A PHARMACEUTICAL PERSPECTIVE ON SMART POLYMERS IN DRUG DELIVERY: SYSTEMATIC REVIEW

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ABSTRACT

New drug development is aimed to ensure that the drug is delivered to the desired place in correct quantity. Low drug solubility, drug degradation, or rapid clearance of drug from the body may decrease the effectiveness of a drug. The polymers are effective means for the delivery of small molecules, proteins, genes, or peptides. Polymers are macromolecules having very large chains, and contain a variety of functional groups. They can be attached with other low or high molecular-weight materials, and can be modified as per the requirement. Polymers are nowadays becoming highly significant in the field of drug delivery due to their effectiveness in drug targeting. Advances in polymer science have led to the development of many novel drug-delivery systems. A proper modification of their surface and bulk properties can help in the utilization of polymers for many drug-delivery systems. The present review is aimed to highlight the design and applications of polymers, biodegradable and non-biodegradable polymers, polymer design and characterization, and recent advancements in polymer technology.

Keywords: Biopolymers, Controlled drug delivery, Biodegradable polymers, Novel drug delivery system, Synthetic polymers.

INTRODUCTION

A polymer is a large molecule or macromolecule composed of several repeated subunits called 'monomers. The term polymer' is derived from the ancient Greek word 'polus' meaning many and 'meros' meaning parts. It refers to a molecule whose structure is composed of multiple repeating units, by which a characteristic of high relative molecular mass is given to the polymer. The units composing polymers are from molecules of low relative molecular mass. The term polymer was termed in 1833 by Jons Jacob Berzelius. The modern concept of 'polymers as covalently bonded macromolecular structures' was proposed in 1920 by Hermann Staudinger, who worked on polymers for almost one decade. Due to their broad range of properties, the polymers play a significant role in everyday life. Polymers range from synthetic plastics such as polystyrene to natural polymers such as DNA and proteins that are fundamental to biological structure. Polymers, both natural and synthetic, are created via polymerization of many small molecules, known as monomers. Their consequently large molecular mass imparts them unique physical properties like toughness, visco-elasticity, and a tendency to form glasses and semi-crystalline structures. [1, 2]

The advancement in novel drug-delivery systems has been attained due to extensive use of polymers in drug delivery. A proper consideration of surface and bulk properties can help in the designing of polymers for various drug delivery systems. Polymers can be utilized as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. They can also be used as film coatings to mask the unpleasant taste of a drug, to enhance drug stability and to modify the drug release. Around sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of medicines that are needed to fight a variety of life-threatening diseases. Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on in use of natural biocompatible polymeric material in designing of dosage

form for oral controlled release administration. [2, 3] Figure 1 indicating the overview of intelligent polymers and some of its different applications.

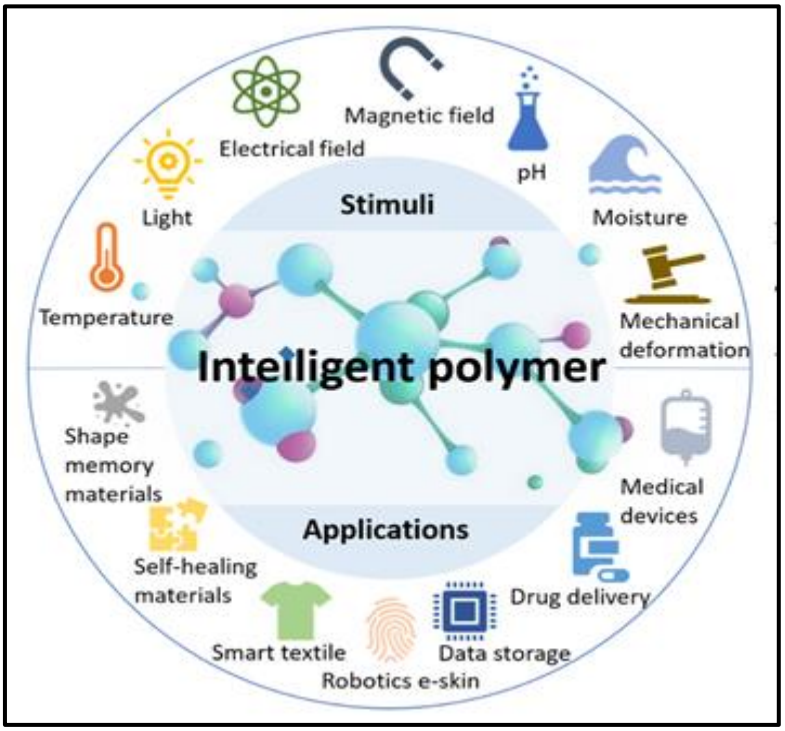

Figure 1. Shows an overview of intelligent polymers and some of its many uses. Diagram adapted and recreated from the Jingcheng et al., 2021 (Note: Reprinted from – "Jingcheng L, Reddy VS, Jayathilaka WA, Chinnappan A, Ramakrishna S, Ghosh R. Intelligent polymers, fibers and applications." Polymers. 2021 Jan;13(9):1427. under the Creative Commons Attribution (CC BY) license [4].

POLYMERS USED IN DRUG DELIVERY [3, 4, 5]

In previous days polymers were utilized for non-biological uses for their specific physical properties, like poly (urethanes) for elasticity, poly (siloxanes) or silicones for insulating ability, poly (methyl methacrylate) for physical strength and transparency, poly (vinyl alcohol) for hydrophilicity and strength, poly (ethylene) for toughness, and poly (vinyl pyrrolidone) for suspending ability.

Cellulose-Based Polymers

Ethyl cellulose is insoluble but dispersible in water, so acts as aqueous coating system for sustained release applications. Carboxymethyl cellulose is a super disintegrant and emulsion stabilizer. Hydroxyethyl and hydroxypropyl celluloses are soluble in water and alcohol so used for tablet coating. Hydroxypropyl methyl cellulose is a binder for tablet matrix and tablet coating. Cellulose acetate phthalate is an enteric coating polymer.

Hydrocolloids

Alginic acid is used in oral and topical pharmaceutical products as thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions. It also acts as binder and disintegrant. Carragenan is a viscosity enhancer. Chitosan is utilized in cosmetics and controlled drug delivery applications, mucoadhesive dosage forms and rapid release dosage forms. Hyaluronic acid causes reduction of scar tissue in cosmetics.

Starch-Based Polymers

Starch is employed as glidant, diluent and disintegrant in tablets and capsules and tablet binder. Sodium starch glycolate is super disintegrant for tablets and capsules in oral delivery.

Plastics and Rubbers

Silicones are used as pacifier, therapeutic devices, implants and medical grade adhesive for transdermal delivery. Polychloroprene septum is used in injection, plungers for syringes, and valve components. Polyisobutylene is a pressure sensitive adhesive for transdermal delivery. Polycyanoacrylate acts as a biodegradable tissue adhesive in surgery and a drug carrier in nano and microparticles. Poly (vinyl acetate)

is a binder for chewing gum. Polystyrene petridishes and containers have utility in cell culture. Polypropylene provides tight packaging, heat shrinkable films and containers. Poly (vinyl chloride) is used to make blood bag, hoses and tubing. Polyethylene is employed in transdermal patch backing for drug in adhesive design, wrapping, packaging and as containers. Poly (methyl methacrylate) is used to make hard contact lenses and poly (hydroxyethyl methacrylate) is used for soft contact lenses. Acrylic acid and butyl acrylate copolymer provide high cohesive strength - pressure sensitive adhesive for transdermal patches.

The major polymers used most commonly pharmaceutical industries are as follows:

1. Hydroxy Propyl Methyl Cellulose (HPMC or Methocel)

It is white to off-white fibrous powder or granules that swell in water to produce a viscous colloidal solution. It dissolves slowly in cold water, insoluble in hot water, soluble in most polar solvents, insoluble in anhydrous alcohol, ether and chloroform. It has a density of 1.39 gm/c.c. It acts as coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder and viscosity-increasing agent It is mainly used in the controlled release formulations. It comes in various grades like Methocel K100 Premium LVEP 2208 100, Methocel K4M Premium 2208 4000, Methocel K15M Premium 2208 15 000, Methocel K100M Premium 2208 100 000, Methocel E4M Premium 2910 4000, Methocel F50 Premium 2906 50, Methocel E10M Premium CR 2906 10 000, Methocel E3 Premium LV 2906 3, Methocel E5 Premium LV 2906 5, Methocel E6 Premium LV 2906 6, Methocel E15 Premium LV 2906 15 and Methocel E50 Premium LV 2906 50.

1. Hypromellose

Hypromellose is white to off-white fibrous powder with molecular weight 10 000–1 500000. The pH is 5.5–8.0 for a 1% w/w aqueous solution; bulk density is 0.341 g/cm3 and tapped density is 0.557 g/cm3. The melting point is 190–2000C (browning) and 225–2300C (charring). Glass transition temperature is 170–1800C. It is soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether. Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder and in film-coating. It acts as a matrix former in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in wet or dry-granulation processes. The high-viscosity grades may be used to retard the release of drug from a matrix. The concentrations of 2–20% w/w are used for film-forming solutions to film coat tablets. Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

2. Ethyl cellulose (Aqua coat, Ethocel, Cellulose ethyl ether)

Ethyl cellulose is a tasteless, free flowing, white to light tan coloured powder. It is chemically resistant to alkalis and salt solutions, although it is more sensitive to acidic materials than cellulose esters. Ethyl cellulose is subjected to oxidative degradation in the presence of sunlight or UV light at elevated temperatures so must be stored in a dry place and well-closed container at a temperature of 7–320C. It is a coating agent, micro encapsulating agent, tablet binder and viscosity enhancer. Ethyl cellulose coatings are used to alter the release of a drug, to mask an unpleasant taste, or to increase the stability of a formulation. Sustained release tablet formulations may also be produced using ethyl cellulose as a matrix former. Ethyl cellulose dissolved in an organic solvent can be used to produce water insoluble films.

3. **Eudragit (Polymeric methacrylates)**

Polymethacrylates (Eudragit) are synthetic cationic and anionic polymers of dimethyl amino-ethyl methacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Eudragit E is cationic polymer based on dimethyl amino-ethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH 5). Eudragit E is available as a 12.5% solution in propanol/acetone in the ratio 60:40. It is light yellow in colour with the characteristic odour of the solvents. Eudragit L and S are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L and approximately 1:2 in Eudragit S. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats, which are resistant to gastric media, but soluble in intestinal fluid.

Eudragit acts as film former, tablet binder and tablet diluent. Polymethacrylates are primarily used in tablet formulations as film coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, Eudragit L and S types are used as enteric coating agents, since they

are resistant to gastric fluid. Different types are available which are soluble at different pH values, e.g. Eudragit L 100 is soluble at > pH 6, Eudragit S 100 is soluble at > pH 7. Eudragit RL and RS are used to form water insoluble film coats for sustained release products. Eudragit RL films are more permeable than those of Eudragit RS, and by mixing the two types together, films of varying permeability can be obtained. Eudragit L 100–55 is a redispersible powder and used for aqueous enteric coating. Polymethacrylates are also used as binders in both aqueous and organic wet granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct compression processes in quantities of 10–50%. Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and to prepare gel formulations for rectal administration.

5. Xanthan gum (Corn sugar gum, Keltrol, Rhodigel)

Xanthan gum is produced by the bacterium *Xanthomonas campestris*, which is found on cruciferous vegetables such as cabbage and cauliflower. Chemically it is a polysaccharide with D-glucose backbone like cellulose, but every second glucose unit is attached to a trisaccharide consisting of glucuronic acid and mannose molecule. The mannose closest to the backbone has an acetic acid ester on carbon 6, and the mannose at the end of the trisaccharide is linked through carbons 6 and 4 to the second carbon of pyruvic acid. Xanthan gum occurs as a cream or white-coloured, odourless, free flowing, fine powder. It is practically insoluble in ethanol and ether, soluble in cold or warm water. Its aqueous solutions are stable over a wide pH range (pH 3-12) and temperature of 10-600C. It should be stored in a well-closed container in a cool, dry place. It acts as a stabilizer, suspending agent and viscosity enhancer. It has also been used to prepare sustained release matrix tablets.

6. Guar gum

Guar gum is obtained from endospermic seeds of *Cyamopsis tetragonolobus* belonging to the family Leguminosae. It has the molecular weight 25,000 Daltons and melting point 900C (with blackening). Guar gum occurs as nearly odourless, white to yellowish-white powder with a bland taste. Chemically it is polysaccharides composed of galactose and mannose. It is made up of a linear chain of β-D-mannopyranose joined by β (1–4) linkage with α-D-galacto pyranosyl units attached by 1, 6- links. Synthetic derivatives of guar gum such as guar acetate, guar phthalate, guar acetate phthalate, oxidized guar gum and sodium carboxymethyl guar have also been investigated for their pharmaceutical applications. Guar gum has been used to formulate orally administered colon-targeted 5- Fluorouracil (5-FU) tablets for colon cancer to deliver the drug (5-FU) directly into colon.

BIOPOLYMERS [6, 7, 8]

Biopolymers are polymers that occur in nature like carbohydrates and proteins. Cellulose is the most easily available biopolymer in the world; 40 percent of all organic matter is cellulose. Starch is found in corn, potatoes, wheat, tapioca etc. Annual world production of starch is over 70 billion pounds, and most of it is used for non-eating purposes like making paper, cardboard, textile sizing, and adhesives. Other examples of biopolymers are collagen and gelatin. Collagen is the most abundant protein found in mammals. Gelatin is denatured collagen, and is used in sausage casings, capsules for drugs and vitamin preparations, and in photography. Casein, commercially produced mainly from cow's skimmed milk, is used in adhesives, binders, protective coatings etc. Polyesters are produced by bacteria, and can be made commercially on large scales through fermentation processes. Some biopolymer examples are proteins, carbohydrates, DNA, RNA, lipids, nucleic acids, peptides, and polysaccharides (such as glycogen, starch and cellulose).

A number of other natural materials can be turned into biopolymers like:

- Lactic acid, which is commercially produced on large scale through the fermentation of sugar obtained from sugar beets or sugar cane, or from the conversion of starch from corn, potato peels. It can be polymerized to produce poly (lactic acid), which has commercial applications in drug encapsulation and biodegradable medical devices.

- Triglycerides make up a large part of the storage lipids in animal and plant cells. They are promising raw material for producing plastics. These natural raw materials are abundant, renewable, and biodegradable, making them attractive feedstocks for bio-plastics, a new generation of environmentally friendly plastics.

- Starch-based bio-plastics are important because starch is the least expensive and easily available. Eating utensils, plates, cups etc. can be made with starch-based plastics.

- Many water soluble biopolymers such as soy protein and casein form flexible films when properly plasticized. Although such films are regarded mainly as food coatings, they also have potential use as non-supported stand-alone sheets for food packaging.

- Starch-protein compositions have the characteristic of meeting nutritional requirements for farm animals. Hog feed is recommended to contain 13-24% protein, alongwith with starch.

- Polyesters are produced from natural resources like starch and sugars through large scale fermentation processes, and used to manufacture water-resistant bottles and eating utensils.

- Poly (lactic acid) is employed for recyclable and biodegradable packaging due to its clarity. It is used to make bottles, yogurt cups, and candy wrappers. It has also been used for food service ware, lawn and food waste bags, coatings for paper and cardboard as well as fibers for clothing, carpets, sheets and towels. In biomedical applications, it is used for sutures, prosthetic materials, and materials for drug delivery.

- Triglycerides have recently been used for manufacture of agricultural equipment, automotive industry, construction etc. Fibers other than glass can also be used in the process, like fibers from jute, hemp, flax, wood, straw or hay.

Biopolymer Classification

There are four main types of biopolymers namely:

i) ***Sugar based biopolymers***

Starch or sucrose is used for manufacturing polyhydroxy butyrate. 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.

ii) 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. This polymer is not present in animal tissues, but only in vegetables.

iii) Biopolymers based on synthetic materials

Synthetic compounds that are obtained from petroleum can also be used for making biopolymers such as aliphatic aromatic copolyesters. Though these polymers are manufactured from synthetic components, they are completely compostable and bio-degradable.

Cellulose based biopolymers

They are used for packing cigarettes and confectionary. Cellulose is composed of glucose and constitutes the primary constituent of plant cellular walls. It is obtained from natural resources like cotton, wood, wheat and corn.

Biopolymer Environmental Benefits

Some of the environmental benefits of biopolymers are:

- These polymers are carbon neutral and can always be renewed. These are sustainable as they are composed of living materials.
- These polymers can reduce carbon dioxide levels in the atmosphere and also decrease carbon emissions. This happens because biodegradation of these compounds can release carbon dioxide that can be reabsorbed by crops grown as a substitute in their place.
- They are compostable, means there is less chance of environmental pollution by them.
- They reduce dependency on non-renewable fossil fuels. They are easily biodegradable and can decrease air pollution, which greatly reduces the harmful effect of plastic use on the environment. Long term use of biopolymers will reduce the use of fossil fuel.

Biodegradable and non- biodegradable polymers [9, 10, 11, 12]

Biodegradable polymers

The polymers that can be degraded in the environment rendering biocompatible end-products are termed as biodegradable polymers. Such polymers disappear in the environment after serving their function. Two

major processes are involved in the degradation of bonds between monomers in the polymer chains and the erosion of bulk polymer. All polymers share the property that they degrade markedly under the influence of UV light or gamma-radiation. Thermal degradation also has a great influence on non-degradable polymers. Mechanical degradation affects those biodegradable polymers that are subjected to mechanical stress. All biodegradable polymers contain hydrolysable or oxidizable bonds. This makes the material sensitive to moisture and heat. Thus the characteristics of biodegradable polymers (especially mechanical and rheological properties) are extremely sensitive to stocking, processing and use conditions.

There are mainly two types of biodegradable polymers namely natural polymers and synthetic polymers. The natural polymers include collagen and gelatin. Collagen is bio-compatible, non-toxic, easy to isolate and purify. However it is has poor mechanical strength, does not give reproducible release rates and immunogenic in some cases, so less used. Atelocollagen is a substitute of collagen and is lesser immunogenic. Gelatin is a thermoreversible polymer, which has easy availability, low immunogenity and fair mechanical strength. Synthetic bio-degradable polymers include polycaprolactone, polyparadioxane, polyphosphoesters, polyanhydride, polyphosphagenes, polylactide (PLA), polyglycolide (PGA) and polylactide coglycolide (PLGA). Among these PLA, PGA and PLGA are most widely employed. These polymers are biocompatible with living tissues and their degradation products are easily eliminated from body. They have been widely employed for drug delivery since they are able to protect the drug from enzymatic attack. Lupron Depot, Zoladex and decapeptyl are examples of PLGA peptide drug delivery systems. PLGA has been used to encapsulate drug into microparticles or nanoparticles so that the plasma level of drug is maintained due to its slow release from biodegradable packing. Thus drug toxicity is reduced and patient compliance is enhanced. The structure and properties of synthetic bio-degradable polymers has been depicted in Table 1.

Table 1: Synthetic biodegradable polymers

Polymer	Structure	Tg (0C)	Tm (0C)	Tensile strength (MPa)	Percent Elongation
Polyglycolide (PGA)	-O-CH2-CO-	35	225	75	~0
Polylactide (PLA)	-O-CH-CH3-CO-	55	175	45	3
Polycaprolactone (PCL)	-O-(CH2)5-CO-	-60	60	32	750
Poly 1,4-dioxane - 2 one (PDO)	-O-CH2-CH2-O- CH2-CO-	-14	110	36	440
Poly trimethylene carbonate (PTMC)	-O-(CH2)3-O-CO-	-15	52	1.2	830
Poly hydoxy butyrate (PHB)	-O-CH-CH3-CH2-CO-	5	175	26	3

Tg= Glass Transition temperature, Tm= Meltin

Polymer degradation is a change in the properties; tensile strength, colour, shape 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. Degradation may be induced by high energy radiation, ozone, atmospheric pollutants, mechanical stress, biological action and hydrolysis. Various routes for degradation of high molecular weight polymers are biodegradation, solubility, thermodegradation, photolysis and hydrolysis. The degradation routes for low molecular weight polymers are structure weakening, brittleness and high surface area. The various factors that affect degradation of polymers are divided into three types:

ii) Chemical factors:

Chemical composition, Distribution of repeat units in multimers, Presence of ionic groups, Presence of unexpected units or chain defects, Configuration structure, Molecular weight, Molecular-weight distribution, Annealing.

ii) Morphological factors:

Amorphous/semi-crystalline, microstructures, residual stresses, Presence of low molecular weight compounds, Processing conditions, Sterilization process, Storage history, Shape, Site of implantation, Adsorbed compounds (water, lipids).

iii) Physicochemical factors:

Ion exchange, ionic strength, and pH, physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, cracking, etc).

Non-biodegradable polymers

The polymers that do not undergo degradation are non-biodegradable polymers. These polymers are mostly used in diffusion controlled systems. Since the polymers are not degraded themselves by environmental factors, there is no initial burst release of drug in such systems. The release kinetics is determined by the thickness and permeability of polymer, the release area and the solubility of drug. The examples of such polymers are silicone, cross linked PVA and EVA. These polymers are approved as safe for consumption by FDA. EVA is impermeable to many drugs, and hence used as surrounding coating for drug core to reduce the rate of drug release. However PVA is permeable to lipophilic drugs, so used as controlled elution membrane in the release area. The PVA layer thickness is varied to get varying release kinetics. Silicone can be permeable or impermeable depending upon the grade used and layer thickness. The non-biodegradable polymers have been used in design of implants for treatment of eye diseases (retinitis, uveitis, CMV, diabetic nephropathy etc). Other non-biodegradable polymers recently developed are block copolymers and parylene. Table 2 comprising the advantages and disadvantages of the Polymers.

Table 2. Advantages and Disadvantages of Polymers (Adpated from the Ogay V, etal., 2020, under common creative licences)

Source	Polymer	Advantages	Disadvantages
Natural	Collagen	The most abundant protein, capable of altering its mechanical properties by crosslinking, safety, biocompatibility	Strong burst release, causing inflammation, swelling, ectopic bone formation and osteolysis
	Chitosan	Biocompatibility, biodegradability, antibacterial and wound healing activity, bioadhesion, presence of functional groups on the surface, enabling physical and chemical functionalization	Requirement for additional modifications for controlled and sustained release of osteopromotive drugs
	Hyaluronic acid	Good biocompatibility, biodegradability, high viscoelasticity, hydrophilicity, non-immunogenicity, capability to modification, low burst release, sustained drug release	Low mechanical and physical properties, fast degradation rate, complicated crosslinking method
	Alginate	Good biodegradability, biocompatibility, non-immunogenicity, capability of modification, significant promotion of the proliferation and osteogenic differentiation	Poor cell attachment ability, limited availability of cellular adhesion sites
	Fibrin	Adhesion, hemostasis, sealant capability, presence of multiple binding sites	Requirement for additional modification

	Poly (ε-caprolactone)	Elasticity, biocompatibility, bioabsorbtion and biodegradability	Limited polymer-cell interaction due to its hydrophobicity and mechanical properties, used as one of the scaffolds components
Synthetic	Poly (lactic-co-glycolic acid)	Biocompatibility, biodegradability, increased adhesion and cell viability and proliferation, sustained release of GF, induced osteogenic differentiation, quick integration with surrounding tissues	Rapid biodegradation
	Polyethylene glycol	Hydrophilicity, biocompatibility, non-immunogenicity, biodegradability	Absence of functional groups on the surface, used as one of the composite components

DESIGN OF POLYMERS [13, 14]

Polymerization is the process of combining many small molecules (monomers) into a covalently bonded network. During the polymerization process, some chemical groups may be lost from each monomer. For example, in the polymerization of PET polyester, the monomers are terephthalic acid (HOOC-C6H4-COOH) and ethylene glycol (HO-CH2- CH2-OH) but the repeating unit is -OC-C6H4-COO-CH2-CH2-O- , which corresponds to the combination of the two monomers alongwith removal of two moles water. Each monomer that is incorporated into the polymer is known as a repeat unit or monomer residue. Laboratory synthetic techniques of polymer synthesis are generally divided into two categories, step-growth polymerization and chain-growth polymerization. The essential difference between the two is that in chain growth polymerization, monomers are added to the chain one at a time only, such as in polyethylene; whereas in step-growth polymerization chains of monomers may combine with one another directly, such as in polyester. However, some newer methods such as plasma polymerization do not come into any of the types. Synthetic polymerization reactions may be carried out with or without a catalyst.

Biological synthesis

There are three main classes of biopolymers: polysaccharides, polypeptides, and polynucleotides. In living cells, they may be synthesized by enzyme-mediated processes, such as the formation of DNA catalyzed by DNA polymerase. The synthesis of proteins involves multiple enzyme-mediated processes to transcribe genetic information from the DNA to RNA and then translate that information to synthesize the specified protein from amino acids. The protein may be modified further following translation in order to provide appropriate structure and functioning. There are other biopolymers such as rubber, suberin, melanin and lignin.

Modification of natural polymers

Naturally occurring polymers such as cotton, starch and rubber are being used for years before synthetic polymers such as polyethene and perspex appeared in the market. Many commercially important polymers are synthesized by chemical modification of naturally occurring polymers. The examples include reaction of nitric acid and cellulose to form nitrocellulose and the formation of vulcanized rubber by heating natural rubber in the presence of sulphur. The methods in which polymers can be modified include oxidation, cross-linking and end-capping. The gas separation by membranes has acquired increasing importance in the petrochemical industry and is now a relatively well-established unit operation for production of polymers. The process of polymer degassing is necessary to suit polymer for extrusion and pelletizing, increasing safety, environmental, and product quality aspects. Nitrogen is generally used for this purpose, resulting in a vent gas primarily composed of monomers and nitrogen.

APPLICATIONS OF POLYMERS [15-21]

Pharmaceutical applications of polymers range from their use as binders in tablets and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to mask the unpleasant taste of a drug, to increase drug stability and to modify drug release characteristics. Pharmaceutical polymers are widely used to achieve taste masking; controlled release (e.g., extended, pulsatile, and targeted), enhanced stability, and improved bioavailability. In the biomedical area, polymers are generally used as implants and are expected to perform long term service. In general, the desirable polymer properties

in pharmaceutical applications are film forming (coating), thickening (rheology modifier), gelling (controlled release), adhesion (binding), pH-dependent solubility (controlled release), solubility in organic solvents (taste masking), and barrier properties (protection and packaging). In conventional dosage forms, the use of polymers is justified as follows:

a) Polymers in tablets

In tablet the polymer are used as binder and disintegrants. Binders are those polymers, which bind the powder particle in a damp mass and polymer used for this purpose are ethyl cellulose, HPMC, starch, gelatin, polyvinyl pyrrolidine, alginic acid, glucose and sucrose. Disintegrants like starch, cellulose, alginates, polyvinyl pyrrolidine and sodium CMC decrease the time of dissolution and give fast action of drug.

b) Polymers in capsules

The polymer are used in the capsule as the plasticizers on which the flexibility and strength of the shell is dependent. The release rate of the capsule is controlled by using the polymers.

c) Polymers as natural coating agents

Natural polymers like shellac and zein were being used as coating agents, but they are hardly able to meet present-day requirements. Organic solvents should be reserved for special applications only. Low molecular weight type of methylcellulose and hydroxypropyl methylcellulose can be processed as aqueous solutions. Ethyl cellulose and cellulose acetate phthalate are available as aqueous dispersions, so-called pseudolatexes. The solubility properties of Eudragit acrylic polymers are adjusted to the conditions of the digestive tract. They satisfy particularly stringent requirements in terms of purity. Further they show high stability during storage.

d) Polymers for Transdermal Drug Delivery Systems (Patches)

In the formulation of transdermal patches various polymers are used. The baking material is also prepared from the polymer for supporting drug in drug reservoir.

e) Film Coating of Solid Dosage Forms

Chitosan has the film forming abilities to suit itself as a coating agent for conventional solid dosage like tablets. Furthermore its gel and matrix forming abilities make it useful for solid dosage forms, such as granules, micro particles, etc. Combination of positively charged chitosan with negatively charged biomolecules, such as gelatin, alginic acid, and hyalouronic acid, has been tested to yield novel matrices with unique characteristics for controlled release of drugs.

f) Polymers as Disperse Systems

Dispersed systems consist of particulate matter known as the dispersed phase, distributed throughout the dispersion medium with the help of dispersing agent. The biphasic systems like emulsion and suspension use polymers like poly vinyl pyrolidine, ethyl cellulose, gum acacia, tragacanth gum etc for dispersing one phase into another phase i.e. water phase disperse in oil phase or vice versa. In the oil in water in oil type emulsion the dispersion of drug content is very difficult but it is easily produced using polymer as a dispersing agent.

Synthetic biodegradable polymers are mainly used in the biomedical area specially tissue engineering and controlled drug delivery. In tissue engineering, biodegradable polymers can be designed to provide a polymer scaffold that can withstand mechanical stresses, provide a suitable surface for cell attachment and growth, and degrade at a controlled rate. In the field of controlled drug delivery, biodegradable polymers offer tremendous potential either as a drug delivery system alone or in conjunction to a medical device.

Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media. Guar gum has been used as matrix former for controlled release of isoniazide and diltiazem. It shows synergistic effect with xanthan and kappa carragenan. Gellan gum has been used in pharmaceutical dosage forms as a swelling agent, as a tablet binder, and as a rheology modifier. In situ gel-forming ability of xyloglucan and borax–guar gum complexes for colon specific drug delivery has also been studied. One of the most recent applications of gums is as film formers. Recent concepts and products such as breath films, cough strips, flu, and sore throat strips have all been made on the basis of film-forming ability of gums. Xanthan gum is found in a number of drug formulations including cefdinir oral suspension and nitazoxanide tablets. It is a highly branched glucomannan polysaccharide with excellent stability under acidic conditions. Xanthan is generally used in solution and suspension products for its thickening property. Because of its very rigid structure, its aqueous solution is significantly stable over a wide pH range. Oxymorphone

hydrochloride extended-release tablets contain TIMERx, which consists of xanthan gum, and locust bean gum for controlled delivery.

Polysaccharides and their derivatives can be used as a rate controller in sustained release formulations due to their gelling property. Polysaccharides are claimed to effectively treat local colon disorders if they are used in colon targeting delivery systems, which utilize the colonic microflora. Inulin, amylase, guar gum, and pectin are specifically degraded by the colonic microflora and used as polymer drug conjugates and coating. It has been shown that drug release in the colon can be maximized if the hydrophobicity of the gums is modified chemically or physically using other conventional hydrophobic polymers. In cancer therapy, polysaccharides are used as immunomodulators. A few polysaccharides, either alone or in combination with chemotherapy and/or radiotherapy, have been used clinically in the treatment of various cancers.

It was suggested that iron stabilized into a polysaccharide structure can be used to treat anemia. The product can also be used in resonance imaging as well as in separation of cells and proteins utilizing magnetic fields due to its magnetic properties. Alginic acid and its salts are anionic polymers that can offer gelling properties. Alginic acid and its derivatives have found applications as a stabilizing agent, binding agent and drug carrier. The antibiotic griseofulvin, which is supplied as oral suspension, contains sodium alginate stabilized with methylparaben. Alginic acid and ammonium calcium alginate can be found in metaxalone tablets. Alginate microbeads can be used to entrap drugs, macromolecules, and biological cells.

Chitosan is obtained from chitin, which can be found in shrimp, crab, and lobster shells. It is a cationic polymer and has been investigated as an excipient in controlled delivery formulations and mucoadhesive dosage forms because of its gelling and adhesive properties. The bitter taste of natural extracts such as caffeine has been masked using chitosan. Chitosan can potentially be used as a drug carrier, a tablet excipient, delivery platform for parenteral formulations, disintegrant, and tablet coating. Because of its cationic nature, chitosan can make complexes with negatively charged polymers such as hyaluronic acid (HA) to make a highly viscoelastic polyelectrolyte complex. Gels based on chitosan and ovalbumin protein have been suggested for pharmaceutical and cosmetic use. In veterinary area, chitosan can be used in the delivery of chemotherapeutics such as antibiotics, antiparasitics, anesthetics, painkillers, and growth promoters. As an absorption enhancer, a protonated chitosan is able to increase paracellular permeability of peptide drugs across mucosal epithelia. Chitosan can also be mixed with nonionic surfactants like sorbitan esters to make emulsion like solutions or creams.

Pectin is a ripening product of green fruits such as lemon and orange skin. Pectins, including high and low ester and amidated, are used in food all over the world. It is an edible plant polysaccharide, has been shown to be useful for the specific drug delivery. Pectin is known as a suspending and thickening agent, but it is also claimed to reduce blood cholesterol level and to treat gastrointestinal disorders. Pectin can be found in amlexanox oral paste HA consists of N acetyl-d-glucosamine and betaglucoronic acid and has been used as fluid supplement in arthritis, in eye surgery, and to facilitate healing of surgical wounds. Hyaluronan is biocompatible and nonimmunogenic and has been suggested as a drug carrier for ophthalmic, nasal, pulmonary, parenteral, and dermal routes.

haracterization of Polymers [22, 23, 24]

IR spectroscopy, 1H and 13C NMR spectroscopy are used for the characterization of the polymers. There are a number of biophysical techniques for determining sequence information in polymers. 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 spectrometry can also be employed for polymer characterization. Nucleic acid sequence can be determined using gel electrophoresis and capillary electrophoresis. The mechanical properties of polymers 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 polymers upon stimulation by pH, temperature, ionic strength or other binding partners. The major parameters for polymer characterization are as follows:

Molecular Mass

The molecular mass of a polymer differs from typical molecules, in that polymerization reactions produce a distribution of molecular weights and shapes. The distribution of molecular masses can be summarized by the number average molecular weight, weight average molecular weight, and polydispersity. Some of the most common methods for determining these parameters are colligative property measurements, light scattering techniques, viscometry and size exclusion chromatography. Gel permeation chromatography is an especially useful technique used to determine the molecular weight distribution parameters based on the

polymer's hydrodynamic volume. Gel permeation chromatography is often used in combination with Low-angle laser light scattering (LALLS).

Molecular Structure

Many of the analytical techniques used to determine the molecular structure of unknown organic compounds are also used in polymer characterization. Spectroscopic techniques such as ultraviolet-visible spectroscopy, infrared spectroscopy, Raman spectroscopy, nuclear magnetic resonance spectroscopy, electron spin resonance spectroscopy, X-ray diffraction, and mass spectrometry are used to identify the functional groups in polymers.

Morphology

Polymer morphology is a microscale property that is largely dictated by the amorphous or crystalline portions of the polymer chains and their influence on each other. Microscopy techniques are especially useful in determining these properties, as the domains created by the polymer morphology are large enough to be viewed using modern microscopy instruments. Some of the most common microscopy techniques used are X-ray diffraction, Transmission Electron Microscopy, Scanning Transmission Electron Microscopy, Scanning Electron Microscopy, and Atomic Force Microscopy. Polymer morphology on a mesoscale (nanometers to micrometers) is particularly important for the mechanical properties of many materials. Transmission Electron Microscopy in combination with staining techniques, but also Scanning Electron Microscopy, Scanning probe microscopy are important tools to optimize the morphology of polymeric materials.

Thermal properties

Thermal analysis, particularly differential scanning calorimetry is a powerful tool to find out glass transition temperature. Changes in the compositional and structural parameters of the material usually affect its melting transitions or glass transitions and these in turn can be linked to many performance parameters. For semi-crystalline polymers it is an important method to measure crystallinity. Thermogravimetric analysis can also give an indication of polymer thermal stability and the effects of additives such as flame retardants. Other thermal analysis techniques are typically combinations of the basic techniques and include differential thermal analysis, thermo-mechanical analysis, dynamic mechanical thermal analysis, and dielectric thermal analysis.

Mechanical Properties

The characterization of mechanical properties in polymers typically refers to a measure of the strength of a polymer film. The tensile strength and Young's modulus of elasticity are significant parameters for describing the stress-strain properties of polymer films. Dynamic mechanical analysis is the most common technique used to characterize this viscoelastic behavior. Other techniques include viscometry, rheometry, and pendulum hardness

Recent advancement in polymer technology [25-28]

The newer technological developments in polymers include drug modification by chemical means, carrier based drug delivery and drug entrapment in polymeric matrices that are placed in desired body compartments. These technical developments in drug delivery/targeting approaches improve the efficacy of drug therapy and thus improve human health. Polymer chemists and chemical engineers, pharmaceutical scientists are engaged in bringing out predictable, controlled delivery of drugs [29].

Smart polymers have enormous potential in various applications. In particular, smart polymeric drug delivery systems have been explored as “intelligent” delivery systems able to release the drugs, at the appropriate time and site of action, in response to specific physiological triggers. These polymers exhibit a non-linear response to a small stimulus leading to a macroscopic alteration in their structure/properties. Synthesis of new polymers and cross-linkers with greater biocompatibility and better biodegradability would enhance current applications. The most fascinating features of the smart polymers arise from their versatility and sensitivity. Development of smart polymer systems may lead to more accurate and programmable drug delivery [30, 31]. Figure 2 showing the schematic representation of trigger dependent polymers.

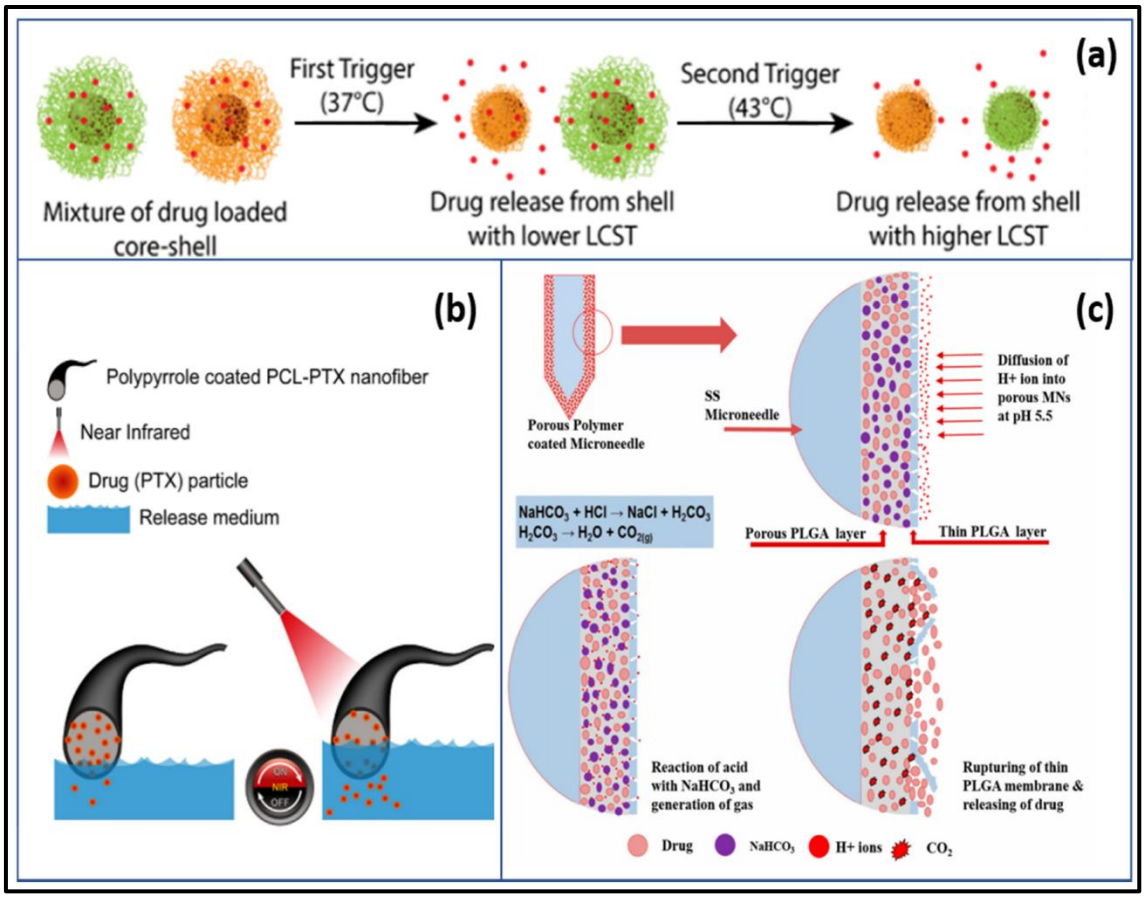

Figure 2. The trigger-dependent sustained release of a drug from a combination of nanoparticles with different trigger sensitivities is shown schematically (b) Schematic representation of the drug release from the PPy-coated fibre triggered by NIR (c) an illustration of the pH-responsive release system in schematic. (Note: Reprinted from – "Jingcheng L, Reddy VS, Jayathilaka WA, Chinnappan A, Ramakrishna S, Ghosh R. Intelligent polymers, fibers and applications." Polymers. 2021 Jan;13(9):1427. under the Creative Commons Attribution (CC BY) license [4]. https://www.mdpi.com/2073-4360/13/9/1427

Novel drug delivery systems

To deliver drugs efficiently to specific organs, a range of methods (e.g., micelles, liposomes, and polymeric nanoparticles) have been designed. In recent decades, significant advances in drug-delivery systems have enabled better drug administration. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug targeting systems are under research and development. Among the several drug carriers, soluble polymers, microparticles made of natural and synthetic polymers, microcapsules, cells, lipoproteins, liposomes, nanoparticles, dendrimers and micelles are valuable [32, 33].

Drug delivery carriers

Colloidal drug carrier systems such as types of polymers, micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticles dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. During development of these formulations, the priority is to obtain systems with optimized drug loading and release properties, long shelf life and low toxicity. Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation [34].

Controlled drug delivery

Controlled drug delivery is the use of formulation components to release a therapeutic agent at a predictable rate *in- vivo* when administered by a particular route. Controlled Drug Delivery (CDD) occurs when a

polymer 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 /cyclic over a long period or it may be triggered by the environment. Controlled-release 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 insolubilized by covalent 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, hydrophobic polymers are converted to small water soluble molecules by backbone cleavage. The choice of a particular erosion mechanism is dictated by the specific application. 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. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value (toxic level) and a minimum value (effective level) [34,35].

Administration of a variety of drugs encapsulated in polymeric particles has been extensively investigated leading to complete absorption of drugs in systemic circulation and control drug release over a predetermined time span resulting in improved patient compliance and better therapeutic effects. Lupron®Depot is a microsphere formulation of leuprolide with duration of one, three or four months using PLA or PLGA in the treatment of prostate cancer and endometriosis. Nutropin®, a commercial PLGA microsphere formulation product of human growth hormone, is used for two weeks or one month duration. As a synthetic anti-somatotropic agent for the treatment of acromegaly and endocrine tumors, Octreotide encapsulated in PLGA microspheres, commercialized as Sandostatin® LAR® is taken on a monthly basis. In addition, Trelstar® Depot for triptorelin, Somatuline LA® for lanreotide, Arestin® for minocycline, Risperdal Consta® for risperidone have been commercialized as parenteral microsphere formulation products for extended duration. Micellar nanoparticles incorporating paclitaxel or cisplatin are in clinical trial phase. There are also oral dosage formulation commercial products for which osmotic pressure is the major driving force in release mechanism, including Procardia XL® for nifedipine and Glucotrl XL® for glipizide [36, 37].

CONCLUSION

The new technology in polymer based drug release system offer possibilities in administration of drugs. The goal in designing sustained release drug delivery system using polymers is to reduce frequency of dosing, to increase the effectiveness of the drug at the required site thereby minimizing or eliminating side effects and providing uniform drug delivery. Polymer usage in delivery systems has received much attention because of the fact that there is more feasibility in dosage form control and sustaining drug release by polymers. Polymers are advantageous in the fact that they show usually an improved pharmacokinetic profile as compared to small molecule drugs with longer circulation time and they also have the potential for tissue targeting. The widespread use of polymers especially biopolymers will depend on developing technologies that can be successful in the marketplace. Guiding sufficient number of drug molecules in desired time directly to the target organs is the strategy of present day therapy. Polymers have aided to accomplish this purpose and will continue to enable this effort in the coming future.

CONFLICT OF INTEREST

There is no any Conflict of interest.

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