Oksanen T, Ismael HR, Afouna MM, Yliperttula M, Samy AM, Viitala T. Factorial design formulation optimization and in vitro characterization of curcumin-loaded PLGA nanoparticles for colon delivery. *J Drug Deliv Sci Tech* 32: 10-20, 2016.

29. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloid Surface B* 75 (1): 1-18, 2010.

30. Graves RA, Ledet GA, Glotser EY, Mitchner DM, Bostanian LA, Mandal TK. Formulation and evaluation of biodegradable nanoparticles for the oral delivery of fenretinide. *Eur J Pharm Sci* 76: 1-9, 2015.

31. Chawla JS, Amiji MM. Biodegradable poly(o-caprolactone) nanoparticles for tumor-targeted delivery of tamoxifen. *Inter J Pharm* 249: 127-138, 2002.

32. Sinha VR, Singla AK, Wadhawan S, Kaushik R, Kumria R, Bansal K, Dhawan S. Chitosan microspheres as a potential carrier for drugs. *Inter J Pharm* 274 (1-2): 1-33, 2004.

33. Elzoghby AO, Gelatin-based nanoparticles as drug and gene delivery systems: Reviewing three decades of research. *J Control Rel* 172 (3): 1075-1091, 2013.

34. Lu Z, Yeh TK, Tsai M, Au JLS, Wientjes MG. Paclitaxel-loaded gelatin nanoparticles for intravesical bladder cancer therapy. *Clin Cancer Res* 10: 7677-7684, 2004.

35. Nobs L, Buchegger F, Gurny R, Allémann E. Biodegradable nanoparticles for direct or two-step tumor immunotargeting. *Bioconjugate Chem* 17 (1): 139-145, 2006.

36. Rieux Ad, Fievez V, Garinot M, Schneider YV, Préat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. *J Control Rel* 116 (1): 1-27, 2006.

37. Bagre AP, Jain K, Jain NK. Alginate coated chitosan core shell nanoparticles for oral delivery of enoxaparin: In vitro and in vivo assessment. *Inter J Pharm* 456 (1): 3-40, 2013.

38. Gu J, Chen X, Xin H, Fang X, Sha X. Serum-resistant complex nanoparticles functionalized with imidazole-rich polypeptide for gene delivery to pulmonary metastatic melanoma. *Inter J Pharm* 461 (1-2): 559-569, 2014.

39. Panyam J, Labhasetwar V. B iodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv Drug Deliver Rev* 55 (3): 329-347, 2003.

40. Kim BG, Kang IJ. Evaluation of the effects of biodegradable nanoparticles on a vaccine delivery system using AFM, SEM, and TEM. *Ultramicroscopy* 108: 1168-1173, 2008.

41. Chakraborty C, Sarkar B, Hsu CH, Wen ZH, Lin CS, Shieh PC. Future prospects of nanoparticles on brain targeted drug delivery. *J Neurooncol* 93: 285-286, 2009.

42. Zhang C, Zheng X, Wan X, Shao X, Liu O, Zhang Z, Zhang Q. The potential use of H102 peptide-loaded dual-functional nanoparticles in the treatment of Alzheimer's disease. *J Control Rel* 192: 317-324, 2014.

43. Jose S, Sowmya S, Cinu TA, Aleykutty NA, Thomas S, Souto EB. Surface modified plga nanoparticles for brain targeting of Bacoside-A. *Eur J Pharm Sci* 63: 29-35, 2014.

44. Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. *Pharmacol Reports* 64: 1020-1037, 2012.