Review Article

Evolving trends in biopolymer based drug delivery systems: An overview

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ABSTRACT

An efficient drug delivery system deals with the administration of a drug to its target site, to achieve the desired therapeutic effect. The drawbacks with conventional drug delivery systems had led to the search for efficient drug formulations and new routes of drug delivery. Modern day drug delivery systems focus on improving the efficacy of the drugs by modifying the carriers and increasing the bioavailability. Also the newly emerging drug delivery systems (DDS) tend to target the pharmacodynamics and pharmacokinetics of the pharmaceutical compound. Over the past few decades, biopolymer based drug delivery systems have been gaining attention. The use of biopolymers as drug carriers has been attributed to their biodegradability and their non-toxic nature. This review focuses on the different biopolymer based drug delivery systems used recently.

Keywords: Drug delivery systems, biopolymers, biodegradability.

INTRODUCTION

Drug delivery deals with the administration of a pharmaceutical compound to its target site in order to achieve the desired effect. Conventional routes of drug administration include oral and intravenous. Based on the disease and type of drug, the preferred route is selected. The different routes of drug delivery include oral, parenteral and transdermal. Oral administration of still remains to be one of the major ways of drug administration.[1]

Although conventional methods prove to produce the desired effect, they seem to have several draw backs such as less bioavailability, lower controlled release, and non-specific side effects due to prolonged use.[2] One major drawback of conventional drug delivery systems is very moderate controlled release. Modern day drug delivery systems also known as DDS consist of a multi displinary approach towards the development of therapeutic compound. DDS takes into consideration all the important aspects of drug formulation and drug delivery such as the pharmacokinetics, pharmacodynamics, and drug related toxicity and drug targeting. Controlled release of drugs can be achieved by employing different bio-based carriers or by using different drug formulations. The various drug carriers used include biopolymers, nano particles, micro particles, microcapsules, micelles, gels, pro drugs and liposomes. Biopolymer based drug delivery systems have been studied in recent times, due to their biodegradability and biocompatibility and sustained drug release ability. Biopolymers are biological macromolecules which make up most of the important structures in living beings. These natural polymers perform important functions both intra cellularly and extracellularly.[3]For the development of an efficient DDS the nature of the polymer, its bio conjugation property, its loading efficiency and degradation have to be taken into account.[4]

The commonly used natural polymers in drug delivery systems include collagen and albumin. Synthetic polymers have gained importance in the recent years owing to their biodegradable nature. Synthetic polymers such as polylactic acid, polyglycolic acid and poly (lactic-co-glycolic) acid have gained importance as biomaterials. Many different natural and synthetic polymers have been used as carriers till date, depending on its nature and efficiency and some biopolymers are still in the research phase.[5]

BIOPOLYMERS USED IN DRUG DELIVERY

Natural polymers

Albumin

Albumins are monomeric globular proteins, the most common albumins being serum albumins. Serum albumin, the main protein constituent of the human blood plasma, aids in transport of fatty acids, metals, amino acids and helps in maintaining the osmotic blood pressure. Albumin comprises of 585 amino acids and three domains which form a heart shaped molecule, the resolution of the three dimensional structure of albumin was determined crystallographically and was found to be 2.8 Angstrom.[6] Albumin is water soluble and degradable in nature, which makes it a potent biomaterial.[7]Albumin can be fabricated into microspheres or nano spheres depending on the type of drug used, also it being used as drug carrier intravenously. Another application of albumin as a biomaterial includes its use in cardiovascular devices as coating material, albumin composites are used as surgical adhesives.[8, 9]

Collagen

Collagen is a major structural protein, which gives structure and support to the tissues connecting them with the skeleton. Collagen combined mineral crystals with hydroxyl apatites makes up bones and teeth. Collagen, a rod-type polymer contains about 1000 amino acids. The integrity and strength of collagen are attributed to the compactly packed fibrils. Collagen is used for the regeneration of tissues and its role in drug delivery systems has been studied extensively.[10]Collagen and its composites have been used as biomaterials due to its biodegradable nature.[11]Collagen has been processed into fibrous matrix materials, sponges, films, shields and tubes. The structural integrity of collagen has led to its use in tissue engineering as scaffolds. Collagen based composites containing recombinant human bone morphogenetic protein 2 (rhBMP-2) was studied for bone development on adult rat parietal bone, and the carrier collagen aided in the delivery of protein also it was absorbed after 8 weeks of administration whereas the collagen implant remained surrounded by a fibrous connective tissue.[12]

Collagen based drug delivery carriers have been studied extensively for many decades. When collagen sponges were investigated for local delivery of gentamicin it was found that, they had more specificity and increased bioavailability due to the porous matrix. Also this type of novel drug delivery system reduced the soft tissue infection in patients who underwent intra-abdominal related surgeries. There was no systemic side effects reported in around 1 million people who were treated with the collagen-gentamicin implant.[13]

Cellulose

Cellulose a commonly found polysaccharide, an organic polymer is composed of glucopyranose units joined together by β-1,4 linkages. The glucose residues are held together by strong inter and intra molecular hydrogen bonds which form a 3D lattice like structure. Many cellulose molecules together form microfibrils, many layers of microfibrils form the cellulose fibre (Figure 1). The supramolecular structure of cellulose is responsible for the structural integrity of plants. Cellulose maybe crystalline, amorphous or paracrystalline cellulose is less ordered due to the less degree of hydrogen bonding. Cellulose is hydrophilic which accounts for its biodegradable nature.[14]

Cellulose of plant and bacterial origin is used in used in the preparation of biomaterials. Microbial cellulose based sutures have been investigated in recent times.[14]Different modified forms of cellulose such cellulose ether, oxycellulose, methyl cellulose and sodium carboxymethyl cellulose are used in different types of drug delivery. Also some forms or derivatives are also being used as coatings for tablets.[15]

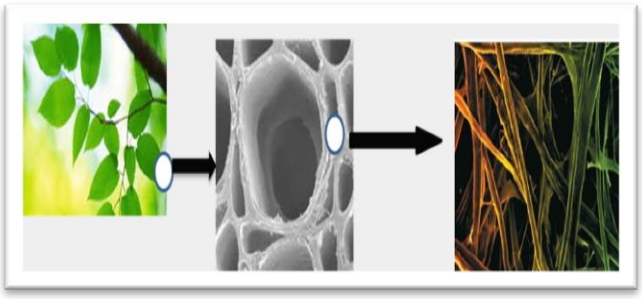

Figure 1: This figure shows the interior structure of cell wall which is composed of microfibrils

Synthetic biopolymers

Synthetic biopolymers are derived from plant or microbial sources. These polymers can either be biodegradable or non-biodegradable. The various synthetic biopolymers include PLA, PGA, PHA and polyanhydrides.

Polylactic acid (PLA)

Polylactic acid an aliphatic polyester is synthesized either from lactic acid obtained from agricultural sources (Figure 2) or by ring opening polymerization of lactide. Its thermoplastic nature has attracted interest commercially. PLA is processed into films and other packaging material. Various composites of PLA have been made in order to improve its mechanical properties. The most common composites of PLA include PLGA which is a combination of polylactic acid and poly glycolic acid.[16,17]

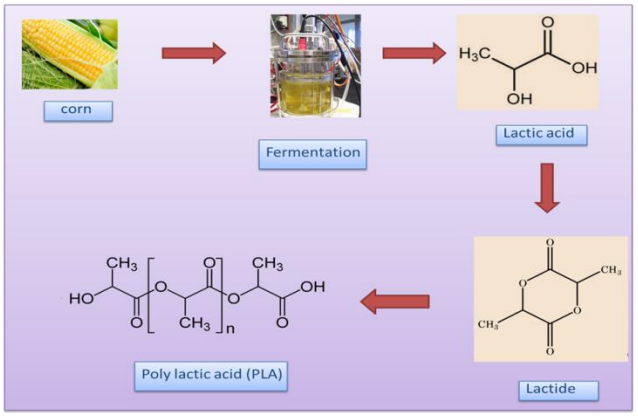

Figure 2: Schematic representation of PLA production in industries

Owing to the hydrophilic surface of PLA, surface modification needs to be done in order to be used in drug delivery systems. Chemical modification is done by copolymerization i.e. polymerizing PLA with other monomers or by cross linking reactions. As far as the surface chemistry is concerned, PLA is hydrophilic in nature, in order to be used in drug delivery applications, surface modification is done either via physical or chemical means. The Chemical modification is done via surface hydrolysis, ie PLA is treated with an alkali, to introduce side chain functional groups.PLA oligomers are prepared as micro particles microspheres microcapsules containing the drug and administered. This biodegradable polymer based systems aid in controlled release of the

drug. Also surface modification of PLA helps in targeted drug delivery.PLA microspheres containing prednisolone and PLA microparticles were administered parenterally and compared, the micro particles showed a sustained drug release.[18]

Another emerging technique is the usage of PLA nano particles loaded with the drug of interest. Nano particles are preferred in drug delivery owing to their Nano size and large surface area. Surface modified PLA NPs when targeted to the brain micro vascular endothelial cell showed less toxicity when compared to PACA NPs and the drug was stable due to the adsorption on the surface of the PLA NP complex.[19]

Poly glycolic acid

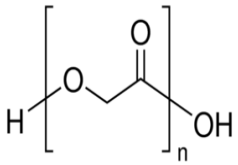

Figure 3: General structure of polyglycolic acid

Polyglycolic acid is thermoplastic polymer which can be synthesized either by polycondensation of glycolic acid or by ring opening polymerization of glycolide (Figure 4), another rarely used method is solid-state polycondensation of halogen acetates. Commercially polyglycolic acid is synthesized from glycoside, the cyclic diester of glycolic acid by ring opening polymerization. Glycolide is heated under reduced pressure conditions and catalysed by catalysts such as antimony trioxide, zinc lactate and stannous octanoates (Fig 4).

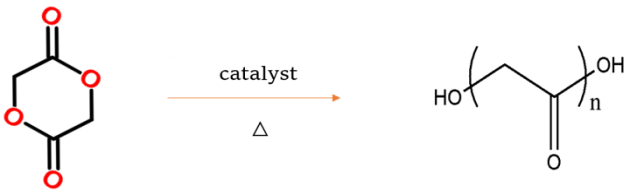

Figure 4: Schematic representation of ring opening polymerization of glycolide

It is linear aliphatic polyester which is insoluble in most organic solvents. It is a highly crystalline polymer, has a melting point of around 225-230°C. Due to its excellent mechanical properties and biodegradable nature it is produced commercially from renewable resources.[20] PGA's hydrolytic instability has restricted its usage in many fields. In order to improve its properties, it is fabricated with various copolymers, such as with lactide, caprolactone are made. Polyglycolic acid has various biomedical applications due to its fibre forming properties. Resorbable sutures were the first investigated biomaterial with PGA.

Polyglycolic acid sutures are available commercially under the trade name Dexon.[17] Further PGA based fabrics were used in tissue engineering as scaffolding matrix, owing to its good mechanical properties, crystallinity and biocompatible nature. PGA based drugs tend to show controlled release drug profiles and degrade in their microenvironment, which have made them potential candidates as drug carriers. Redmon et al., 1989 investigated the drug release mechanism of PGA microspheres loaded with prednisolone-21-acetate prepared using solvent extraction precipitation and freeze drying method. PGA microspheres prepared by the solvent extraction precipitation method, had large surface area and showed rapid release, whereas PGA microspheres prepared by freeze drying method had less surface area which aided in gradual drug release mechanism.[21] Indium-111 labeled PGA microspheres, were studied for their distribution in tissues. The radio labeled microspheres showed accumulation in liver within 8 hrs of drug administration, after which the drug showed gradual release.[22]

Poly (lactic-co-glycolic acid) (PLGA)

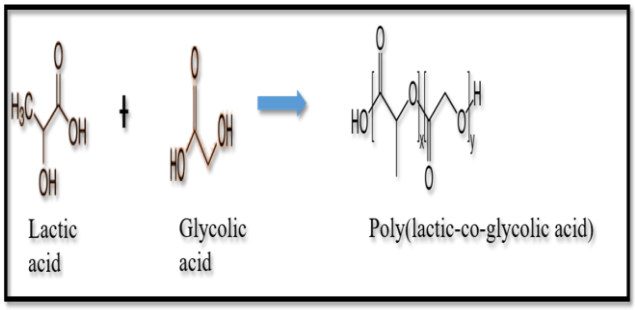

Figure 5: Schematic representation of Polylactic-co-glycolic acid formation

PLGA, an aliphatic copolymer composed of lactic acid and glycolic acid (Figure 5). PLGA has a glass transition in the range of 40-60° C and their crystallinity varies from amorphous to completely crystalline depending on the molar ratio of the monomers. PLGA breaks down into lactic acid and glycolic acid by the hydrolysis of its ester linkages. The biocompatibility of PLGA has made it an effective biomaterial to be used in many biomedical devices such as grafts, sutures, prosthetic devices and surgical films. Controlled biodegradability is another aspect of PLGA, which have made them interesting biomaterials. Nano ceramics such as hydroxyl apatite and tricalcium phosphate blended composites of PLGA are used in bone tissue engineering as scaffolds.[23,24] Composites containing PLGA and metallic magnesium were used as dental bone grafting biomaterial. The PLGA scaffold, used as a dental implant was found to increase bone regeneration.[25] In another study, an aqueous solution of biopolymer containing recombinant human bone morphogenetic protein-2(rhBMP-2) with PLGA micro particles have been employed for osseous regeneration in rat calvarium.[26] Over the past few decades extensive research has been done on PLGA as drug delivery carriers. Biodegradable polymers promote controlled drug release mechanism which is an important

reason for their use in drug delivery systems. PLGA microspheres loaded with a neuro active drug when implanted in rat brain, showed a non-specific astrocytic proliferation of brain cells and after 60 days of implantation the PLGA microspheres were degraded.[27]

Poly-ε-caprolactone (PCL)

Poly-ε-caprolactone is aliphatic polyester synthesized via ring opening polymerization of caprolactone, a cyclic ester. Poly-ε-caprolactone; a semi crystalline biopolymer has a glass transition temperature of -60° C and a melting temperature of 60° C. Also like many biopolymers PCL degrades through the hydrolysis of its ester linkages.[28]Poly-ε-caprolactonehas been reported to be degraded by bacteria and fungus.[29, 30] The usage of Poly-ε-caprolactone in biomedical applications has been attributed to its biodegradable nature. Poly-ε-caprolactone scaffolds containing bone morphogenetic protein-7 when implanted subcutaneously showed bone regeneration properties.[31]Poly-ε-caprolactonehas also been used in advanced drug delivery systems due to their controlled drug release profile. Taxol encapsulated in PCL microspheres, showed a drug loading efficiency of 20%.[32]

Polyhydroxylalkanoates

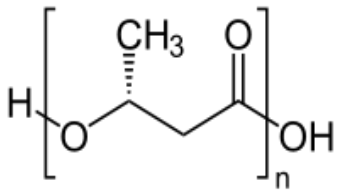

Figure 6: General structure of polyhydroxylalkanoates

They are a group of linear aliphatic polyesters synthesized by bacteria. The most common PHA includes Polyhydroxy butyrate (PHB). They have properties similar to that of conventional plastics which make them a good alternative to petro plastics. Biodegradability of PHA is another reason why it is commercially produced apart from its physical properties. Commercial production of PHA requires optimization of parameters for the production of microorganisms. Downstream processing of PHA is also an important aspect which has to be taken into account. PHA has been used as films and other packaging material.[33] Copolymers of PHA are used in biomedical applications and are also used in drug delivery systems.[34]

Polyanhydrides

Polyanhydrides are aliphatic or aromatic polymers which are hydrolytically unstable in nature. Due to their hydrophobic nature, it is soluble in organic solvents. Aliphatic polyanhydrides are easily degradable when compared aromatic polyanhydrides. They are used in drug delivery systems.[35, 36]

Poly ortho esters

Polyorthoesters are amorphous, biodegradable polymers which are extensively used in drug delivery systems. Polyorthoesters degrade at a very fast rate, and their degradation is pH sensitive. Owing to their hydrophobicity they can absorb drugs such as doxorubicin and they can be used as efficient drug delivery carriers.[37]

CONCLUSION

The evolution of new drugs and innovative ways of administration are being explored in the current era. Extensive research has been done in the pharmaceutical sector for the development of new drug delivery platforms. A combinatorial approach of polymer science and drug chemistry has to be delved into to develop a competent biopolymer based drug delivery system. Varied biopolymers of plant and microbial origin are used as biomaterials and drug carriers. Though many polymers and biopolymers have been studied and explored, some of the biopolymers are still in the investigation phase. More research needs to be done on novel biopolymers as biomaterials and drug delivery carriers.

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REFERENCES

1. Liechty WB, Kryscio DR, Slaughter BV, Peppas NA, Polymers for drug delivery systems, Annual review of chemical and biomolecular engineering, 1, 2010, 149-173.
2. Reddy PD, Swarna latha D, Recent advances in novel drug delivery systems, International Journal of PharmTech Research, *2*(3), 2010, 2025-2027.
3. Jeong, B, Kim SW, Bae YH, Thermo sensitive sol–gel reversible hydrogels, Advanced drug delivery reviews, *54*(1), 2002 ,37-51.
4. Angelova N, Hunkeler D, Rationalizing the design of polymeric biomaterials, Trends in biotechnology, 17(10), 1999, 409-421.
5. Jain R, Shah NH, Malick AW, Rhodes CT, Controlled drug delivery by biodegradable poly (ester) devices: different preparative approaches, Drug development and industrial pharmacy, *24*(8), 1998, 703-727.
6. He XM, Carter DC, Atomic structure and chemistry of human serum albumin, *Nature*, 3581992, 209-215.
7. Prinsen BH, Albumin turnover: experimental approach and its application in health and renal diseases, Clinicachimicaacta, 347(1), 2004, 1-14.
8. Chuang VT, Kragh-Hansen U, Otagiri M, Pharmaceutical strategies utilizing recombinant human serum albumin, Pharm Res, 19(5), 2002, 569–77.
9. Uchida M, Ito A, Furukawa KS, Nakamura K, Onimura Y, Oyane A, Ushida T, Yamane T, Tamaki T, Tateishi T, Reduced platelet adhesion to titanium metal coated with apatite, albumin–apatite composite or laminin–apatite composite, Biomaterials, 26(34), 2005, 6924-6931.
10. Tsung J, Burgess DJ, Biodegradable polymers in drug delivery systems, In Fundamentals and Applications of Controlled Release Drug Delivery, Springer US,107-123.
11. Lee CH, Singla A, Lee Y, Biomedical applications of collagen, International Journal Pharmaceutics, 221, 2001 1–22.

12. Murata M, Huang BZ, Shibata T, Imai S, Nagai N, Arisue M, Bone augmentation by recombinant human BMP-2 and collagen on adult rat parietal bone, International Journal of Oral and Maxillofacial Surgery, 28(3), 1999, 232-7.

13. Ruszczak Z, Friess W, Collagen as a carrier for on-site delivery of antibacterial drugs, Advanced drug delivery reviews, *55*(12), 2003, 1679-1698.

14. Klemm D, Heublein B, Fink HP, Bohn A, Cellulose: fascinating biopolymer and sustainable raw material, Angew ChemInt Ed, 44, 2005, 3358–3393.

15. Kamel S, Ali N, Jahangir K, Shah SM, El-Gendy AA. Pharmaceutical significance of cellulose: a review, Express Polymer Letters, 2(11), 2008, 758-78.

16. Nair LS, Laurencin CT, Polymers as biomaterials for tissue engineering and controlled drug delivery, Adv Biochem Eng Biotechnol, 102, 2006, 47.

17. Pfister DP, Larock RC, Thermophysical properties of conjugated soybean oil/corn stoverbiocomposites, Bioresource Technology, 101, 2010, 6200–6206.

18. Smith A, Evaluation of poly (lactic acid) as a biodegradable drug delivery system for parenteral administration, International journal of pharmaceutics, 30(2-3), 1986, 215-220.

19. Huafang W, Yu H, Wangqiang S, Changsheng X, Polylactic acid nanoparticles targeted to brain microvascular endothelial cells. Journal of Huazhong University of Science and Technology [Medical Sciences], 25(6), 2005, 642-644.

20. Vroman I, Tighzert L, Biodegradable polymers, Materials, 2, 2009, 307–344.

21. Redmon MP, Hickey AJ, DeLuca PP, Prednisolone-21-acetate poly (glycolic acid) microspheres: influence of matrix characteristics on release, Journal of controlled release, 9(2), 1989, 99-109.

22. Hazrati AM, Akrawi S, Hickey AJ, Wedlund P, Macdonald J, DeLuca PP, Tissue distribution of indium-111 labeled poly (glycolic acid) matrices following jugular and hepatic portal vein administration, Journal of controlled release, 9(3), 1989, 205-214.

23. Shi X, Wang Y, Ren L, Gong Y, Wang DA, Enhancing alendronate release from a novel PLGA/hydroxyapatite microspheric system for bone repairing applications, *Pharmaceutical Research, 26*, 2009, 422.

24. Ehrenfried LM, Patel MH, Cameron RE, The effect of tri-calcium phosphate (TCP) addition on the degradation of polylactide-co-glycolide (PLGA), *Journal of Materials Science: Materials in Medicine, 19*, 2008, 459.

25. Brown A, Zaky S, Ray H, Sfeir C, Porous magnesium/PLGA composite scaffolds for enhanced bone regeneration following tooth extraction, Acta bio materialia, 11, 2015, 543-553

26. Kenley R, Marden L, Turek T, Jin L, Ron E, Hollinger JO, Osseous regeneration in the rat calvarium using novel delivery systems for recombinant human bone morphogenetic protein-2 (rhBMP-2), J Biomed Mater Res, 28 ,1994, 1139–1147.

27. Menei P, Daniel V, Montero-Menei C, Brouillard M, Pouplard-Barthelaix A, Benoit JP, Biodegradation and brain tissue reaction to poly (D, L-lactide-co-glycolide) microspheres, Biomaterials, 14(6), 1993, 470-478.

28. Nair LS, Laurencin CT, Polymers as biomaterials for tissue engineering and controlled drug delivery, In Tissue engineering I , Springer Berlin Heidelberg , 2005, 47-90.

29. Benedict CV, Cook WJ, Jarrett P, Cameron JA, Huang SJ, Bell JP, Fungal degradation of polycaprolactones, Journal of Applied Polymer Science, 28(1), 1983, 327-334.

30. Benedict CV, Cameron JA, Huang SJ, Polycaprolactone degradation by mixed and pure cultures of bacteria and a yeast, Journal of Applied Polymer Science, 28(1), 1983, 335-342.

31. Williams JM, Adewunmi A, Schek RM, Flanagan CL, Krebsbach PH, Feinberg SE, Hollister SJ, Das S, Bone tissue engineering using polycaprolactone scaffolds fabricated via selective laser sintering, Biomaterials, 26(23), 2005, 4817-4827.

32. Sinha VR, Bansal K, Kaushik R, Kumria R, Trehan A, Poly-ϵ-caprolactone microspheres and nanospheres: an overview, International journal of pharmaceutics, 278(1), 2004, 1-23.

33. Reddy CSK, Ghai R, Kalia V, Polyhydroxyalkanoates: an overview, Bioresource technology, 87(2), 2003, 137-146.

34. Pouton CW, Akhtar S, Biosynthetic polyhydroxyalkanoates and their potential in drug delivery, Advanced Drug Delivery Reviews, 18, 1996, 133.

35. Kumar N, Langer RS, Domb AJ, Polyanhydrides: an overview, Advanced Drug Delivery Reviews, 54, 2002, 889.

36. Jain JP, Modi S, Domb AJ, Kumar NJ, Role of polyanhydrides as localized drug carriers, Control Release 103(3), 2005, 541-63.

37. Heller J, Barr J, Ng SY, Abdellauoi KS, Gurny R, Poly(orthoesters): synthesis, characterization, properties and uses, Advanced Drug Delivery Reviews, 54, (2002), 1015–1039.

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