

**Review article****Polymeric systems as controlled release drug products: A review***Abu bakar\*, Ujjwal Nautiyal, M Senthil Kumar, Bharat Bhusan**Himachal Institute of Pharmacy, Ramphur Ghat Road, Paonta Sahib, Distt-Sirmour, HP - 173025***ARTICLE INFO:****Article history:**

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**ABSTRACT**

The use of various new techniques and therapeutic systems to obtain a controlled drug release in microbial infections is a more and more exploited approach in the modern pharmaceutical technology. Growing interest in this field arises successfully on the one hand from the often unsuccessful research for effective and non-toxic new drugs and the other hand from new knowledge of the biochemical events around and inside infected tissue cell or organ. Following administration leads to distribution of active ingredient over the entire body and reaches not only the target cells, tissues or body parts but also interacts with healthy cells. This leads to toxicities and low therapeutic efficiency, and prompts the search for novel therapeutic strategies. Various new techniques have been explored, including conjugates obtained by linking drugs to various natural and synthetic polymers (macromolecular pro-drugs), liposome's, nanoparticles, micro particles, drug antibody conjugates as well as various pro-drug concepts. Unfortunately some of these systems have disappointed early expectations. Therefore a strong interest was developed in the potentially promising drug delivery systems, and polymeric carrier's electrostatically linked to the drug. This review is an attempt to understand the role of biopolymers and polymeric systems in targeted and controlled drug delivery.

**1. Introduction**

Over the past several years, there has been a growing recognition that the discovery of effective therapeutic agents involves designing compounds that possess appropriate "Pharmaceutical" or "drug-like" properties in addition to high affinity for their biological targets. The pharmaceutical or drug-like properties include solubility, permeation across barriers such as the intestinal epithelium or blood-brain barrier, and metabolic and excretory clearance. Appropriate balance of these properties enables drug molecules to attain and maintain sufficient systemic and/or target concentrations to exert therapeutic effects through optimum absorption, distribution, metabolism, and excretion (ADME) processes. The ADME processes, in conjunction with the biological properties, define therapeutic profiles of drug molecules[1].

A drug that is absorbed poorly, rapidly metabolized, or rapidly excreted via the renal or hepatic route will not attain its full therapeutic potential and will result in short half life. Such a drug will require higher doses to achieve sufficiently high systemic or target concentrations for efficacy; this may not be practical in some cases or may cause adverse effects in others. Thus, good pharmaceutical or drug-like properties are often defined as physicochemical properties of drug candidates that

enable a drug candidate to navigate through the physical, biochemical, and physiological barriers posed by the ADME processes. The pharmaceutical properties of a drug candidate are optimized by de novo designing appropriate physicochemical attributes into the molecule or via formulation of the drug candidate with agents that can improve certain aspects of the physicochemical properties.

**2. Deficiencies of chemotherapy**

Despite progress made in chemotherapy, the overall success rate has remained modest and unsatisfactory. Thus, with most of the disease caused by microbes, complete eradication is rare. Remission of limited duration and reappearance of symptoms are frequent as a result of a variety of deficiencies associated with present day antimicrobial drugs. Typical deficiencies include the following:

- I. Inadequate water solubility.
- II. Decreased bioavailability.
- III. Decreased serum half-life.
- IV. Excessive systemic toxicity.

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V. Monophasic salt-like or charged structure, which inhibits membrane penetration and cell entry through normal passive diffusion.

VI. Lack of cell specificity, due to the lack of the cell specificity drug application will be excessively wasteful, and healthy tissues will be exposed to toxic side effects.

VII. Bacterial drug resistance.

VIII. Irrational use of drug.

### 3. Prodrugs and controlled release drug products

Pro-drugs and controlled release drug products are hot spots in the field of medicine, especially pro-drug conjugates, for the treatment of various microbial infections can overcome the limitations of conventional drug delivery systems. A pro-drug is a pharmacological substance (drug) that is administered in an inactive (or significantly less active) form. Once administered, the pro-drug is metabolized *in-vivo* into an active metabolite. The rationale behind the use of a pro-drug is generally for absorption, distribution, metabolism and excretion (ADME) optimization. Pro-drugs are usually designed to improve oral bioavailability, with poor absorption from the gastrointestinal tract usually being the limiting factor. Additionally, the use of a pro-drug strategy increases the selectivity of the drug for its intended target. An example of this can be seen in many chemotherapy treatments in which the reduction of adverse effects is always of paramount importance.

Almost all drugs possess some undesirable physiochemical and biological properties. Their therapeutic efficacy can be improved by minimizing or eliminating the undesirable properties while retaining the desirable ones. This can be achieved through physical, biological or chemical means.

- **Physical approach** includes modifying the design of the doses form as sustained release or controlled release form. These preparation release the desired amount of drug, thus helps in the improvement of half life of the drug substance.
- **Biological approach** is to change the administration route for the desired drug candidate.
- And the last but the best approach is **chemical approach** which includes enhancing drug activity, selectivity while minimizing the adverse and toxic effects. This approach is also known as prodrug design.

These three aspects of drug design are very important and can be fulfilled by the use of polymeric systems in drug delivery. Polymer systems for drug release have been widely used in medicine, since they enable the slow and gradual release of the active ingredient, with better targeting within the body, such as towards areas of infection, inflammation or tumors.

### 4. Polymers

Polymers are high molecular mass compounds formed by polymerization of monomers. The simple reactive molecules

from which the repeating structural units of a polymer are derived are called monomer. Schematically polymers are subdivided into biopolymers and synthetic polymers according to their origin. Polymers make up many of the materials in living organisms, including, for example, proteins, cellulose, and nucleic acids. Moreover, they constitute the basis of such minerals as diamond, quartz, and feldspar and such man-made materials as concrete, glass, paper, plastics, and rubbers.

The word polymer designates an unspecified number of monomer units. When the number of monomers is very large, the compound is sometimes called a high polymer. Polymers are not restricted to monomers of the same chemical composition or molecular weight and structure. Some natural polymers are composed of one kind of monomer. Most natural and synthetic polymers, however, are made up of two or more different types of monomers. Such polymers are known as copolymers[2].

#### 4.1. Biopolymers

Biopolymers are polymers produced by living organisms. Since they are polymers, biopolymers contain monomeric units that are covalently bonded to form larger structures. The name "Biopolymer" indicates that it is a bio-degradable polymer. There are three main classes of biopolymers naming, polynucleotides, polypeptides and polysaccharides[3-6]. Examples of biopolymers include Proteins, Carbohydrates, DNA, RNA, Lipids, Nucleic acids, Peptides, and Polysaccharides (such as glycogen, starch and cellulose). The most common and the most abundant biopolymer on this planet is Cellulose.

Biopolymers are carbon neutral and compostable which means there is less chance of environmental pollution from this compound and can be renewed easily. These are sustainable as they are composed of living materials. One more advantage of biopolymers includes biodegradability which makes them a perfect formulation material in pharmaceuticals. Because of the biodegradable nature of biopolymers they also help in the reduction of pollution[3].

Although natural polymers and their derivatives are used widely in pharmaceutical dosage forms to deliver drugs, however, their use has been hampered by the synthetic materials. These natural polysaccharides hold advantages over synthetic polymers, generally because they are non toxic, less expensive and easily available from renewable resources. Biopolymers can be modified to have tailor-made materials for drug delivery systems and thus can compete with synthetic biodegradable materials available commercially. Natural polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical sectors for controlled drug delivery systems. Various kinds of natural polymers such as acacia, agar, alginate, carrageenan, chitosan, dextrin, gellan gum, guar gum, inulin, karaya gum, locust bean gum, pectin, starch, xanthan gum etc., are used in the food industry and are regarded as safe for human consumption.

These polysaccharides are obtained usually as plant exudates containing various sugars other than glucose and having significant quantities of oxidized groups in addition to their normal polyhydroxy format. In many cases, water-soluble polysaccharides are generally similar to the exudates of components of land and marine plants and their seeds. These components result from normal metabolic processes, and many times, they represent the reserve carbohydrates in that system. Natural gums are often preferred over synthetic polymers due to their nontoxicity, low cost and easy availability. It should be noted that many "old" materials compete successfully today after almost a century of efforts to replace them. It is the usual balance of economics and performance that determines the commercial realities. Natural gums have been modified to overcome certain drawbacks like uncontrolled rate of hydration, thickening, drop in viscosity on storage, microbial contamination etc.

Recent trend towards the use of nontoxic products demands the replacement of synthetic additives with natural one. Many natural polymeric materials have been successfully used in sustained-release tablets.

#### **4.2 Types of biopolymers[7,8]**

Biopolymers can be also be classified as sugar based biopolymers, starch based biopolymers, cellulose based biopolymers and synthetic biopolymers on the basis of the source by which they are obtained.

##### **4.2.1 Sugar based biopolymers**

Starch or Sucrose is used as input for manufacturing Polyhydroxybutyrate. Sugar based polymers can be produced by blowing, injection, vacuum forming and extrusion. Lactic acid polymers (Polylactides) are created from milk sugar (lactose) that is extracted from potatoes, maize, wheat and sugar beet. Polylactides are resistant to water and can be manufactured by methods like vacuum forming, blowing and injection molding.

##### **4.2.2 Starch based biopolymers**

Starch acts as a natural polymer and can be obtained from wheat, tapioca, maize and potatoes. The material is stored in tissues of plants as one way carbohydrates. It is composed of glucose and can be obtained by melting starch. It can be found in vegetables like tapioca, corn, wheat and potatoes.

##### **4.2.3 Cellulose based biopolymers**

This polymer is composed of glucose and is the primary constituent of plant cellular walls. It is obtained from natural resources like cotton, wood, wheat and corn.

##### **4.2.4 Biopolymers based on synthetic materials**

Synthetic compounds that are obtained from petroleum can also be used for making biodegradable polymers such as aliphatic

aromatic copolyesters. Though these polymers are manufactured from synthetic components, they are completely compostable and bio-degradable. Biopolymer can be obtained from either animal products or agricultural plants.

Biopolymers may be naturally occurring materials: most materials formed in nature during the life cycles of green plants, animals, bacteria and fungi are polymers or polymer matrix composites. Biopolymers include the polysaccharides such as cellulose, starch, the carbohydrate polymers produced by bacteria and fungi and animal protein based biopolymers such as wool, silk, gelatin and collagen: biopolymers, especially the carbohydrate origin, have been found very promising industrial application in various forms.

- I. Acacia gum
- II. Agar- agar
- III. Alginate
- IV. Chitin and Chitosan
- V. Carrageenans
- VI. Cellulose and its derivatives
- VII. Chitin and its derivatives
- VIII. Collagens
- IX. Dextrin
- X. Enzymes
- XI. Gums and Mucilage
- XII. Hemi cellulose
- XIII. Hyaluronic acid.
- XIV. Khaya gum
- XV. Locust bean gum
- XVI. Nucleic acids
- XVII. Pectin
- XVIII. Starch
- XIX. Sterculia gum
- XX. Tara gum and
- XXI. Xanthane gum

##### **Few approved by FDA**

- I. Polylactic acid (PLA)
- II. Polyglycolic acid (PGA)
- III. Poly(lactic-co-glycolic acid) (PLGA)
- IV. Polycaprolactone (PCL)
- V. PHA (polyhydroxyalkanoate), specially PHB
- VI. (polyhydroxybutyrate)

Because of their availability, biodegradability, as well as biocompatibility, polymeric systems are used for a variety of applications such as water treatment, textile and paper, cosmetics, food and health supplements, agriculture, biotechnology, and various medical applications[9].

### 4.3 Structural characterization of biopolymers

There are a number of biophysical techniques for determining sequence information. Protein sequence can be determined by Edman degradation in which the N-terminal residues are hydrolyzed from the chain one at a time, derivatized, and then identified. Mass spectrometer techniques can also be used. Nucleic acid sequence can be determined using gel electrophoresis and capillary electrophoresis. Lastly, mechanical properties of these biopolymers can often be measured using optical tweezers or atomic force microscopy. Dual polarisation interferometry can be used to measure the conformational changes or self-assembly of these materials when stimulated by pH, temperature, ionic strength or other binding partners.

### 4.4 Polymers as drug carriers

Modification of biologically active compounds is possible by the preparation of their conjugates with polymeric carriers. This is one of the best methods for altering and controlling their pharmacokinetics, biodistribution, and toxicity. Polymer used for preparing the drug conjugates may be either natural or synthetic in nature, but must meet certain requirements in order to maximize their potential as polymeric drug carriers with controlled drug delivery. Polymers having their own antibacterial activity and property of controlled drug delivery can increase the therapeutic index of the antimicrobial drugs.

### 4.5 Requirements for polymeric drug carriers

Polymeric drug carrier requires these properties for being an effective drug carrier:

- I. Biodegradability
- II. Biocompatibility
- III. Hydro solubility
- IV. Chemical composition

#### 4.5.1 Biodegradability

To prevent rapid excretion by kidneys observed with low molecular weight compounds, the candidate carrier must be sufficiently large. However, its backbone must comprise segments amenable to hydrolytic and enzymatic cleavage in order to allow for the biodegradation and resultant catabolic elimination following drug release. If non-biodegradable such as the synthetic polymers with carbon-carbon backbone, the polymer should have a molecular weight not exceeding the renal threshold 30000 - 50000. The failure to comply with this requirement will result in deposit and accumulation in various organs. However, the biodegradability of a polymeric carbon backbone can be increased if the latter is equipped with peptide, saccharide or nucleotide sequences, as they are recognized and biodegraded by the numerous enzymes present in the lysosomal compartment of the cell.

#### 4.5.2 Biocompatibility

The polymeric backbone must be non-toxic, non-immunogenic, and nonthrombogenic in order to avoid any carrier-generated toxic, immunogenic and blood clotting side effects. Polymer should have to be totally biocompatible for avoiding the immune response.

#### 4.5.3 Hydro-solubility

Solubility in aqueous media is a necessary criterion for any polymer intended to be used as a drug carrier in the biomedical field. Such polymer should be linear and highly flexible. This will have the advantage of increasing the positive entropy of the solution, and therefore favors the dissolution process and the presence of intra or extra chain hydrophilic entities such as hydroxyl and amino terminals. These hydrophilic entities are of excellent utility as they are capable of undergoing effective hydration. The ability to incorporate charged species into the polymer also leads to its hydro-solubility property.

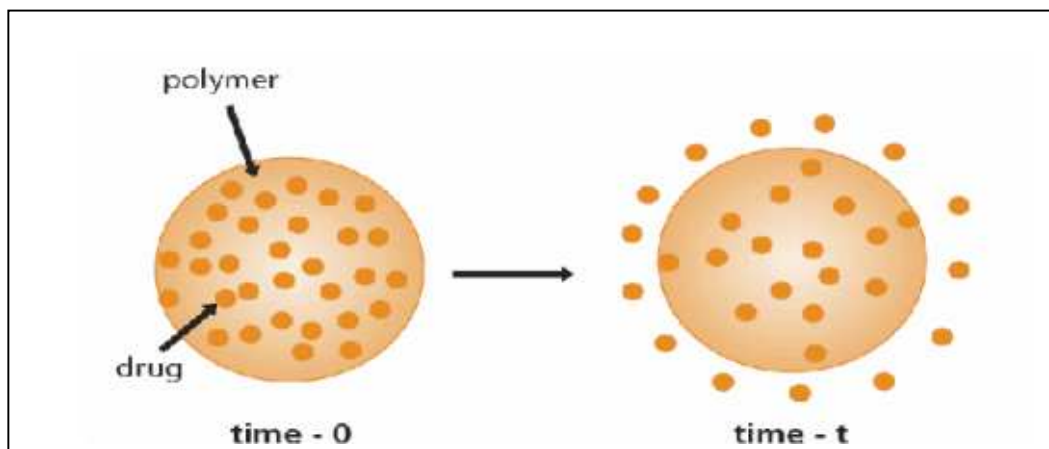
#### 4.5.4 Chemical composition

The carrier macromolecule must comprise reactive functional groups suitable for drug anchoring and release. These groups should be separated from the principle chain by short side chains or spacers. The presence of spacers will serve to diminish the steric inaccessibility due to the polymeric backbone. By their nature, the spacers should be stable in the blood stream but susceptible to either enzymatically catalyzed or pH-dependent hydrolysis in the lysosomal compartment. Likewise, polymeric carriers should display the ability to be directed to predetermine cell types. This can be achieved by the incorporation of targeting moieties such as cationic functions and antibodies. The presence of cationic functions, including tertiary amino groups, is required in the carrier backbone as this will facilitate adsorptive pinocytotic cell entry and therefore prevent problems related to potential ionicity or polarity of the monomeric drug, and on the other hand, increase drug selectivity for the transformed cell, given that many types of cancer cell are characterized by negative surface charge. Also the macromolecular carrier should incorporate an interposition, between the spacer bearing units, of subunits lacking drug-binding abilities along the principle chain. This will prevent multifunctional drug binding by reducing spacer density in the molecule.

### 4.6 Controlled drug delivery

Controlled drug delivery is the use of formulation components and devices to release a therapeutic agent at a predictable rate in vivo when administered by an injected or non-injected route. To do this, pharmacist and analyst skills are needed to develop and measure release from the formulation, i.e. a polymer or device construction. Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a pre-designed manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective

therapies while eliminating the potential for both under and overdosing. An example of Controlled drug delivery was shown in figure 1.



**Figure1:** Controlled drug delivery

Controlled-release methodologies can be classified on the basis of the mechanism that controls the release of the active agent from the delivery device diffusion, osmosis, or polymer erosion. The various polymer erosion mechanisms are of 3 basic types. Type I erosion refers to water-soluble polymers that have been in solubilized bycovalent cross-links and that solubilize as the cross-links (type IA) or backbone (type IB) undergo a hydrolytic cleavage. In type II erosion, polymers that are initially water insoluble are solubilized by hydrolysis, ionization, or protonation of a pendant group.

In type III erosion, hydrophobipolymers are converted to small water soluble molecules by backbone cleavage

The choice of a particular erosion mechanism is dictated by the specific application[10]. The role of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in figure 5 in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, remaining constant, between the desired maximum and minimum, for an extended period of time[11] Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to 1 month (Lupron Depot) to 5 years (Norplant)[12].

From a polymer chemistry perspective, it is important to appreciate that the mechanisms of controlled-release require polymers with a variety of physico-chemical properties. Several types of polymers have been tested as potential drug delivery systems, including nano- and micro-particles, dendrimers, nano- and micro-spheres, capsosomes and micelles. In these systems,

drugs can be encapsulated or conjugated into polymer matrices[13].

## 5. Conclusion

In the treatment of a pathophysiological process, it is desirable that the drug reaches its site of action at a particular concentration. For being effective therapeutic dose range must be constant over a sufficiently long period of time. In summary, the chemical nature of the many types of polymeric drug carriers available facilitates the distribution and interaction of drugs with their target tissue. These carriers also protect their drug from degradation and prevent their side effects. Polymers possessing a unique strength in their application towards drug delivery application which enables the new advancement in the formulation of future drug delivery systems. Although drug delivery technologies, if appropriately applied, should be able to improve therapeutic outcomes, these technologies are required in some instances to simply enable therapy, as is the case with gene therapy and drug targeting.

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