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Importance of Biodegradable Polymers in Pharmaceutical Industries Developing Oral Drug Delivery System and Overview on Topical Drug Delivery

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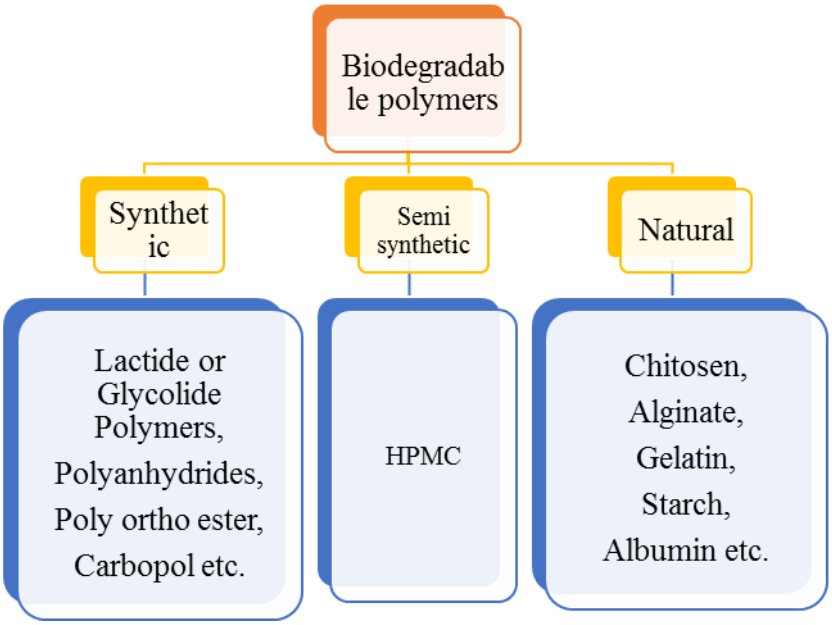
ABSTRACT

Last many decades organic and synthetic polymers have been used in many of the Pharmaceutical industries for the development of various pharmaceutical dosage forms, Surgical preparations, or various packaging materials and also used in tissue engineering. In recent years Polymers have been playing an important role as a drug carrier. Biodegradable polymers cannot create any harm after introducing to them in the human body. Their degradation products can be easily metabolized and excreted from the body. Polymers are used in the complex delivery of drugs they have insurmountable advantages such as developing controlled or sustained delivery systems and developing novel drug delivery systems with some particular properties such as chemical, mechanical, biological, etc. It helps to prevent the adverse effect of the drug by reducing the dose. In the current situation Biodegradable polymers found to boon for the pharmaceutical industry.

INTRODUCTION:

According to literature in the 1980s Biodegradable polymers came into existence. The most widely used synthetic polymers were man-made polymers derived from polyester families such as PLA, PGA, PGLA, etc., and natural polymers such as polysaccharides, lipids, proteins, etc. derived from natural sources such as plants, microorganisms, animals, etc. Biodegradable polymers are linear, branched, or cross-linked formed by many of the smaller molecules called monomers (1). For the last two years, biodegradable polymers have been used as popular choices for topical drug delivery systems, oral drug delivery, surgical preparations (2), and widely used in tissue engineering or three-dimensional engineering (3,4) and biomedical devices. Polymeric dosage forms do not show any adverse effect on the human or animal body, it dissolves and degrade in the body fluids and is easily metabolized and excreted from the body (5). Bioavailability is a crucial concern for various APIs (BCS class II and IV) delivered through the oral route. When an active pharmaceutical ingredient or therapeutic molecule is encapsulated in a polymeric material, some major criteria are taken into consideration such as the timing of retention, encapsulation efficacy which leads to improvement of bioavailability of therapeutic molecules (6). The application of polymers in the pharmaceutical industry is to develop a novel drug delivery system to formulate immediate release, modified release, extended-release, gastro retentive dosage form (7). In addition, natural as well as synthetic polymers have been utilized for intestinal systems and it was reported that the release of drug in these formulations mainly rely on factors related to biodegradable polymers such as; molecular weight, the degradation mechanism of the polymer, drug permeability and solubility as well as polymer-drug compatibility (8). To formulate hydrogel polymeric gelling agents such as HPMC, Gelatin, carbomer was most commonly used polymers at a concentration of 0.5% to 10%. Carbomers are commercially available in many grades such as carbomer 934P, 940, and 941.



Classification of Biodegradable polymers

Figure No. 1: Classification of Recently used polymers (9).

1. SYNTHETIC POLYMERS

1.1. Lactide or Glycolide Polymers

Lactide or Glycolide Polymers are aliphatic polyesters synthesized from lactic acid and glycolic acid. These polymers have hydrophilic nature therefore these polymers are widely applicable to formulate a controlled release drug delivery system. Polylactic acid was obtained from poly-condensation of Dextro or Levo-lactic acid or open ring polymerization of lactide and a cyclic dimer of lactic acid. The organic isomer is L-lactide and the synthetic blend is composed of DL-lactide. The monomer of PLA may easily be produced by fermentation of carbohydrate feedstock (10). The solubility of these polymers is depending on the type and composition of monomers. It has been demonstrated by Gilding and Reed in 1979 that the aqueous uptake increased as the glycoside ratio in the copolymer increased. Aliphatic polyesters undergo bio-degradation by bulk erosion. The lactide/glycolide polymer chains are cleaved by hydrolysis to the monomeric acids and are eliminated from the body through the Kreb's cycle primarily as carbon dioxide and in urine(11).

1.2. Poly Anhydrides

Poly anhydride is a copolymer of methyl vinyl and maleic anhydride, which provides a hydrophobic backbone with hydrolytically labile anhydride linkages. This polymer is non-

cytotoxic, biocompatible, and has very good sustained-release properties. Recently, for cancer chemotherapy poly anhydride was used by the researcher. Nano-carriers have been approved by the FDA. Degradation of Aliphatic polyanhydrides occurs within some days as compared to aromatic polyanhydrides. Polyanhydrides are used as the surface-eroding polymer. It was synthesized by the dehydration of di-acid molecules by melt poly-condensation. *In vivo*, polyanhydrides polymer was nontoxic, biocompatible, di-acid monomers that can be metabolized and eliminated by poly-condensation. Degradation times can be altered from days to years depending on the hydrophobicity of monomers. It has very good biocompatibility. This polymer-based drug delivery is widely used for vaccines and localized tumor therapy(12).

1.3. Poly-Ortho esters

Poly Ortho-ester belongs to a family of polymers identified as biodegradable polymers suitable for formulating orthopedic implants which were prepared along with water-soluble excipients. Poly Ortho esters are one of the polymers that contain acid versatile linkages in their backbone which facilitates the manipulation of hydrolysis rate utilizing acidic or basic excipients physically encapsulated in the matrix. In addition, the hydrolysis of such polymers can be predominantly confined to the outer surface and the resultant surface erosion allows excellent control of the release kinetics of the incorporated therapeutic agent. With the addition of lactide segments as part of the polymer structure, degradation times ranging from 15 to hundreds of days can be achieved. The degradation of the lactide segments produced carboxylic acids, which catalyzed the degradation of the Ortho-ester (13,14).

2. SEMI-SYNTHETIC POLYMERS

These polymers are mostly derived from organically occurring polymers by chemical modifications. In one of the literature, it was used in fabricating thread and materials like films glasses, etc**.** HPMC is a semisynthetic polymer recently used in the large-scale manufacturing process in pharmaceutical industries (15).

2.1. Hydroxy Propyl Methyl Cellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is hydrophilic and it is widely applied in drug delivery through the oral route and topical route by the researchers. It possesses the great swelling ability and attractive surface properties. The swelling property of HPMC

significantly affects the release rate of drugs. It can get adsorbed on the surface of drugs or biomolecules. HPMC has gelling property therefore it was used to formulate topical preparations such as topical cream, gel, etc. (16).

3. NATURAL POLYMERS

3.1. Chitosan

Chitosan is a polysaccharide copolymer composed of randomly distributed β (1-4)-linked D-glucosamine and N-acetyl-d-glucosamine obtained by partial alkaline deacetylation of chitin, with different molecular weights, degree of deacetylation, and viscosities. Chitin has good mechanical strength, it was biocompatible, bioactive, and biodegradable, but it has limited utilization due to low solubility. Therefore, it was converted into chitosan by de-acetylation in the presence of hydroxide at a high temperature. Chitin was extracted from marine organisms. Glycosidic linkages were composed of large polymeric chains. Chitosan is soluble in organic solutions with a pH lower than 6.5 and insoluble in sulfuric acid and phosphoric acid. Due to its solubility, chitosan is used to fabricate films, hydrogels, pastes, nanoparticles, and Nano-films. Chitosan-based drug delivery system used to treat cancer, fungal and bacterial disease and increase the biocompatibility of drugs for various diseases (17,18).

3.2. Alginates

Alginate is a high molecular weighted hydrophilic polymer associated with certain cations which influence its properties and are exchangeable. Alginate has anti-oxidative and anti-inflammatory properties and it was found stable in the stomach acidic gastric solution and can gradually dissolve under alkaline conditions in the small intestine which was claimed by the researchers. Different drugs are not released in the gastric tract, the hydrated sodium alginate was transformed into a porous, insoluble layer of alginic acid. Once the dosage form moved into the higher pH of the intestinal tract, the alginic acid layer was converted into a soluble viscous layer. This pH condition of alginate can be exploited to customize release profiles. Sodium alginate is soluble in water however; calcium alginate is insoluble in water. A mixed sodium/calcium alginate shows intermediate behavior by absorbing water and swelling to form a gel (19,20).

Controlled release drug delivery system

Diffusion-controlled systems can be divided into reservoir and matrix systems. In the reservoir system, drug molecule was compacted in the polymeric membrane. The release of the drug is controlled by the biodegradable polymeric membrane. Sometimes non-biodegradable polymers were used in this type of system. Matrix systems are based on a polymer matrix in which the drug is homogeneously dispersed with polymer. Drug release is controlled by polymer erosion, drug diffusion, and/or by a combination of both (13).

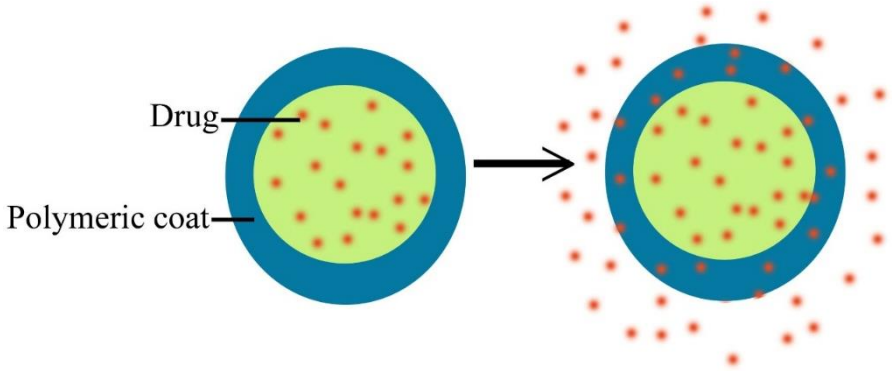


Figure No. 2: Reservoir system

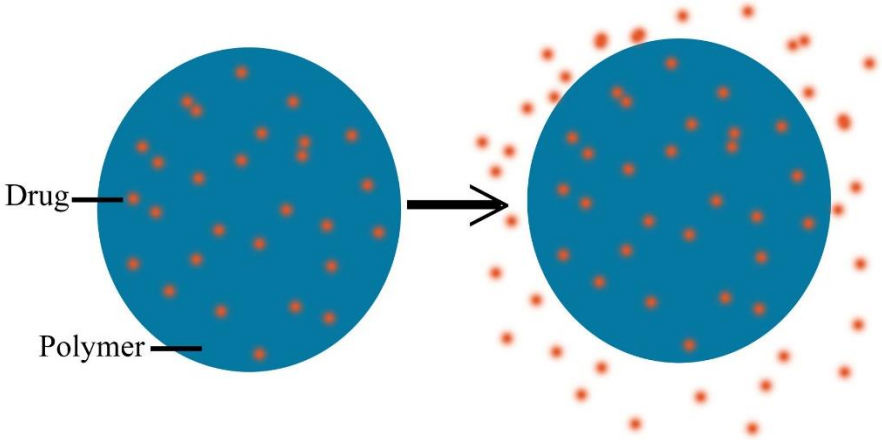


Figure No. 3: Matrix system

4. Case study: Drug release from polymeric coating using the oral dosage form

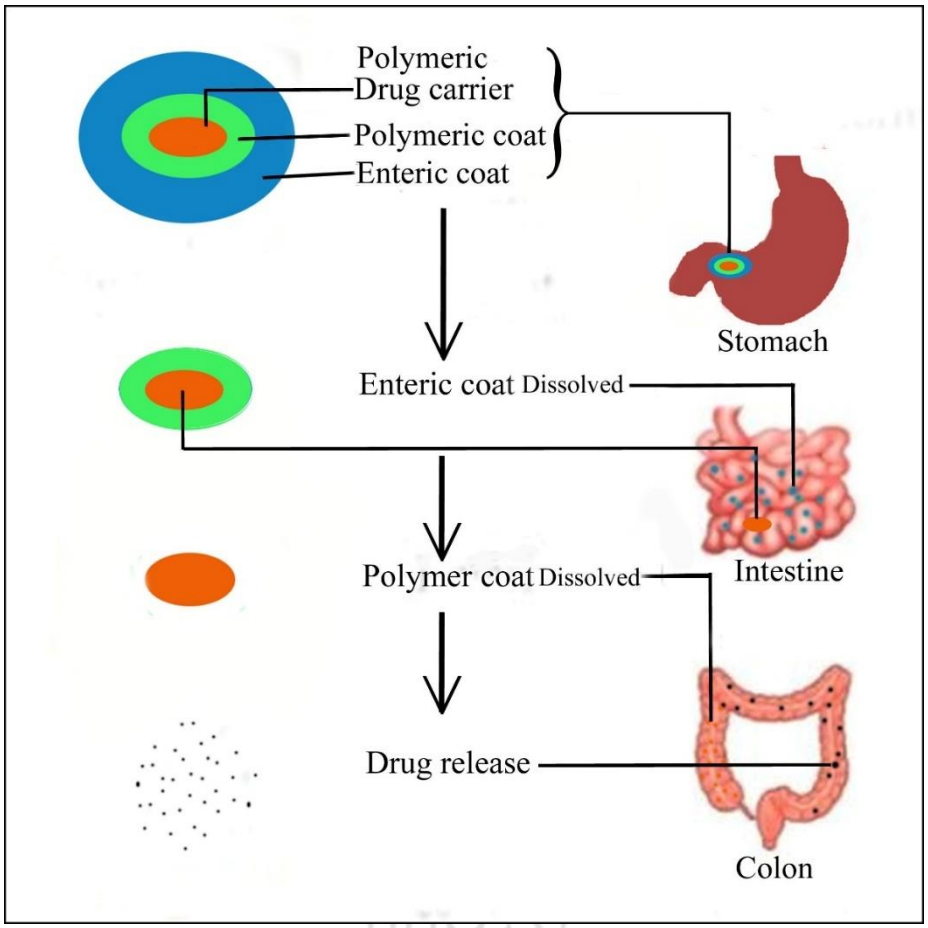


Figure No. 4: Schematic representation of enteric-coated drug release from the polymeric coating (21)**.**

According to the literature, the pH of the colonic region was moderately higher than the pH of the upper GI tract, and this can be used as a targeting strategy for the colonic drug delivery system. A colon-targeted drug delivery system was fabricated by using pH-dependent polymers such as CAP, HPMCP, and copolymers of methacrylic acid such as methyl methacrylate, this polymer were the most widely used synthetic co-polymers for colonic drug delivery that offers muco-adhesiveness and pH-dependent drug release. The ideal polymer should be able to withstand the low pH of the stomach and the proximal part of the small intestine but be dissolved by the pH of the terminal ileum and the colon. Colon-targeted drug delivery can be achieved with film-coated tablets or capsules. The polymeric coat was coated with an enteric coat this combination system may be superior to tablets coated with a single polymer for colon-targeted drug delivery. However, the tablets coated only with pH-sensitive enteric polymers still face the problem of premature drug release due to the variability of pH

in the GI tract. Released drug from the tablet was less in the simulated gastric fluid and intestinal fluids while extensive drug release was observed in the colonic fluid.

5. TOPICAL HYDROGEL BASE

Hydro gels are semisolid preparation in which aqueous phase was constrained within a three-dimensional, polymeric matrix in which physical or chemical cross linking has been introduced. Hydrogels are a multi-compartmental system made up of cross linked polymeric networks due to the presence of hydrophilic functional groups in the structure they can absorb large quantities of physiological media and swell without dissolving and losing their integrity (22). Natural polymer, Synthetic polymer and Semisynthetic polymers were used to formulate gels because of their gelling property. Carbomer is a synthetic high molecular weighted, cross linked, acrylic acid based polymer widely available under the commercial name Carbopol which is a widely used polymer in the formulation of ocular (23), topical gel. 934, 940, 980 this graded carbopol are commercially available (17,24–26).

5.1. Gel preparation

Gels containing Carbopol, HPMC, SCMC etc. at concentrations 0.5% to 10% were prepared by dissolving each polymer into the selected solvent (Water) adding a mixture of cross-linking agents made of propylene glycol and glycerol. Recently carbopol is widely use to prepare topical formulation. Dissolved Carbomer in distilled water for 4 to 5 hours and mixed with a magnetic stirrer until all the bubbles or entrapped air were removed. Lubricating agents, Preservatives were added in Carbopol dispersion and neutralized with TEA until the pH value reached 5.0, 6.0 or in some cases 7.0 (25).

5.2. Evaluation methods

5.2.1. pH measurement

The pH was measured in each polymeric gel using digital pH meter, which was calibrated using buffered solutions at pH 4, 7 and 10 (27).

5.2.2. Viscosity

Viscosity was measured by using Brookfield viscometer using preferable spindle number and preferable rpm usually spindle number 64 and 10 to 12 rpm was used because of high viscosity (27).

5.2.3. Spreadability

The apparatus is made up of wooden blocks containing two glass slides with scale having a pan mounted on a pulley. The formulation was placed between the two glass slides and the load was put into the mounted pan. After putting load glass side was shifted in above direction. Time and scale were noted.

The following formula is used to calculate Spreadability:

$$S = (M \times L)/T$$

Where,

S = Spreadability.

M = weight tied on upper slide,

L = length of glass slide,

T = time in sec (27).

CONCLUSION

Natural, semisynthetic, and synthetic biodegradable polymer based particulate systems have emerged as a promising and safe choice for the delivery of drugs and vaccines as it protects the biomolecules of drug and antigens from degradation from drastic change in environment of stomach and intestinal lumen. Biodegradable polymers are widely used in cosmetic industries to formulate creams, gels, lotions etc. Biodegradable polymers based particulate system are better than the traditional one for targeted drug delivery, controlled release, immediate release, modified release, extended release, gastro retentive dosage form. Reduction in dosing frequency and providing stability to the bio-molecular drugs with technological advancements and for better understanding of the physicochemical properties like size, shape, and charge of polymer based particulate systems and much more efficient

delivery systems for drugs and vaccines can be developed. Hydrogel based drug delivery can be used for topical, ocular, transdermal routes. The present review article represents the importance of biodegradable polymers for developing novel drug delivery systems in pharmaceutical industries.

LIST OF ABBREVIATIONS

PLA= Polylactic acid

PGA= Polyglycolic acid

PGLA= Poly D, L-lactic-co-glycolic acid

HPMC= Hydroxypropyl methylcellulose

CAP= Cellulose acetate phthalate

HPMCP= Hydroxypropyl methylcellulose phthalate

SCMC= Sodium carboxymethylcellulose

GI= Gastrointestinal

FDA= Food and Drug administration

BCS= Biopharmaceutical classification system

API= Active pharmaceutical ingredient

TEA= Triethanolamine

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