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Article in *Research Journal of Pharmacy and Technology* · January 2017

DOI: 10.5958/0974-360X.2017.00168.8

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REVIEW ARTICLE

Polymers used in the Designing of Controlled Drug Delivery System

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ABSTRACT:

Polymers are becoming very important in the drug delivery field. To control the drug release rate from the formulation, polymers are being used as the main tool. Polymers can be used as taste masking agents, to enhance stability of drug and to modify drug release characteristics. Biodegradable materials are used in medicine and other areas. In recent years there has been increase in use of biodegradable polymers. Biodegradable polymers are of two classes; synthetic and natural polymers. Natural polymers offer few advantages than synthetic polymers. Although polymers are used extensively as pharmaceutical packaging, this review is concerned with the use of polymers in the formulation of various dosage forms.

KEYWORDS: Polymers, drug delivery system, controlled drug delivery, biodegradable polymers, drug release mechanism.

INTRODUCTION:

Polymers are compounds with high molecular masses formed by monomers. The word poly means 'many' and meros means 'units or parts' in Greek.

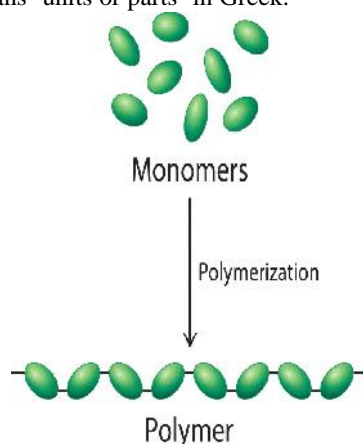


Fig 1: Polymerization

Because of their unique properties polymers are used in pharmaceuticals. The new technology in polymer based drug release system offer possibilities in administration of drugs. Pharmaceutically these polymers are used as a binder in tablets, flow controlling agents in liquids, suspensions and emulsions, as film coating agents to mask unpleasant taste of drug, protective and stabilizing agents.

The goal in designing sustained release drug delivery system is to reduce frequency of dosing, to increase the effectiveness of the drug at the required site thereby minimizing or eliminating side effects, providing uniform drug delivery. Sustained release has received most of the attention because of the fact that there is more feasibility in dosage form.

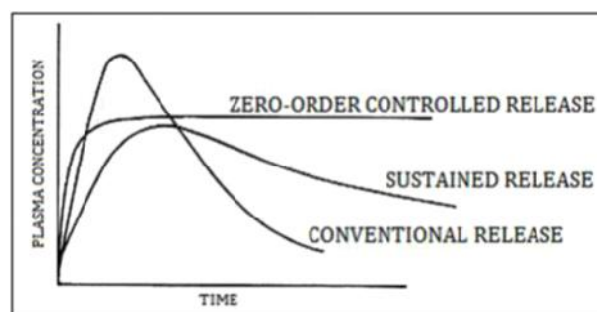


Fig 2: Differences between zero order controlled release, sustained release and conventional release of drug.

The polymers are used extensively in our daily routine life. Significant advances have been made in development of various drug delivery devices with the help of polymers. The earliest drug delivery system introduced in 1970s were based on polymer formed from lactic acid.

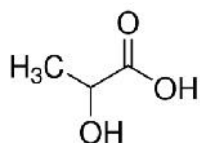


Fig 3: Lactic Acid

The biodegradable polymers are highly desirable because they degrade in the body to biologically inert and compatible molecules. By incorporating drugs in biodegradable polymers, dosage forms that release the drug over a prolonged time can be prepared in variety of shapes and sizes.

The three advantages that polymeric drug delivery products can offer are;

1. Localized delivery of drug :

The product can be implanted directly at the site where drug action is needed and hence systemic exposure of the drug can be reduced. Especially for toxic drugs which are related to various systemic side effects.

2. Sustained delivery of drug :

The drug encapsulated is released over extended period and hence eliminates the need for multiple injections. This feature can improve patient compliance especially for drugs for chronic indications, requiring frequent injection.

3. Stabilization of the drug :

The polymer can protect the drug from the physiological environment and hence improve its stability in vivo. This feature makes this technology attractive for the delivery of labile drugs like proteins¹.

The continuous release of drugs from the polymer matrix could occur either by diffusion of the drug from the polymer matrix, or by the erosion of polymer or by combination of two mechanisms.

For a given drug, the release kinetics from the polymer matrix are governed predominantly by some factors, viz. the polymer type and the excipients present in the system. The subsequent sections will focus on each of these factors to describe their role on drug release characteristics of a polymeric system².

Polymer type:

Silicon derivatives have been used in the past for fabrication of controlled release matrix systems, but now water soluble or biodegradable polymers are used. Polymers that are sufficiently polar can interact with an aqueous medium and generate sufficient energy to disperse polymer chains from glassy state. Although many polymers have been widely used in drug delivery, hydro-polymers such as cellulose ether perhaps the most often used. Water-insoluble polymers such as ethyl cellulose have been reported to have utility in controlled release matrix systems.

Some important parameters, which need consideration during the selection of polymer include viscosity, hydration rate and glass transition temperature.

Excipients:

The physicochemical properties of excipients present in the system should be well controlled to provide reproducible performance. Studies of possible interactions between excipients in the solid dosage forms are necessary because these interactions can affect the drug release and bioavailability. The presence of hydrophobic diluents can result in a more resistant gel layer which reduces the infiltration of aqueous medium and drug diffusion. The addition of soluble fillers enhances the dissolution of soluble drugs, while insoluble fillers affect the diffusion rate. Incorporation of surfactants may result in an increase in drug release rate through improved wetting or solubilization. Binding agents used during the granulation process coat the drug particles and also change the rheology of the gel layer, leading to retardation in release rates. However, the degree of retardation is determined by the swelling and hydrating capacities of the binding agent, amount of binder added and the method of addition. Other excipients such as plasticizers, may enhance drug release rates, due to the increased dissolution rate of plasticized polymer, while generally used lubricants will retard drug release rates because of their hydrophobic nature³.

THE POLYMERS:

Polymers in the technology of prolonged release drug formulations macro-molecules have also found the application in the technology of prolonged release drug formulations. They are mainly intended to ensure the constant concentration of the therapeutic agent in the certain time (e.g. 8-24 hours), in the patient body. The group of these drugs, therefore, can eliminate the drug multiple dosing during a day and reduce total daily dose of it. The prolonged drug forms are usually applied in the therapy of cardiac and alimentary tract diseases, coronary vessels, diabetics, psychiatric disorders. The absorption of the therapeutic agent using prolonged release drug forms can be reduced by coating, incorporation, complexation or bonding on the ionites.

Polymer Classification

The polymers are classified in to various types based on different categories. They are

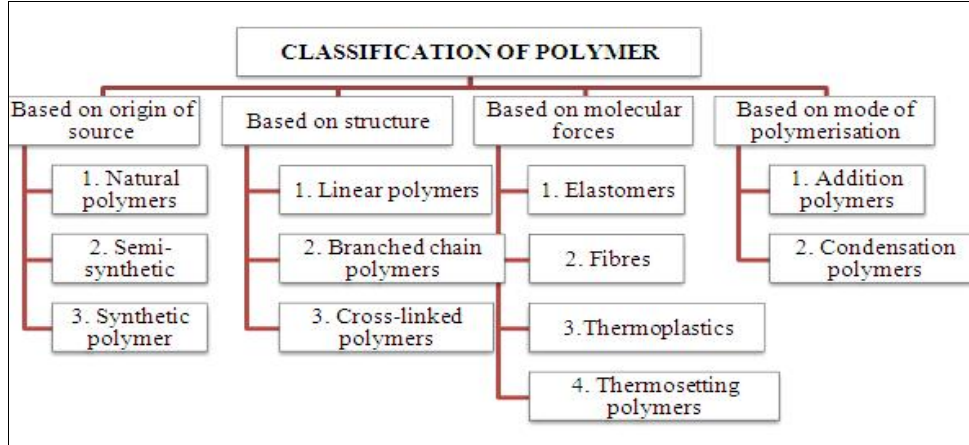


Fig 4: Classification of polymers.

Examples of polymers based on origin are

1) Natural polymers:

Ex: Chitosan, pectin, alginate, gelatin, albumin, collagen, cyclo dextrin.

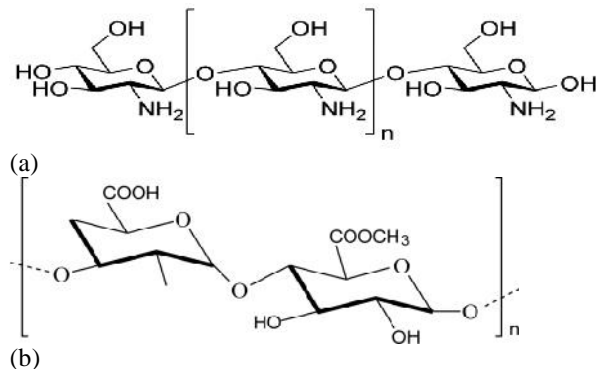


Fig 5: Chemical structure of (a) chitosan and (b) pectin

2) Synthetic polymers:

Ex: Polyethylene, polylactic acid, polypropylene, polyglycolic acid, polyhydroxybuterate, polyanhydride, polyacrylamide.

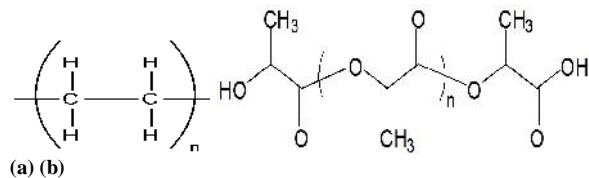


Fig 6: Chemical structure of (a) polyethylene and (b) polylactic acid

3) Semi synthetic polymers:

Ex: Hydroxyl propyl cellulose, methyl cellulose, hydroxyl propyl methyl cellulose, hydroxyl ethyl cellulose, sodium CMC(carboxy methyl cellulose).

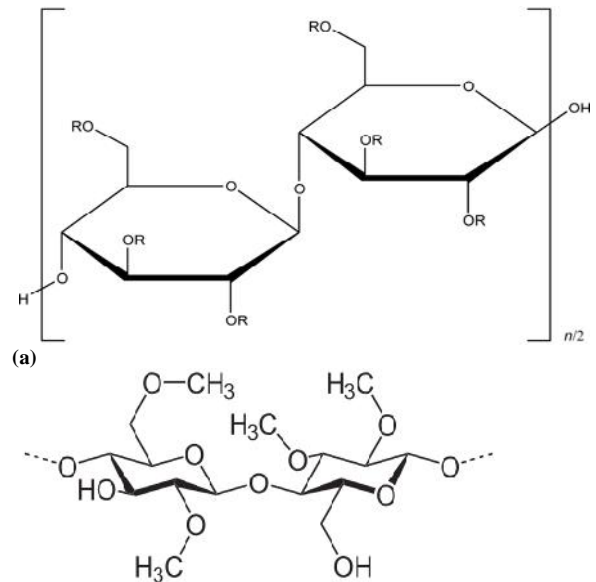


Fig 7: Chemical structure of (a) Hydroxyl propyl cellulose and (b) methyl cellulose

Based On Degradation Polymers Are Classified In To Various Types,

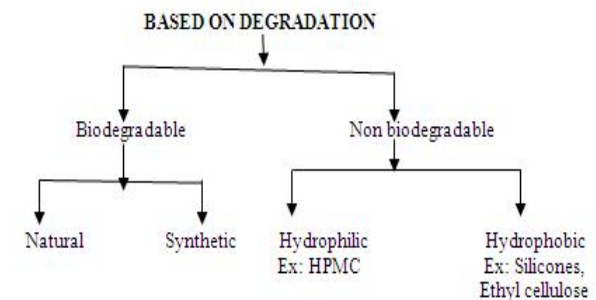


Fig 8: Classification of polymer based on degradation

Biodegradable macromolecules are definitely more preferred from the toxicological point of view. In the technology of prolonged release drug formulation, natural polymers and their modified derivative (e.g. starch, cellulose) as well as synthetic polymers are used e.g., polyacrylamides, polyacrylates and polyethyleneglycol.

An appropriate selection of the polymer matrix is necessary in order to develop a successful drug delivery system.

A major disadvantage with non-degradable polymer is that a surgery is required to harvest these polymers out of the body once they are depleted of the drug. Hence, non-degradable polymers can be used only if removal of the implant is easy.

Degradable polymers do not require surgical removal and hence are preferred for drug delivery applications. They degrade to smaller absorbable molecules, it is important to make sure that the monomers are non toxic in nature. The most commonly used polymers for this

application are Polylactide (PLA) and Poly Lactide co Glycolide (PLGA). These polymers have been used in biomedical applications for more than 20 years and are known to be biodegradable, biocompatible and non toxic.

DRUG DELIVERY SYSTEM:

A device that delivers therapeutic agents to desired body location and provides release of therapeutic agents time to time, such a system by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefits is derived and concentration above or below this range can be toxic or produce no therapeutic benefit at all. The progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this controlling the pharmacokinetics, pharmacodynamics, immunogenicity, non specific toxicity and efficacy of drugs were generated. These strategies often called Drug Delivery System DDS.

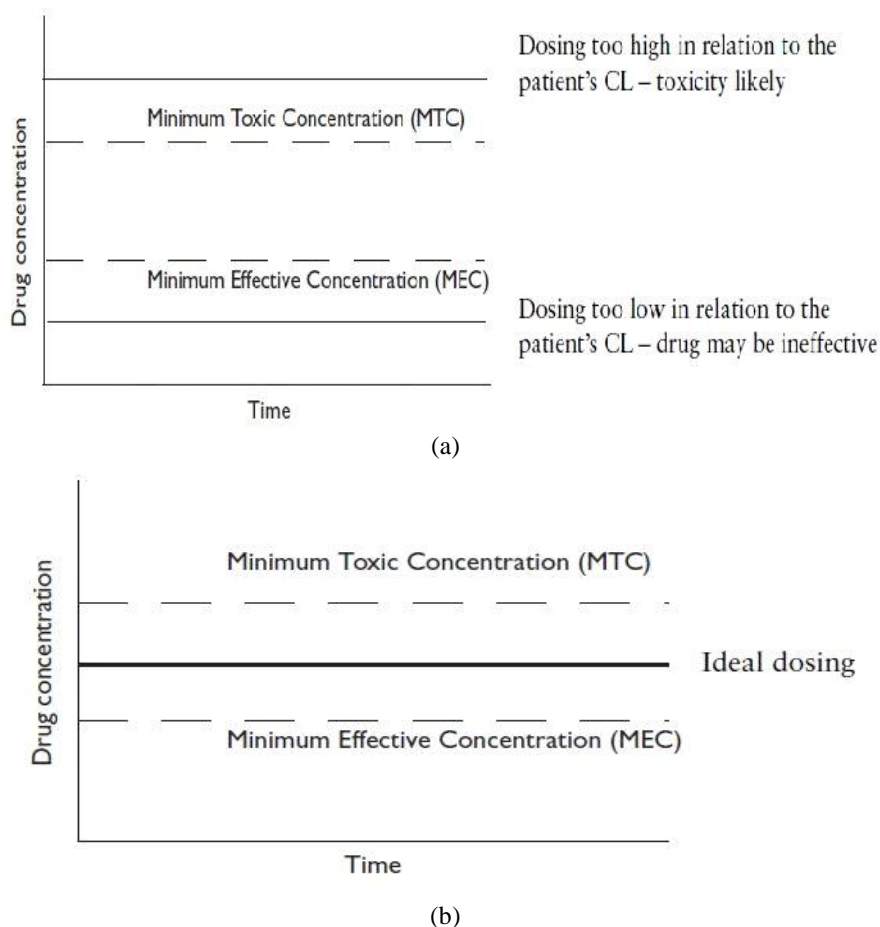


Fig 9: (a) plasma drug concentration above MTC and MEC (b) ideal plasma drug concentration

NOVEL DRUG DELIVERY SYSTEM:

To deliver drugs efficiently to specific organs, a range of organic systems novel ways have been designed. Recently significant advances in drug delivery system have enabled more effective drug administration. To minimize drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability and the fraction of drug accumulated in the required zone, various drug delivery are under development. Among the several drug carriers one can name soluble polymers, micro particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, nanoparticles, Dendrimers and micelles ^{4,5}.

CONTROLLED DRUG DELIVERY:

Controlled drug delivery is the use of formulation components and devices to release a therapeutic agent at a predictable rate when administered. 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 predesigned 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 the dose and overdosing.

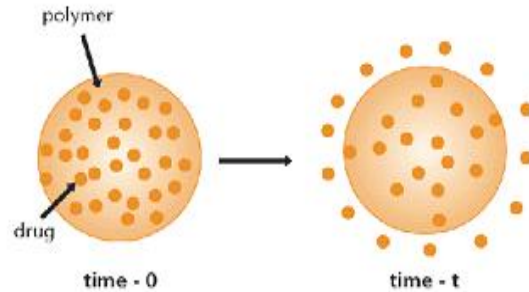


Figure 10: Example of controlled drug delivery.

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.

- a) Type I erosion, hydrophobic polymers are converted to small water-soluble molecules by backbone cleavage.
- b) Type II erosion, polymers that are initially water insoluble are solubilized by hydrolysis, ionization, or protonation of a pendant group.
- c) Type III erosion refers to water-soluble polymers that have been insolubilized by covalent cross-links and that solubilize as the cross-links (type IA) or backbone (type IB) undergo a hydrolytic cleavage ⁶.

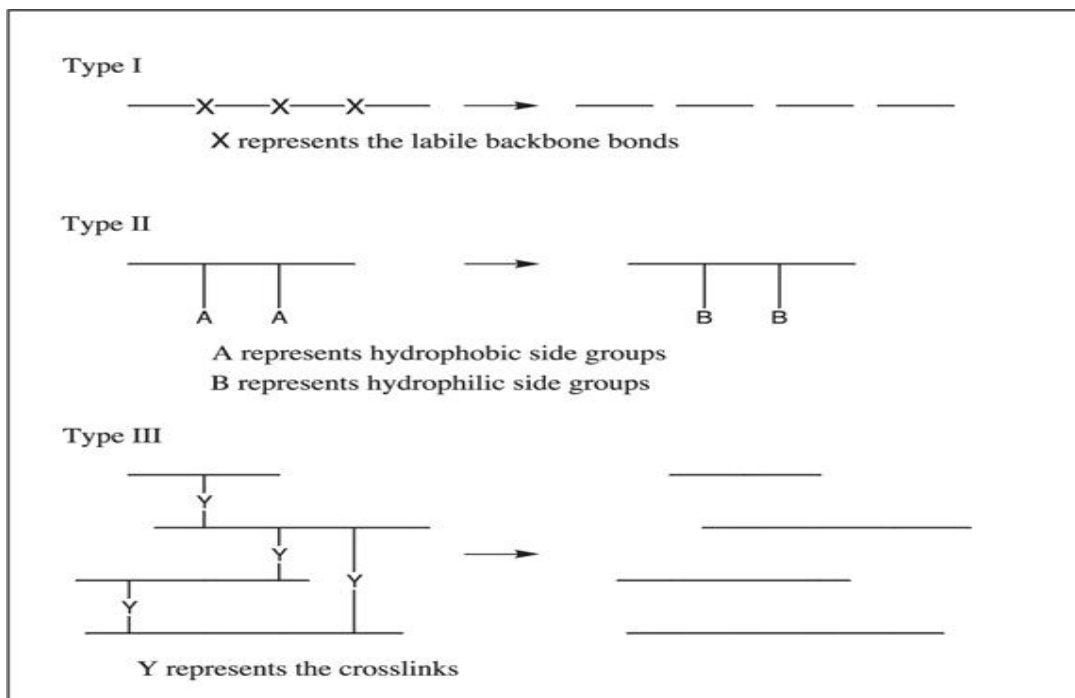


Fig. 11: Types of erosion mechanisms.

The role of many 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 12 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. 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).

The advantages of using controlled delivery system is to maintain the drug level with in a desired range, the need for fewer administration and increase patient compliance

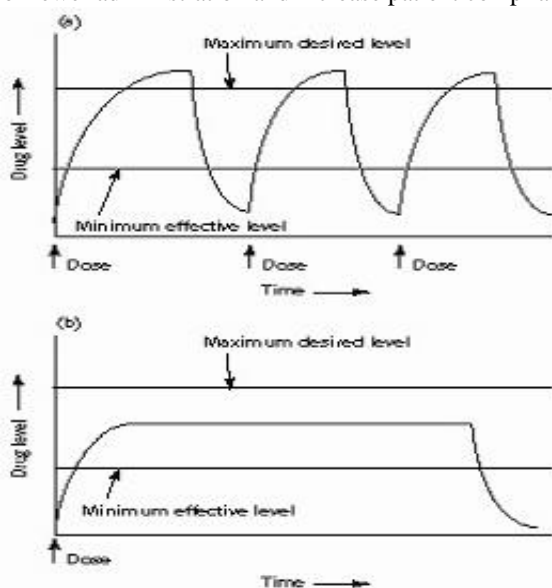


Figure 12: .Drug level in blood with a)Traditional drug dosing , b)Controlled delivery dosing.

Polymers in the Technology of Prolonged Release Drug Formulations

The crystals, pellets and granules of the drug might be coated with several polymer layers, according to the expected release rate. The therapeutic agent is gradually released as result of the polymer erosion or diffusion or is rinsing out from the polymer coating (Figure 13). Methylcellulose, polyvinyl pyrrolidone and polyvinyl alcohol are predominantly applied as the coating substances. The analogous effect can be obtained by coating of the therapeutic agent with polymeric layers, soluble in different parts of the alimentary tract or under enzymes.

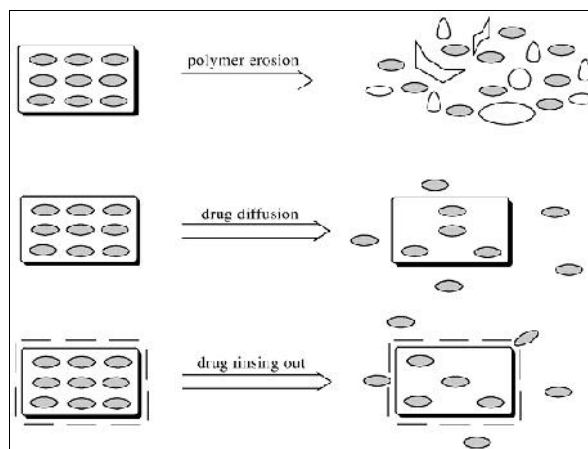


Figure.13: The mechanism of controlled release of the therapeutic agents.

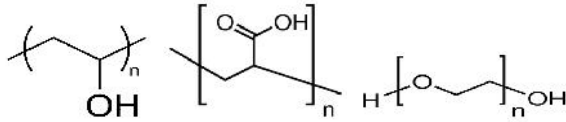
The drug release based on the diffusion takes place when polymers insoluble in the alimentary tract (e.g.: ethyl cellulose, nitrocellulose, cellulose acetate, acrylic and methacrylic ester copolymers) are applied as the coating agents. The coating tablets containing porophors (acrylic and methacrylic ester copolymers, starch, cellulose acetate phthalate or microcrystalline cellulose) are also used. The solubility of these tablets is increased as the effect of porophors dissolution and swelling⁷.

The incorporation method is relying on the suspension of the therapeutic agent on the prolonged released carrier. Most often as the carriers are used: hydrophobic polymers (e.g.: methylcellulose, acrylic acid polymers) as well as lipophilic polymers and some carriers insoluble in the alimentary tract (e.g.: polyvinyl chloride, polyethylene, cellulose acetate, ethyl cellulose, polystyrene, polyamide, silicone resin and acrylic and metacrylic acids ester copolymers). For instance, when the hydrophilic carrier is used, the tablet is consecutively swelled after passing the alimentary tract followed by creation of high viscous hydrogels, which prolonged the drug release. The drug release suspended on the lipophilic carrier is dependant on pH and the presence of enzymes. Matrix tablets contained water insoluble carriers, however, are stable in the alimentary tract environment. Therefore, the drug is gradually release via the capillaries. The complexation method involves the creation of poor soluble, therapeutic agent-polymer complexes. The drug is released due to the gradual decomposition of this complex. This technique is also used to produce skin and mucosa antiseptics (iodophors). The iodophors are the complexes of iodine with water-soluble polymers, which perform a role of carrier. They are high active against bacteria, viruses, fungi and protozoa. The bonding of the drug on the ionites method is usually applied for acidic or basic drugs. It relies on release of the drug based on ion exchange in the alimentary tract.

Biomaterials For Delivery Systems:

For controlled drug delivery formulations, the polymers must be chemically inert and free of leachable impurities with appropriate physical structure, minimal undesired aging, and be readily processable. Few examples are

- a. Poly (2-hydroxy ethyl methacrylate)
- b. Poly (N-vinyl pyrrolidone)
- c. Poly (methyl methacrylate)
- d. Poly (vinyl alcohol)
- e. Poly (acrylic acid)
- f. Polyacrylamide
- g. Poly (ethylene-co-vinyl acetate)
- h. Poly (ethylene glycol)
- i. Poly (methacrylic acid).



(a) (b) (c)
Figure.14: Structure of (a) Poly (vinyl alcohol), (b) Poly (acrylic acid), (c) Poly (ethylene glycol)

However in recent years the use of polymers were extended towards medical applications and drug targeting, few examples are

- a. Polylactides (PLA)
- b. Polyglycolides (PGA)
- c. Poly (lactide-co-glycolides) (PLGA)
- d. Polyanhydrides
- e. Polyorthoesters

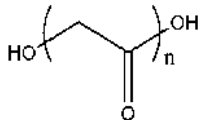


Figure.15: Structure of Polyglycolides

The Polylactides and Polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products both desirable and potentially undesirable must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials.

DRUG RELEASE MECHANISM:

The release of drugs from the erodible polymers may occur by any of the mechanisms as shown in Fig. 16.

In mechanism 1, the drug is attached to the polymeric backbone by a labile bond, this bond has a higher reactivity toward hydrolysis than the polymer reactivity to break down.

In mechanism 2, the drug is in the core surrounded by a biodegradable rate controlling membrane. This is a reservoir type device that provides erodibility to eliminate surgical removal of the drug-depleted device.

In mechanism 3 describes a homogeneously dispersed drug in the biodegradable polymer. The drug is released by erosion, diffusion, or a combination of both.

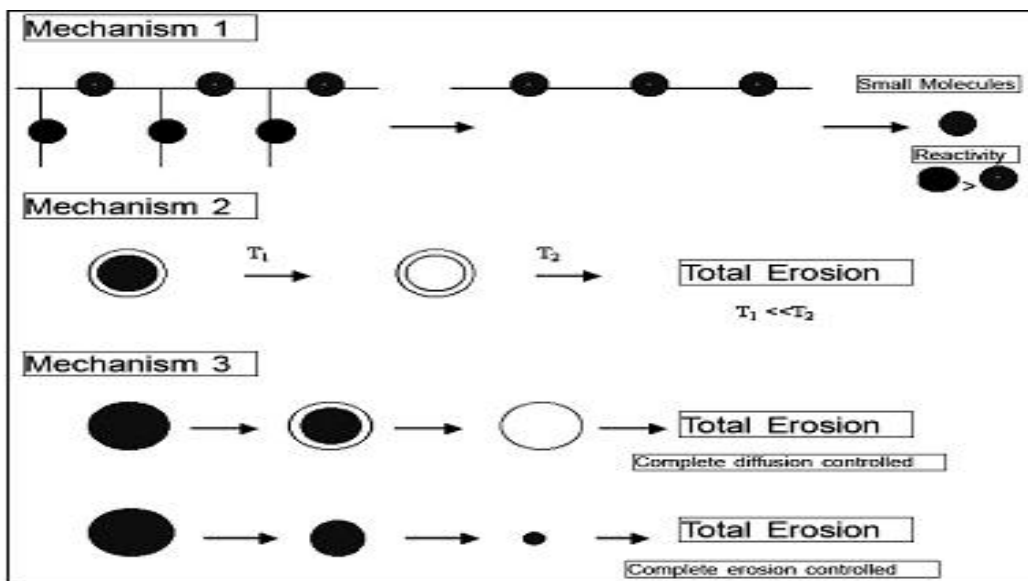


Figure 16: Schematic representation of drug release mechanism

Polymer Morphology:

Morphology of the polymer matrix plays an important role in governing the release characteristics of the encapsulated drug. The polymer matrix could be formulated as either micro/nano-spheres, gel, film or an extruded shape (such as cylinder, rod etc). The shape of the extruded polymer can be important to the drug release kinetics. For example, it has been shown that zero order drug release can be achieved using a hemispherical polymer form. Polymer microspheres are the most popular form due to manufacturing advantages as well as ease of administration (injectability by suspending in a vehicle). Polymer microspheres can be manufactured by using various techniques such as spray drying, solvent evaporation etc. The type of technique used affects factors such as porosity, size distribution and surface morphology of the microspheres and may subsequently affect the performance of the drug delivery product.

Excipient with Polymeric Matrix:

Polymeric drug delivery products can be formulated with excipients added to the polymer matrix. The main objective of having excipients in the polymer matrix could be either to modulate the drug release, or to stabilize the drug or to modulate the polymer degradation kinetics. Recent studies by Schwendeman and coworkers have shown that by incorporating basic salts as excipients in polymeric microspheres, the stability of the incorporated protein can be improved. It has shown that these basic salts however, also slow the degradation of the polymer. Similarly, hydrophilic excipients can accelerate the release of drugs, though they may also increase the initial burst effect².

Polymer degradation:

Polymer degradation is a change in the properties - tensile strength, colour, shape, etc - of a polymer or polymer based product under the influence of one or more environmental factors such as heat, light or chemicals. Deteriorative reactions occur during processing, when polymers are subjected to heat, oxygen and mechanical stress, and during the useful life of the materials when oxygen and sunlight are the most important degradative agencies. In more specialized applications, degradation may be induced by high energy radiation, ozone, atmospheric pollutants, mechanical stress, biological action, hydrolysis and many other influences. The mechanisms of these reactions and stabilization processes must be understood if the technology and application of polymers are to continue to advance. The study of all these processes has made extensive use of modern instrumental analytical methods and the various spectrometric, chromatographic and thermal analysis techniques have been particularly prominent.

Recent Developments in Use of Polymers for Drug Delivery Systems:

The oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration¹.

A large number of both natural and synthetic polymers have been studied for possible application in drug delivery. The great advantage of synthetic polymers is their advantageous properties and a wide choice availability. Two promising synthetic polymers which have been developed for biomedical applications are polyvinylpyrrolidone and polyethylene glycol acrylate based hydrogels. Both of them are biodegradable and forms copolymers with natural macromolecules. On the other hand, natural polymers have the advantage of high biocompatibility and less immunogenicity. Among the natural polymers studied a special mention has to be made to collagen and gelatin. Other natural polymers include chitosan, alginate, starch, pectin, casein and cellulose derivatives. The composites of some of the above natural polymers with synthetic polymers give added advantage as carriers for drug delivery by complimenting the properties of each other. Some researchers have prepared collagen poly-HEMA hydrogels in the laboratory as an implant for delivering anticancer drugs such as 5-fluorouracil, mitomycin and bleomycin for solid fibrosarcoma in rat model. The same hydrogels have been used with some modifications for the delivery of model protein bovine serum albumin and vaccines such as tetanus and diphtheria toxoids in mice. Hybrid copolymers of collagen with biodegradable synthetic polymers polyethyleneglycol 6000 and polyvinylpyrrolidone were developed for the controlled release of contraceptive steroids⁹.

Poly lactides are known to be more hydrophobic as compared to PLGA and take a longer time to degrade. Among the poly lactides, DL-PLA, which is a polymer of D and L-lactide, degrades faster than L-PLA, which is a homopolymer of L-lactide, presumably due to lesser crystallinity. Similarly, the more hydrophobic end-capped PLGA polymers degrade faster than the carboxyl-ended PLGA. In spite of the several apparent advantages of PLA and PLGA based polymers, commercialization of products based on these polymers has certain limitations. One of the major concerns is that more than 500 patents have been issued for various applications of these polymers. Hence, patent infringement may become a concern in developing new products. In addition, PLA and PLGA polymers have certain inherent limitations in terms of flexibility &

stability. Due to these concerns, several new polymers are presently being explored for applications in drug delivery. Some of the new polymers which are in clinical or preclinical development stage are: Polyorthoesters, Polyphosphazenes, Polyanhydrides, Polyphosphoesters². The researchers are also trying use of some copolymers of PLGA for overcoming their limitations.

Factors Affecting Biodegradation Of Polymers

- Chemical structure and composition.
- Distribution of repeat units in multimers.
- Presence of ionic group.
- Configuration structure.
- Presence or unexpected units or chain defects.
- Molecular weight
- Molecular weight distribution.
- Morphology- amorphous/ semi crystalline, microstructures, residual stresses.
- Presence of low molecular weight compounds.
- Processing condition.
- Annealing.
- Sterilization process.
- Shape.
- Site of implantation.
- Adsorbed and absorbed compounds like water, lipids and ions.
- Physicochemical factors like ion exchange, ionic strength and pH.
- Physical factors like shape and size changes, variations of diffusion coefficients, mechanical stresses, stress and solvent induced cracking.
- Mechanism of hydrolysis.

Chemical Structure:

Structure of polymer identifies the pathway by which degradation will take place. For example, in case of peptide linkage, degradation occurs via proteolytic enzymes and in case of benzyl substituted poly ester urea's, a phenylalanine derivatives, chymotrypsin, is responsible for the degradation.

Molecular Weight:

There are two types of enzymes produced by microorganisms, exoenzymes and endoenzymes. Exoenzymes degrade the polymer in a random manner. In case of exoenzymes, the higher the molecular weight the lesser is the enzymatic degradation. While in case of endoenzymes, low molecular weight polymers are degraded at a faster rate. A good example for this hydrocarbons with high molecular weight which undergoes microbial degradation. They are taken up by microbial cells, processed therein and converted to cellular metabolites. Because this process occurs inside the cell and large molecular weight components by enzymatic actions, followed by their uptake and progressing.

Physical Properties:

Water permeability and water solubility of polymer determines the rate with which hydrolysis proceeds and whether surface or bulk hydrolysis will occur. This is the indication of free volume of the polymer and its corresponding hydrophilicity. In case of production of acidic or basic group as a result of polymeric breakdown, autocatalysis is also possible. Polymers can exist either in crystalline or in amorphous forms. The amorphous form is only available for enzymatic attack and penetration by permeants¹⁰.

Morphology:

The morphology of a polymeric material (i.e. amorphousness and semicrystallinity) plays a critical role in enzymatic and nonenzymatic degradation processes. It is now known that degradation of semicrystalline polymers in aqueous media occurs in two stages. The first stage consists of diffusion into amorphous regions with random hydrolytic scission of ester bonds. The second stage starts when most of the amorphous regions are degraded. The hydrolytic attack then progresses from the edge towards the center of crystallites. This phenomenon was first observed by Fischer et al. who investigated the structure of solution grown crystals of PLA stereo polymers by means of chemical reaction. Amorphous polymers are preferable for sustained drug delivery systems because they usually yield a smooth surface and a uniform structure, which retains the drug for long periods of time. In contrast, a semicrystalline polymer generally leads to rough surfaces and porous structures, which are suitable for sustained delivery of drugs. Morphology of the polymers can greatly affect the process of degradation. More irregularity in the structure is better for the degradation, and proteins are a good example for this. Although they are bulky structures, because they are irregular, they are easily degraded. In case of synthetic polymers, these have equivalent repeating units and this property contributes to the crystallization of the polymer, making it difficult for the enzymes to access the hydrolysable groups. It was reasoned that crystallization is less likely to occur in synthetic polymers that have long repeating units, making them more biodegradable. Subtilisin, a non specific protease, was found to be capable of degrading a series of poly amide urethane.

Size:

The size of the polymer samples has also been regarded as an important factor for the degradation of aliphatic polyesters. The degradation rate is much faster in pellets than in fibers. Lam et al. observed a faster degradation of nonporous films as compared with porous films.

The micro particles exhibited a more prolonged drug release profile, indicating that the fusion process may

have substantial advantages for thermo stable drugs requiring long term release. In hollow fibers the release was found to be dependent on the membrane wall and zero order was achieved for as long as 6 months¹¹.

Polymer pH And Ionic Strength:

No major difference was observed between and acidic media. The effects of pH and ionic strength were interpreted in terms of electric potential distribution at the polymer solution interface. Degradation was also found affected by salt concentration in buffer solutions, suggesting that the cleavage of polymer ester bond was accelerated by conversion of the acidic degradation products into neutral salts¹². Therefore one can easily conclude that the alkaline and strong acidic media accelerate the polymer degradation. The difference between the slightly acidic and physiological media, however, is much less pronounced due to autocatalysis by carboxyl end groups. Nevertheless one can assume that for degradation controlled release, drug release should be enhanced. In the case of diffusion controlled release, one should take into account the solubility of the drug in the external medium.

CONCLUSION:

Polymers possessing a unique strength in their application towards drug delivery application which enables the new advancement in the formulating new drug delivery systems which improves the therapy and treatment. The pharmaceutical technology is one of the most important fields of using of polymers. The discovering of new drug forms, e.g.: new therapeutic systems and macromolecular prodrugs is simply demanded by the market and industry presently. The elaboration of new medical and pharmaceutical specimens will also require intensive investigations in chemistry and biomedical polymer areas. As is also evident from this discussion, the spectacular improvement has been achieved with natural compounds applied as initiators, catalysts, organo-catalysts or co-initiators of polymerization of cyclic esters, ether-esters and carbonates. The utilized compounds are primarily friendly for environment, safe, non-toxic and irreplaceable for the synthesis of polymers for the pharmaceutical applications. Promising avenues of research have also emerged for the enzymatic approach. Increasing interest has also been dedicated to the polymers containing natural compounds in macromolecules that have been incorporated into though the polymerization process. Clearly, the future development of biodegradable polymers will be based on discovering macromolecules with not only appropriate chemical, physical and mechanical properties but also suitable biological properties.

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