Recent Advances of Polymers in Pharmaceutical Area: A Review

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Abstract:

Polymers are long chain molecules made up of many same or different small units which called as monomers. Numerous of biological synthetic and hybrid polymers are used for multiple medical application and in pharmaceutical industries. Due to its wide application includes controlling drug release, providing site specific delivery of active pharmaceutical ingredients and improving stability polymer are widely using in medical sector. This review gives a brief information about the history, development and recent advancement in polymers area especially of those which used in pharmaceutical and medical fields.

Keywords: *Polymers, Natural, Synthetic, Bio-degradable, Application, Drug Delivery*

INRODUCTION

Polymers are the material which are made up of repeating subunits of a single molecule and form a large structure called macromolecules. polymers are basically derived from two Greek words in which “poly” means more than two or several and “mers” means unity. These are made by the process called polymerization. Because of their properties these are widely used in the daily life of humans as well as in medical fields in the synthesis of life saving compounds (1). Talking about history, the tradition of human polymer use has been very long since 1839. In research on rubber vulcanization, good year has found a crucial advance that has turned natural rubber into a function engineering material. The first plastic to be industrialized in the 1920s (2). The researcher proposed in 1920 that polymers are long molecules united by structural units by covalent bonding because of the polymers either it is natural or synthetic these are made up of carbon atoms so due to carbon ability of making or we can say bonding ability by sharing of electrons means covalent so that’s why polymers are connected via covalent bonding (3). Polymers have application in various biomedical fields such as drug delivery system, developing scaffolds in tissue engineering implantation of medical devices and artificial organ prosthesis, ophthalmology, dentistry, bone repair, and many other medical fields. The pharmaceutical application of polymers is from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspension and emulsion. Especially biodegradable polymers have been widely used in biomedical fields because of its biocompatibility and biodegradability (4). So used in novel drug delivery system as a n application in implant drug delivery, to minimize the risks and side effects and other types of inconveniences for patients (5).

Characteristics of an ideal polymer:

- It should be non-reactive and biocompatible.
- It should have good mechanical strength.
- It must not affect rate of drug release

- It must not be toxic and its metabolites forms in body also should be non-toxic.
- It must not have to retain in the tissue for long time and should be excretes easily (13).

Generally, polymers are classified into various classification because classification is not only based on its single property or nature so are mainly classified into four categories.

A) Classification based on the mode nature of polymerization:

1) Addition polymers: Polymers that are formed by repeated monomers addition which can be split into two types: Homopolymers and Copolymers
   - Homopolymers are those polymers which are formed by addition of same monomers such as polyethene polypropene, polyvinyl chloride, polyisoprene,
   - Copolymers: the polymers formed by addition of various monomers such as Buna S, Buna N, polyester, alkyd resins.
2) Condensation polymers: formed by the condensation reaction of two different monomers small molecules such as water hydrogen chloride are removed in the reaction.

B) Classification based on source:

1) Natural polymers: Animals and plant polymers such as sugars, nucleotides, proteins, lipids.
2) Semisynthetic polymers: The majority of these polymers are chemically modified naturally occurring polymers, such as cellulose and vulcanized rubber.
3) Synthetic polymers: A large number of man-made polymers including fiber and plastic rubbers are commonly used in everyday life (7).

C) Classification based on structure:

1) Linear polymers: These polymers have only long straight chain. High density polyethene, PVC, polyester are common examples.
2) Branched chain polymers: In these polymers, the monomer units not only combine to produce the linear chain but also forms branches of different lengths with the main chain. Some examples include low-density polythene (1), amylopectin (12) and glycogen (13).
3) Crosslinked polymers or network polymers: Polymers that have a long straight chain but are linked by strong covalent bonds by these chains. In these polymers, the linear polymers originally formed are joined together to create a three-dimensional network structure. Bakelite (11) and melamine (14) are examples.

D) Classification based upon molecular forces:

1) Elastomers: the intermolecular attraction forces between the polymer chains are weakest such as natural rubber and Buna-S-S (5).
2) Fibers: When the intermolecular forces of attraction are the strongest, fibers are considered polymers. H bonding and dipole-dipole are consisting of these powers. As a result of strong molecular force attractions, these polymers have high tensile strength and low elasticity. For example, Terylene, polyacrylonitrile (15).
3) Thermoplastics: Polymers are called thermoplastics, where the attraction forces between elastomers and fibers are inter-molecular. They are linear or slightly branched-chain polymers that become challenging at room temperature. It's possible to mold these into TV, toys, buckets, telephones. For instance, polyethylene (1), polyvinyl chloride (3), nylon 6,6 (9).
4) Thermosetting polymers: The semi-solid substances that undergo permanent changes in chemical composition during heating to give hard and infusible solid mass are called thermosetting polymers due to the extensive cross-linkage of molecules. For example, Bakelite (11), urea-Formaldehyde (16).

Current practices are largely unsustainable in the generation and disposal of synthetic polymers, causing significant global polymer contamination and enormous loss of value for materials. There are a number of different research fronts that produce polymers that have closed loop life cycles. These serious environmental and economic challenges must be addressed. The utilization and fabrication of biodegradable polymers material for life use have improves significantly during the past few years. These materials have complex physical, chemical, biological, biomechanical and degrading property and are therefore favorably prone to degradable polymer implant. A wide range of biopolymers is studied for different application, both natural and manufactured, which are capable of hydrolytic or enzymatic deterioration (8).

E) Classification based on origin:

1) **Natural polymers:** Natural polymers are the type of polymers which are obtained from the natural sources like plants and animals example collagen, polysaccharide, starch, chitosan, carrageenan, ispaghula, acacia, gelatin, agar, shellac, guar gum etc., which is mainly used in the pharmaceutical formulations like collagen is generally used in the formation of shells of capsule that are mainly of two type soft gelatin capsules and hard gelatin capsules. Whereas starch is used as binder, disintegrants in tablet, polyethylene glycol as plasticizers in the transdermal patch etc. (9).

   Collagen: It a type of protein obtains from animals or mammals that is fabricated from glycine proline hydroxyl proline .it is widely used in pharmaceutical applications due to its application in the formulation of controlled drug delivery system because of its good biocompatibility, low antigenicity and degradability upon implantation. It is used as formulation in matrix-controlled drug delivery system and tissue engineering (10).

   Alginate: Also serves as an example of a naturally occurring linear polysaccharide. Alginate are widely used by many pharmaceutical scientists because of its property such as biocompatibility, biodegradability, low toxicity, non-immunogenicity, water solubility, gelling ability, and its high viscosity in aqueous solutions (11).

2) **Synthetic Polymers**: These are polymers produced industrially consisting of a number of molecules linked together with covalent bond. Most commonly used synthetic polymers are polythene and polystyrene. Other examples are polyester, polyanhydrides, polyamides, polyglycolic acid.

Non-Biodegradable Polymers:

These polymers are used in the pharmaceutical formulation to increase the therapeutic efficacy of drug. This polymer is now days used in the drug delivery and tissue engineering (12). Different examples with their chemical name, key properties and applications are given in table 1.

Table 1: Examples of Non-Biodegradable polymers

Chemical name	Key properties	Applications
Poly (ethylene)(PE), HDPE	Strength and lubricity	Orthopedic implant and catheters
Poly (propylene) (PP)	Chemical inertness and rigidity	Drug delivery, meshes and sutures
Poly (tetrafluoroethylene) (Teflon)	Chemical and biological inertness and lubricity	Hollow fibers for enzymes immobilization, vascular graft, guided tissue regeneration and barrier membrane in the prevention of tissue adhesions
Poly(methymethacrylate)	Hard material, excellent optical transparency	Bone cement, ocular lens
Poly (ethylene oxide)	Negligible protein adsorption and hydrogel forming characteristics	Passivation of devices toward protein adsorption and cell encapsulation

Poly (ethylene terephthalate) (18)	Fiber forming properties and slow in vivo degradation	Knitted Dacron vascular grafts, coating on degradable sutures, meshes in abdominal surgery
Poly(sulphones)	Chemical increases, creep resistant	Hollow fibers and membranes for immobilization of biomolecules in extra - corporeal devices
Poly (dimethyl siloxane)	Gel-like characteristics	Filler in silicone breast implants
Poly (ethylene oxide-co-propyl oxide)	Amphiphilicity and gel forming properties	Emulsifier
Poly (vinyl alcohol)	Surfactant and gel-forming properties	Emulsifier in drug encapsulation processes and matrix for sustained drug delivery (29)

Natural and Synthetic Biodegradable Polymers and Fibers

Synthetic as well as natural both are used in medical fields and have very wide applications in pharmaceutical fields also. If we talk about medical fields then it is used in heart valves, stents, cartilage scaffolds means in tissue engineering, joints, making of artificial skin, blood vessels, urinary catheters, ureteral stents, artificial kidney/Hemodialysis membranes and also in nano systems for drug delivery. For example, polymers like poly (lactic co glycolic acid) (PLGA), poly (glycolic acid) (PGA) and others polymers are having very wide application in medical fields due to its biocompatibility and this is due to their product of degradation are eliminated in the form of CO_2 and water.

Polyolefins: Polyolefins polyethylene and polypropylene are very inert and hydrophobic material which do not degrade in-vivo. PE is produced at different molecular weight and different crystallinity. Low density PE with molecular weight is most soft with elastic modulus and has application mainly in packaging. High density can have similar molecular weight but crystallinity of 60% 80% and elastic modulus 400 1500 Mpa. It is used to form stable devices as containers or also for implantation (14).

Teflon: PTEE has an ethylene backbone with four covalent bound. It is a highly hydrophobic, non – degradable materials. It induces only little inflammation in the body and shows some tissue in growth. It is mainly applied as vascular graft (15).

PVC: It has an ethylene backbone with covalent bound chlorine. Its fabrication and application require stabilizers and plasticizer which are the main reason for medical for medical concern against these polymers. Stabilizers mostly frequently Ca/Zn are necessary to prevent auto catalytic cleavage of Hcl and degradation of the polymers during thermal processing (16).

Poly ethers: Ether bonding are biostable polyether ether ketone as hard material for orthopedic application and polyether sulfone for dialysis membrane are main representative of this polymers class in biomedicine.

Polyamide: Naturally, all proteins consist of units likes by amide bonds and highly repetitive protein like collagen or silk fibroin can be classified here. The most important synthetic polyamide with clinical application is nylon. For its high tensile strength, it is used for suture material. Polyamide block copolymers containing soft segment for better elasticity combine the flexibility of poly urethanes with the strength of nylon and therefore became the material of choice for the balloon of catheters for angioplasty (17).

Polyester: Biostable and biodegradable polyesters are used in biomedicine. Biostable polyester contain aromatic group are poly carbonated .

If we talk about biocompatible polymers that are compatible with the inner environment and conditions of mankind means it not creates any harmful and toxic effect on humans and also its metabolites are also non-toxic to humans. so that's why these polymers are largely used in the novel drug delivery and advance drug delivery system and creates a positive impact in the fields of pharmaceutical and medical field.

Some important polymers that used in novel drug delivery system

PLGA: Poly lactic-co-glycolic acid has been among the most attractive polymeric candidates use to fabricate devices for drug delivery and tissue engineering applications. PLGA is a biocompatible and biodegradable polymer which exhibit a wide range of erosion times (19).

PGA: Poly 1 glutamic acid is a polymer of the amino acid glutamic acid. gamma PGA is formed by bacterial fermentation. Gamma PGA has a wide number of potential uses ranging from food and medicine to water treatment. It is widely being used as a drug delivery system in cancer treatment.

POLYLACTIC ACID: It is a biodegradable thermoplastic aliphatic polyester derived from renewable resources, such as corn starch, tapioca roots, chips or starch or sugarcane (20).

PHEMA: Poly 2 hydroxyethyl methacrylate. It is a polymer that forms a hydrogel in water. This gel has the capability which absorb upto 40% of water, exhibited suitable mechanical properties and transparent.

Polypyrrole: It is a type of organic polymer formed by polymerization of pyrrol. Poly pyrrole are conduction polymers, related members being polythiophene, polyaniline and poly acetylene.

PAMAM: It is a class of dendrimer which is made of repetitively branched subunits of amide and amine functionality. PAMAM dendrimer, sometimes referred to by the trade name starburst, have been extensively studied since their synthesis in 1985, and represent the most well-characterized dendrimer family as well as the first to be commercialized like other dendrimers. PAMANs have a sphere -like shape overall, and are typified by an internal molecular architecture consisting of tree-like branching, with each outward "layer", or generation, containing exponentially more branching points.

DEXTRAN: Dextran is can be defined by Leuconosted mesenteroides (lactic-acid bacteria with the help of which dextran is synthesized using sucrose) which contain glucan which is (16)-linked and has side chains that are attached to the backbone of 3-positions of glucose units. The straight chain consists of alpha-1,6 glycosidic-linkages between the backbone of 3-positions of glucose. The branching starts from alpha 1,3 linkages (21), (22).

Application of Polymers in Drug Delivery System

Tablets: Tablets are the most commonly used dosage form for pharmaceutical preparation meant to be taken orally. Release of drug from the tablet can be controlled by altering the design and content of the formulation. In tablet the polymers are used as a Disintegrants and Binder. Starch, cellulose, Alginates, polyvinylpyrrolidone, sodium CMC etc. are used as disintegrants. Polymers used as binders are starch, HPMC, Gelatin, Alginic acid, polyvinylpyrrolidone, Sucrose, Ethyl cellulose. Polymers are used to mask the unpleasant taste of the drug and also for enteric coating of tablets e.g**.,** Shellac and Zein. MCC enhances compressibility of tablet (23).

Capsules: Capsule are generally composed of gelatin. The composition of gelatin gets varied so gelatin re of two types that is hard gelatin and soft gelatin. Fillers such as MCC and starches are used to fill up the volume in capsule. To overcome problem of aggregation various polymers such as starch and sodium starch glycolate are mixed with capsule container (24).

Parenteral: In Parenteral the various polymer like Methacrylic acid act as an Interferon inductor which induce to the interferon in cancer like disease. Methacrylic acid alkyl amide is act as plasma expander which increase the plasma level in body when admixture of drug with polymer presents in body. Some Vaccines are transpired by using polymer because which disintegrate in GIT tract, example Methyl methacrylate.

Recent Advancement and Applications of Polymers

1. Poly propylene and Polyethylene

Biur *et al.*, 2021 worked on the polyethylene materials with in chain ketones from non-alternating catalytic copolymerization. Introduction of reactive polar groups in these chains could help overcome problematic environmental persistence and enhance compatibility with other materials. Meanwhile, in their laboratory studies the team demonstrated that the new material has the same favorable properties as conventional polyethylene, as far as mechanics and processability are concerned (25).

Basit *et al.*, 2001 have studied the effect of Polyethylene Glycol 400 on gastrointestinal transit: Implications for the Formulation of poorly-water soluble drugs. The main purpose of this work is to assess the effect of polyethylene glycol 400 (PEG 400), a pharmaceutical excipient frequently employed to enhance the solubility and bioavailability of poorly water-soluble drugs, on the gastrointestinal transit of liquid and pellet preparations in human subjects using gamma scintigraphy. This work is done by the method that 10 healthy male volunteers each received, on separate occasions, a liquid preparation consisting of 150 ml orange juice (control) or 150 ml orange juice containing 10 g PEG 400 (test). Rapid liquid emptying from the stomach was observed, with no significant difference noted in the gastric residence times of the two preparations. Pellet transit was largely unaffected by the presence of PEG 400. The findings demonstrate that PEG 400 has a marked accelerating effect on small intestinal liquid transit, which in turn has implications for the formulation of poorly water-soluble drugs with PEG 400 (26).

2. HPMC

Hu *et al.*, 2021 prepared composite hydrogels derived from water-soluble chitosan (CS)/hyaluronic acid (HA) and silanized-hydroxypropyl methylcellulose (Si-HPMC) (CS/HA/Si-HPMC) and tested as injectable hydrogels for cartilage tissue engineering when combined without the addition of a chemical crosslinking agent. An injectable hydrogel based on CS/HA/Si-HPMC composites was developed. The CS/HA/Si-HPMC hydrogel displays the tunable rheological with mechanical properties.The CS/HA/Si-HPMC hydrogel is highly porous with high swelling and degradation ratio. Increasing concentration of Si-HPMC promote an organized network in CS/HA/Si-HPMC hydrogels. Injectable CS/HA/Si-HPMC hydrogels have a high potential for cartilage tissue engineering (27).

Fountaine *et al.*, 2016 thermal processing of PVP and HPMC based amorphous solid dispersion. The objectives of the study were to compare and contrast two thermal processing methods, HME and KinetiSol® Dispersing (KSD), and investigate the influence of polymer type, polymer molecular weight, and drug loading on the ability to produce amorphous solid dispersions (ASDs) containing the model compound griseofulvin (GRIS). Dispersions were analyzed by a variety of imaging, solid-state, thermal, and solution-state techniques. Dispersions were prepared by both HME and KSD using polyvinylpyrrolidone (PVP) K17 or hydroxypropyl methylcellulose (HPMC) E5. Powder X-ray diffraction (PXRD) analysis showed that dispersions prepared by HME were amorphous at 10% and 20% drug load; however, it showed significant crystallinity at 40% drug load. PXRD analysis of KSD samples showed all formulations and drug loads to be amorphous with the exception of trace crystallinity seen in PVP K17 and PVP K30 samples at 40% drug load. These results were further supported by other analytical techniques. KSD produced amorphous dispersions at higher drug loads than could be prepared by HME, as well as with higher molecular weight polymers that were not processable by HME, due to its higher rate of shear and torque output (28).

Madhusudhan *et al.*, 2014 developed doxorubicin (DOX) gold nanoparticles (AuNPs) capped with carboxymethyl chitosan (CMC) for effective delivery to cancer cells. The carboxylic group of carboxymethyl chitosan interacts

with the amino group of the doxorubicin (DOX) forming stable, non-covalent interactions on the surface of AuNPs. The carboxylic group ionizes at acidic pH, thereby releasing the drug effectively at acidic pH suitable to target cancer cells. The combination of HPMC-E5 and PVA polymers, showed a better etoposide retardation at pH 7.4 and greater release rate with controlled manner at pH 4.6. The results indicated that LE and in-vitro release profile of etoposide were improved significantly ($p<0.05$) when used a combination of HPMC-E5 and PVA polymers (F3), as compared with other formulas containing a single non-ionic polymer of HPMC-E5 (F1) or PVA (F2) separately (29).

Wang *et al.*, 2004 investigated on bioavailability and pharmacokinetics of cyclosporine a loaded ph sensitive nanoparticle for oral administration. The pH-sensitive cyclosporine A (CyA) nanoparticles were prepared by the solvent displacement method with enteric dissolved polymer of hydroxy propyl methyl cellulose phthalate. The CyA nanoparticles were analyzed by HPLC for yield and encapsulation efficiency, dynamic light scattering for particle size and transmission electron microscopy (TEM) for morphology. The bioavailability of CyA-HP50 and CyA-HP55 nanoparticle colloids were evaluated in rats, compared with the current available CyA microemulsion (Neoral®). The results obtained demonstrated that the pH-sensitive CyA nanoparticles with a particle size of 50–60 nm and encapsulation efficiency over 95% could be reproducibly prepared. The effects of the suspending agents on the bioavailability of CyA-HP55 nanoparticles were observed, and the bioavailability decreased as the concentration of suspending agents or the viscosity of the nanoparticle colloids increased (30).

3. Dextran

Madkhali *et al.*, 2021 prepared injectable dextran sulfate sodium nanoparticles as a potent antibacterial agent. The nanoparticles exhibited significant physicochemical and effective antibacterial properties, with zeta potential of −35.2 mV, particle size of 69.3nm, polydispersity index of 0.6, and percentage polydispersity of 77.8. The DSS nanoparticles were stable up to 102 °C. Differential scanning calorimetry revealed an endothermic peak at 165.77 °C in 12.46 min, while XRD analysis at 2θ depicted various peaks at 21.56°, 33.37°, 38.73°, 47.17°, 52.96°, and 58.42°, indicating discrete nanoparticle formation. Antibacterial studies showed that the DSS nanoparticles were effective against Gram-positive and Gram-negative bacteria. The findings of study demonstrate the antibacterial potency of DSS injectable nanoparticles (31).

4. Chitosan

Shameli *et al.*, 2022 prepared cross-linked chitosan-based hydrogel nanocomposites for treatment of disease. They explained that adsorptive separation and purification, commercial sorbents such as activated carbon, zeolites, activated alumina, and silica gels play key roles. This study presents the influence of zinc oxide (ZnO) on the structural, thermal, and antibacterial characteristics of chitosan. The chitosan composites containing different concentrations of ZnO (0.5–2 mass ratio with respect to chitosan) were prepared using sol-cast transformation method. The composites exhibited significantly lower degradation rate and higher thermal stability than that of chitosan. Similarly, the composites exhibited biocidal activity to gram positive and gram-negative bacteria. Furthermore, higher biocidal activity was possessed by chitosan/ZnO (1:1) composites. The current–voltage characteristics curves also depicted a significant increase in the value of current versus voltage at equimolar concentration of chitosan and ZnO (32).

Guo *et al.*, 2006 investigated novel derivatives of chitosan and their antifungal activities in-vitro. The three kinds of Schiff bases of carboxymethyl chitosan (CMCTS) were prepared, and their antifungal activities were assessed according to Jasso de Rodríguez's method. The results indicated that 2-(2-hydroxybenzylideneamino)-6-carboxymethylchitosan (HNCMCTS) had better inhibitory effects than those of chitosan or CMCTS against Fusarium oxysporium f. sp. vasinfectum, Alternaria solani, and Valsa mali. hydroxybenzylideneamino)-6-carboxymethylchitosan (HCCMCTS) had better inhibitory effects than those of chitosan or CMCTS against Fusarium oxysporium f. sp. vasinfectum, Alternaria solani, and Valsa mali (33).

Conclusion

Polymers are the most important things used in pharmaceutical and medical fields. Without polymers we cannot expect the formation of novel medicine in the pharmaceutical fields and an innovative medical device which is helpful in medical fields. Polymers made a gradual increase in advancement of medicines and especially in pharmacy fields because it helpful as wonderful excipient in make drugs to modify the pharmacokinetic property according to the need of society. because it helps in making controlled, targeted drugs and other advance form of drugs which helpful in boosting the benefits of pharmacokinetics. It also improves the bioavailability. Release and decrease the side effects of potent drugs with decreasing their onset of releasing rate and make release constant. In targeted drug delivery system, polymers are very important to target drug at a specific place. Because of its bio-compatibleness it is safe and effective in all types of drug delivery. So, polymers made very advancement in treatments of various harmful diseases.

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