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SMART CONTROLLED RELEASE POLYMERS AS BACKBONE OF PHARMACEUTICAL DRUG DELIVERY SYSTEM: OLD WINE INTO NEW BOTTLE WITH CHALLENGES AND PROMISES

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ABSTRACT

This review addressed the role of polymer in efficient delivery of active pharmaceutical ingredients. Polymers are the strength of pharmaceutical drug delivery system by controlling the release rate and solving the troubles related with API such as solubility, bioavailability and stability. Polymers play vital role in drug delivery of immediate release dosage form (tablet, capsule) and modified release dosage form (gastro retentive dosage form). Biodegradable polymers pay more attention in drug delivery because of their biocompatible, biodegradable and non-toxic character additionally it show constant release rate of drugs. Now-a-days, synthetic biodegradable polymers are preferred more because they solve the trouble regarding with natural polymer such as lot to lot variation, microbial contamination and uncontrolled rate of hydration. Smart polymers show change in response with altered environmental conditions such as pressure, pH, temperature, change in concentration and ionic strength. In this review, we have included various aspects of polymers and discussed drug release mechanism such as degradation, diffusion and swelling. The recent advances in polymeric drug delivery system include molecularly imprinted polymer (MIPs) also discussed. In addition, this review also include role of various synthetic and natural plant derived biodegradable polymers functional in drug delivery.

KEYWORDS: Polymer, Dissolution controlled, Diffusion controlled, Biodegradable, Natural, Stimuli responsive

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INTRODUCTION

Introduction: History to Till Date

In the preliminary stage of drug delivery, there was no any meticulous method to treat ailment by targeting the diseased site. Development in the field of newer technology such as recombinant DNA and gene therapy had proved valuable in treatment of ailment but, still it lack target site specificity. In current scenario, targeted drug delivery within a specified time period without disturbing the other physiological functioning of body is done effectively by utilizing polymers. Polymers are the elongated organic molecule consisting of numerous uni-molecular structures called monomer (As shown in **Figure 1**). Polymer serves plentiful application in pharmaceutical as well as biomedical areas such as drug delivery, tissue engineering, cosmaceuticals, gene delivery, organ relocation and in ophthalmology. The internal structure of polymers have some unique features that helps in controlling the release rate of drug from formulation [1]. Development in the field of polymers sciences tends to generate diverse novel drug delivery systems such as liposome, polymeric micelles, niosomes, solid lipid

nanoparticles etc. Polymer aids numerous function in pharmaceutical drug delivery such as, it serves the role of binder in tablet formulation, control viscosity and flow property of a variety of liquid formulations (syrup and suspension), used efficiently as coating material to disguise the obnoxious taste of drugs, as adhesive in transdermal drug delivery system, as well as enhance the shelf life of formulation by improving its stability and the most important one is it provide controlled release¬ over extended period of time and augment oral bioavailability. Polymers are used extensively because they solve the problem of drug degradation and enhance their circulation time, if the polymer is non-biodegradable it should not be accumulate in the body and if it is biodegradable the degraded metabolite should be non-toxic and does not show any antigenic reaction [2].

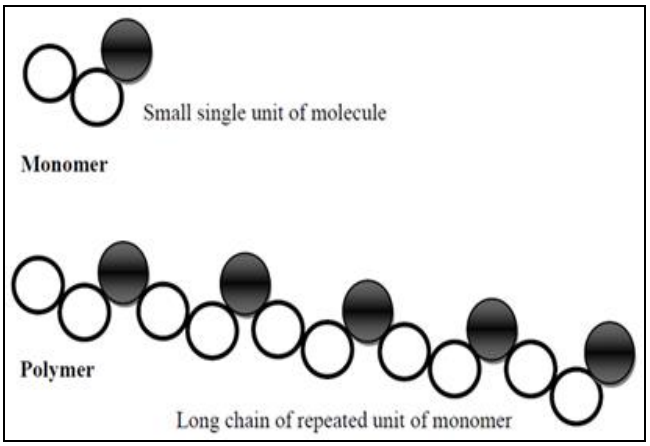


Figure 1: Illustrative Representation of Monomer Unit to Form Polymer

Presence of hydrolytic and proteolytic enzyme is necessary for the chemical degradation of synthetic polymers. In recent research, biodegradable polymers pay much more attention in drug delivery for the reason that they exhibit biocompatible, biodegradable and nontoxic character. The general mechanism of release of drugs from polymer matrix takes place via diffusion. The release of drugs form polymer matrix depends upon the primary concentration of drug as well as polymer chain length. Biodegradable polymer is chiefly inert in nature hence used efficiently in drug delivery system.

Recent research in polymeric drug delivery system involve molecularly imprinted polymer (MIPs) that are generally used to deliver drugs in ocular region, hence, solve the problem related with conventional drug delivery system. Smart polymers are the stimuli responsive polymers show change based on change in environmental circumstances, the numbers of different stimuli are pressure, pH, temperature, change in concentration and ionic strength etc. The utilization of polymers in drug delivery system is not novel idea in past decades; natural polymers had been efficiently applied to deliver herbal medicaments [3, 4, 5]. In 1955, first polymer-drug conjugates (shown in **Figure 2**) were developed, containing mescaline-N-vinyl pyrrolidone. Ten year later in 1966, Frank Davis and Abraham Abuchowski were able to develop the conjugate of polyethylene glycol (PEG) with protein that leads to the discovery of PEGylation process [6].

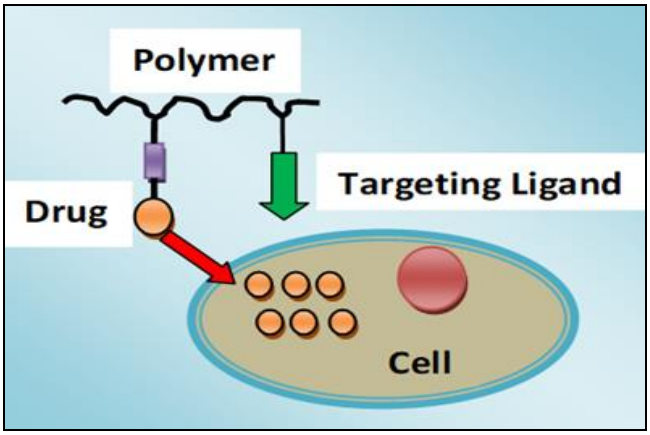


Figure 2: Show Polymer Drug Conjugates

In 1994, HPMA (N- (2hydroxy propyl) meth acrylamide) copolymer conjugates of doxorubicin were developed and clinically tested for the treatment of cancer. In the year 2000, two polymer- protein conjugates (shown in **Figure 3**) PEG-interferon-α and PEG-GCSF (PEG granulocyte colony stimulating factor) were successfully launched in market. First polymeric nanoparticles (albumin entrapped Paclitaxel) were approved in the year 2005 for the treatment of breast cancer [7].

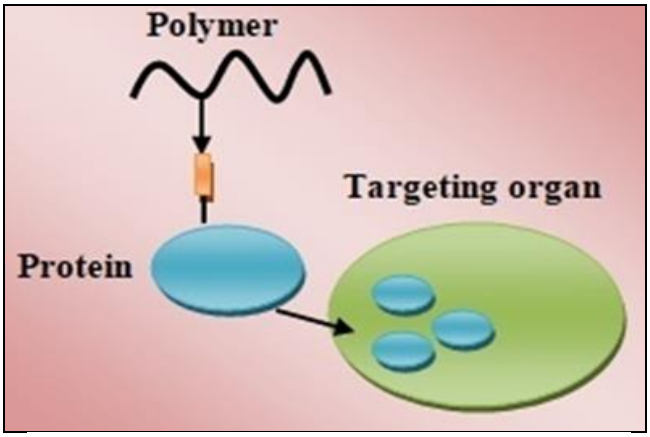


Figure 3: Show Polymer Protein Conjugates

Classification of Polymers

Polymers are classified on the basis of their sources, structure, bio stability, ability to interact with water, thermal response, stimuli responsive and mechanism of polymerization (As shown in **Table 1**). Polymers are the backbone of pharmaceutical drug delivery system. According to their categories they are widely used in pharmaceutical formulation and serve several advantages such as organ specific targeting, reduce nonspecific tissue toxicity, minimize dose, enhance encapsulation efficiency, and improve stability of drugs [8].

Table 1: Show Classification of Polymer

TIM	Types	Example
Source	Natural polymer	Starch, pectin, cellulose
	Semi-synthetic polymer	Cellulose acetate, cellulose nitrate [9]
	Synthetic polymer	Polyester, polyamide, nylon, teflon, terleyne
Structure	Linear polymer	Poly-vinyl chloride (PVC)
	Branched chain polymer	Are the low density polythene
	Crossed linked polymer	Bakelite, melamine
Bio-stability	Biodegradable polymer	
	Polyester	Poly lactic acid, poly glycolic acid, poly hydroxyl butyrate, polyester, poly caprolactone, poly lactide-co-glycolide (PLGA) [1]
	Polyanhydride	Poly adipic acid, poly terpthalic acid, poly sebacic acid [1]
	Polyamide	Poly amino acid
	Others	Polycyanoacrylates, poly urethanes, poly ortho ester
	Non-biodegradable polymer	
	Cellulose derivative	Carboxy methyl cellulose, ethyl cellulose, cellulose acetate
	Silicon	Poly dimethyl siloxane, colloidal silica, polymethacrylate
	Others	Poly vinyl pyrrolidone, ethyl vinyl acetate, poloxamine [1]
Mechanism of polymerization	Addition polymer	Polystyrene, polyethylene, polypropylene, teflon, poly vinyl acetate, poly vinyl chloride
	Condensation polymer	Polysulfone, polyamides [11]
Ability to interact with water	Hydrophobic polymer	Poly vinyl chloride, ammonio-acrylates, ethyl cellulose [9]
	Hydrophilic polymer	HPMC, PEG
	Hydrogels	Polyvinyl pyrolidine
Thermal response	Thermoplastic polymer	Polyethylene, polystyrene, PVC
	Thermosetting polymer	Bakelite [6]
Stimulus responsive	pH	Dendrimers, poly(L-lysine) ester, poly (ethacrylic acid), Carbopol, Eudragit S-100, Eudragit L-100, chitosan
	Organic solvent	Eudragit S-100
	Temperature	Poloxamers, prolastin, PNIPAAM [6]

Polymers Used in Drug Delivery System Basics and Their Ideal Characteristics Functionality of Polymers

Functionalization of polymers has been shown in **Figure 4.** Various benefits through Functionalization has been shown below [9]

- Facilitate extended mechanism of action.
- Provide precise and site-specific drug targeting by numerous novel approaches such as micro particles and nanoparticles.
- Because of their degradability and non-toxic nature biodegradable polymers are used extensively.
- Facilitate excellent mechanical strength to the formulation.

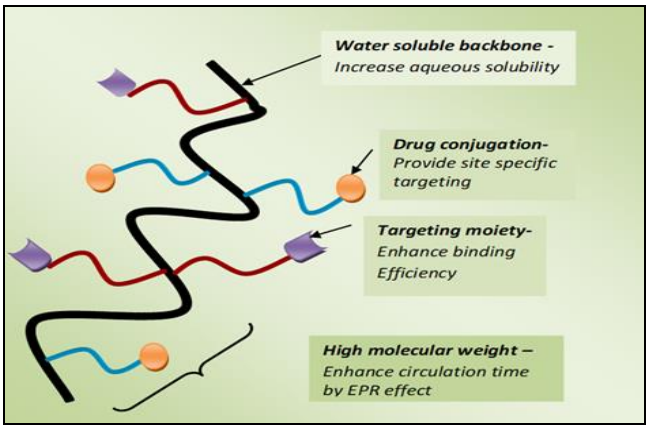


Figure 4: Depict Role of Polymer

Ideal Characteristics of Polymers

- ✓ The nature of polymer must be of nontoxic with less systemic toxicity.

- ✓ Administration of polymer ought to be uncomplicated.
- ✓ Must have superior mechanical in addition to physical strength.
- ✓ Be supposed to cost effective.
- ✓ Ought to be attuned with internal body physiology.

Various roles of polymers in drug delivery are:

1. **Immediate Release Dosage Forms**
2. **Modified Release Dosage Forms**
3. **Extended-Release Dosage Forms**
4. **Gastro Retentive Dosage Forms**

1. Immediate Release Dosage Forms

Tablet

Polymer play role as excipients in formulation of conventional immediate release dosage by protecting the active pharmaceutical ingredient from degradation thus help in formulating stable formulation. It also pretence the obnoxious taste of API and excipients, offer mechanical strength and impart better visual elegance of formulation [4]. It promotes numerous advantages in tablet formulation like diluents (Microcrystalline cellulose) and disintegrants (Starch and cellulose). Polymers including polyvinyl-pyrrolidone and hydroxypropyl methyl cellulose (HPMC) have excellent binding properties thus enhance the flow property and compaction behaviour of granules [10].

Capsule

Capsule is most preferable substitute of oral solid dosage form (tablet) having poor compressibility property. Several polymeric excipients are preferred to increase the bulk of capsule fill. Gelatin is one of the most widely applied shell material for hard (two-piece) and soft (one-piece) capsules. In current study researchers found, HPMC as efficient substitute material for hard gelatin capsule shell [11, 12].

2. Modified-Release Dosage Forms

Conventional dosage form faced numerous hurdles in their systemic absorption because of bioavailability and solubility issue. Thus, pharmaceutical scientists worked on design and development of novel modified release dosage forms [13]. They have property to bind with mucus lining of stomach, float on the surface and enhance the gastric residence time of drugs [14].

3. Extended-Release Dosage Form

Those drugs that have diminutive biological half-life be capable to fabricate as extended-release dosage form thus, prolong the drug retention time in systemic circulation, augment their therapeutic outcomes by reducing frequent dosing [15]. Water immiscible polymers such as ammonium ethacrylate copolymers (Eudragit RL and RS), cellulose derivative (ethyl cellulose, cellulose acetate) and polyvinyl derivatives (polyvinyl acetate) are usually preferred carrier for extended-release dosage form [16, 17].

4. Gastro Retentive Dosage Form

Gastro retentive formulation is substitute of extended-release dosage form, in this type of systems formulation are retained in stomach for prolong period of time by releasing the medicament in situ, that leisurely get absorbed through small intestine. Low density polymers are capable to prolong gastric residence time by joining with mucus lining of stomach [18, 19, 20].

Applicability of Polymer in Various Types of Drug Delivery Systems: Brief Overview

Variety of polymers is available for drug delivery and the same has been listed below

- ✓ Application of polymers in colon targeted drug delivery
- ✓ Application of polymers in mucoadhesive drug delivery system
- ✓ Applicability of polymers in tissue engineering
- ✓ Role of polymers to support floating drug delivery system
- ✓ Role of polymers in fabrication of micro and nanoformulation
- ✓ Applicability of polymers in implantable drug therapy

1. Application of Polymers in Colon Targeted Drug Delivery

Colon is a principal position for the systemic and local delivery of many drugs in several disorders related with large intestine like crohn's disease and colon cancer. Colon targeted drug delivery system serves many advantages due to its closer neutral pH and extended transit time. Polymer serves significant function to support colon targeted drug delivery by preventing the deprivation and release of medicament in stomach

and small intestine [21, 22, 23]. In addition, it makes sure that formulation facilitate controlled release of drugs in proximal colon. Natural polysaccharides such as guar gum, chondroitin sulphate, dextran, chitosan, inulin, amylose, pectin and locust bean gum are used as novel carrier in colon targeted drug delivery system. Pectin is an example of potent carrier used in tablet formulation using Diltiazemhydrochloride and Indomethacin has been developed as model drug for colon targeted delivery system [24, 25]. Formulation prepared by using biodegradable polymers moves as such from the upper gastrointestinal tract and facilitates the release of medicaments in colon. Colon is primary site for bacterial residence and these bacteria release many enzymes which promotes the hydrolytic cleavage of glycosidic bonds [26].

2. Application of Polymers in Mucoadhesive Drug Delivery System

Mucoadhesive polymers serve numerous advantages like, increase in the residence time; enhance penetration, site specific adhesion and enzymatic inhibition thus facilitates buccal drug delivery of some medicaments. Mucoadhesive polymers have potential to deliver drugs having higher molecular weight. Use of lectin and "lectinomimetics" emerges to be the most hopeful area of modern research for the effective delivery of drugs through buccal mucosa. Mucoadhesive polymers also bind to the mucus layer surface of other body parts like ocular, nasal, vaginal and pulmonary etc. [27, 28, 29] The various mucoadhesive polymers that are extensively applicable in drug delivery system are cyanoacrylates, hydroxy propyl cellulose, hyaluronic acid, sodium carboxy methylcellulose, chitosan, gellan and polyacrylic acid [30, 31].

3. Applicability of Polymers in Tissue Engineering

Naturally derived polymers like protein and polysaccharides have proved to be an effective carrier's system for the delivery of active biomolecules in tissue engineering field targeting. Some protein and polysaccharides-based polymers are shown in **Table 2**. Synthetic biodegradable polymer like poly (glycolic acid), poly (lactic acid) and their copolymers play enormous role in synthesis of absorbable sutures and in orthopedic fascination tools such as rods and screws. Now days, researchers pay much more attention towards synthetic polymers because it can be manufactured into various shape having preferred pore that is favourable for tissue growth. The polymer used in tissue engineering should have some characteristics properties such as biocompatibility, biodegradability, capable to facilitate cell growth and propagation and also uphold mechanical strength during tissue rejuvenation process [32, 33, 34].

Table 2: Polymer Used in Tissue Engineering

Protein based polymers	Polysaccharide based polymers
Collagen	Chitosan
Fibrin	Alginate
Gelatin	Starch
Others like soybean or elastin	Chondroitin sulphate

4. Role of Polymers to Support Floating Drug Delivery System

Floating drug delivery system has the property to float over the surface of gastric fluid because of its lower density and thus promote floating of medicaments for longer period of time without impinge on gastric emptying rate. Natural polymers are more preferred for floating drug delivery system due to its biodegradability and target specificity hence target specific region of gastrointestinal tract such as stomach. Along with natural polymers, synthetic polymers also fruitful in floating drug delivery system. Natural polymers include chitosan, pectin, xanthan gum, guar gum, gellan gum, karaya gum, psyllium husk, starch; alginates are most favoured polymers for floating drug delivery system [35]. Synthetic polymers such as Eudragit, hydroxypropyl methyl cellulose and ethyl cellulose are mainly used in floating drug delivery system. Natural polymer such as chitosan facilitates advantage in floating drug delivery system by forming film that decrease the GIT transit time and promote medicament to float on gastrointestinal fluid for up to 12 hrs [36, 38].

5. Role of Polymersi Fabrication of Micro and Nano-formulation

Micro and nano-formulation fabricated from biodegradable and bioerodible polymers are presently applied in drug delivery system due to their safety and controlled release properties. Polyesters and polysaccharides are most preferred biodegradable polymer for controlled drug delivery system. Polyesters are synthetic in nature having ester linkage and are utilized as fibers, films, in composites and elastomers. Polyesters that are intended to formulate biodegradable nanoparticles are polylactide (PLA), polyglycolides,

polycaprolactone (PCL) and poly (lactide-co-glycolide) (PLGA). PLGA has shown promising pharmacokinetic at whole body as well as cellular level [39, 40, 41].

The proposed methods for the preparation of polymeric micro and nano-formulation are top-down approaches, bottom-up approaches, nanoprecipitation method, solvent evaporation method, emulsification evaporation method, ionic gelation or coacervation method and solvent injection method [42, 43, 44]. The effectiveness of most of drugs is dependent upon the particle size, as lesser the particle size provides higher surface area that finally results in increase in solubility and bioavailability [45].

Moreover, its tiny size particles also have the tendency to cross blood brain barrier (BBB) and capability to get absorbed via constricted junction of endothelial cells of skin [46]. Most of the nano-formulation systems are hydrophobic in nature; this is considered as hurdle in nano-delivery system as hydrophobicity facilitates easy clearance of such formulation system from blood circulation via lymphatic system. To address such hurdle surface modification of system is performed by using hydrophilic excipients such as polymers, surfactants and copolymers which includes polyethylene glycol, poloxamers, poloxamines, polysorbate 80 and polyethylene oxides. Surface modification with these excipients also reduces the RES (reticuloendothelial system) uptake of drugs by preventing opsonin-NP binding (opsonisation) and thus, enhances their blood circulation time and provide prolong duration of action [47].

6. Applicability of Polymers in Implantable Drug Therapy

Implantable drug delivery system is vigorously preferred due to their controlled release, continuous drug administration and long-term use. Recently developed technology polymeric micro-needles are promising technique in implantable drug delivery due to their biocompatible nature. These devices are fabricated by numerous polymers such as polydimethylsiloxane (PDMS), polylactic and polyglycolic acid (PLGA), block copolymer hydrogels and polyimide [8].

Examples

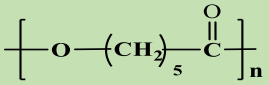
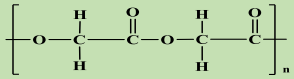
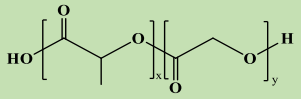
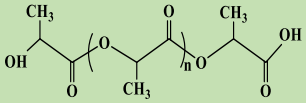
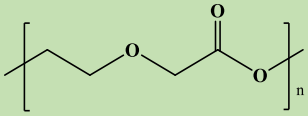
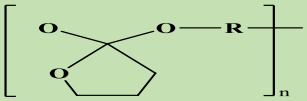
- Gliadel wafer-Implants used in the treatment of brain tumors
- Lupron Depot-Implants used in the treatment of prostate cancer
- Osurdex- Treatment of macular edema and retinal vein occlusion
- Implanon-Used for family planning

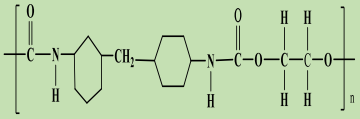
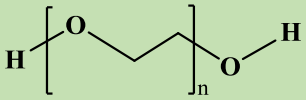
Functionalization of Widely Used Polymers

1. Synthetic Biodegradable Polymer

Biodegradable polymers are the polymer that degrade in the body and do not form any toxic metabolite. Presence of hydrolytic and proteolytic enzyme is necessary for the degradation of synthetic biodegradable polymer [48].

Table 3: Various Synthetic Biodegradable Polymer Used in Drug Delivery System

Polymers	Structure	Application in medicine
Poly(ε-caprolactone) (PCL)		Semi-crystalline in nature, used in preparation of suture, rejuvenate cartilage and bone.
Poly(glycolic acid) (PGA)		Crystalline, used in synthetic absorbable suture, have fiber forming property
Poly(lactic-co-glycolicacid) (PLGA)		Semi-crystalline, provide effective delivery of lipophillic anticancer drugs, proficiently used in transdermal patches.
Polylactic acid (PLA)		Thermoplastic in nature, used in suture, provide controlled release drug delivery.
Polydioxanone (PDS)		Semi-crystalline, excellent flexible property due to presence of ether oxygen in backbone of chain, lower toxicity
Poly(orthoesters)		This biodegradable polymer is mainly preffered for orthopadic application

Polyurethanes		Efficiently used in drug delivery because of its flexible nature.
Poly(ethylene glycol)[PEG]		PEG have wide application in pharmaceutical industry as well as in cosmetics, it is used as excipient, solvent, and as suppositories base.

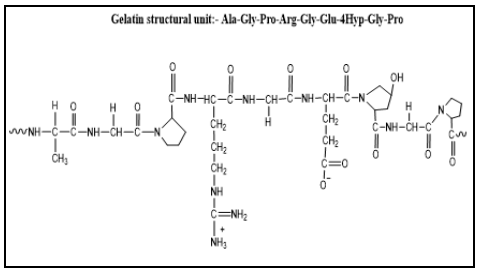
Surface properties of polymer such as hydrophilicity, lubricity and efficiency have an effect on their biocompatibility behavior, additionally it also impinge on their physical properties like permeability, strength and degradability. Some synthetic biodegradable polymers are poly (glycolic acid), poly (ε-caprolactone), poly (lactic-co-glycolic acid) poly lactic acid and polydioxane etc. [49] Some common synthetic biodegradable polymer used in controlled drug delivery system has been shown in **Table 3**.

2. Herbal Polymer

Polymers play an important role in delivery of various types of dosage forms such as solid, semi-solid and liquid. Now days, both synthetic and natural polymers were used most extensively in drug delivery to provide sustained release action, but in current scenarios natural polymers are widely applied in pharmaceuticals because of their biodegradability, biocompatibility, less immunogenicity, non-toxicity, easily available and low cost [50]. Most widely used natural polymers are gelatin and collagen; some other natural polymers are chitosan, starch, pectin, alginate and cellulose derivatives [51].

A) Gelatin

Gelatin is natural polymer biodegradable in nature, obtained from animal skin and dry and green bones. It is thermo reversible polymer, readily available, low immunogenicity, and low affinity to bind with drug molecule and has tendency to form gel (**Structure 1**). The extent of conversion of collagen into gelatin is depending upon the extraction time, temperature, pH, initial treatment and warm water extraction process [52].



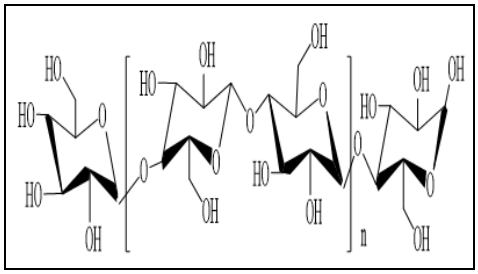
Structure 1: Gelatin

Commercially two type of gelatin are available i.e. procured by acidic and basic pre- treatment condition and these are type-A gelatin (isoelectric point pH is approx 8-9) and type-B gelatin (isoelectric point pH approx. 4-5) [52, 53, 54, 55].

B) Cellulose

Cellulose (**Structure 2**) occurs mainly in the cell wall of plants and used in pharmaceutical industry because of its several advantages [56, 57, 58]. Different derivatives of cellulose are used such as ethyl cellulose, carboxymethyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate phthalate, hydroxypropyl and hydroxyethyl cellulose etc.

- ✓ Ethyl cellulose: hydrophobic polymer used for coating purpose to provide sustained release action.
- ✓ Carboxymethyl cellulose: used as super disintegrants in tablet formulation and as stabilizer in emulsion.
- ✓ Hydroxypropyl methyl cellulose: used as binder in tablet as well as suitable alternative in place of gelatin in capsule shell formulation.
- ✓ Cellulose acetate phthalate: used as enteric coating material.

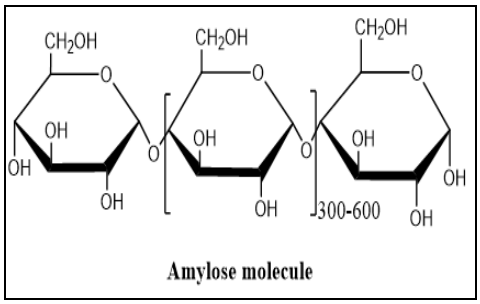


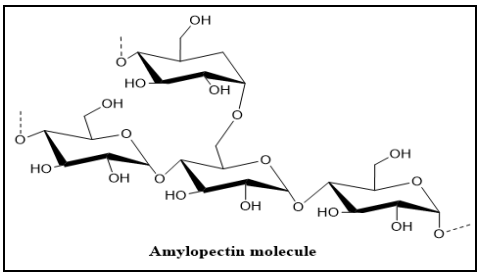
Structure 2: Cellulose

C) Starch

Starch (**Structure 3**) is polysaccharides, primarily present carbohydrate existing in green plants mainly in seeds and underground parts [59, 60, 61]. The principle constituents of starch are amylose and amylopectin. Starch is mainly used in pharmaceuticals due to its numerous properties like:0

- ✓ Used as glidant, diluents, disintegrants and binder in tablet and capsule formulation.
- ✓ Sodium starch glycolate is used as super disintegrants in tablet.

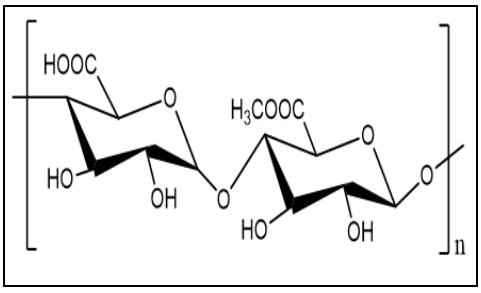




Structure 3: Starch

D) Pectin

Pectin is a multifaceted polysaccharide present in the wall of budding and dividing plant cell. Pectin is extensively used as film coating material in colon specific drug targeting. The composition of pectin vary in plants due to their geographical and botanical variation such as pectin from citrus plant has smaller molecular size than pectin obtained from apple plant [62, 63] (**Structure 4**).



Structure 4: Pectin

Drug Delivery Mechanism Through Various Polymers

There are mainly three basic mechanisms (degradation, diffusion, and swelling) through which release of drug from polymeric material takes place [64].

Degradation and Erosion

Degradation is the phenomena of cleavage of covalent bond by chemical reaction whereas erosion arises by the dissolution without chemical alteration. Biodegradable polymers undergoes degradation process, PLGA is one of the most commonly and effectively used biodegradable polymer, after hydrolysis it forms biologically acceptable two monomer unit lactic acid and glycolic acid and metabolizes in body through Krebs's cycle with lesser systemic side effect. The degradation of polymer is surface phenomena generally occur only at the surface (polyorthoesters and polyanhydride follow this degradation process) and it affects the release rate [65]. Hence, release rate of drugs is proportional to its surface area. (Shown in **Figure 5A**)

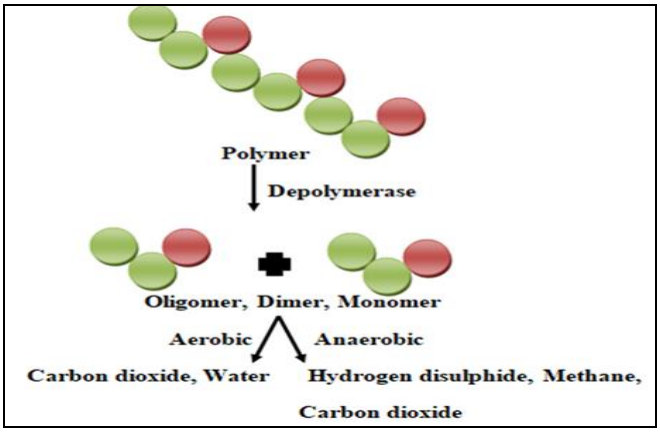


Figure 5A: Show the Degradation Mechanism of Polymer

Diffusion

Diffusion is the process in which the drug moves out from the polymer matrix into the outside environment [66]. The release through nonporous membrane follows diffusion as release mechanism. As release rate increases the rate of diffusion decreases. (Shown in **Figure 5B**)

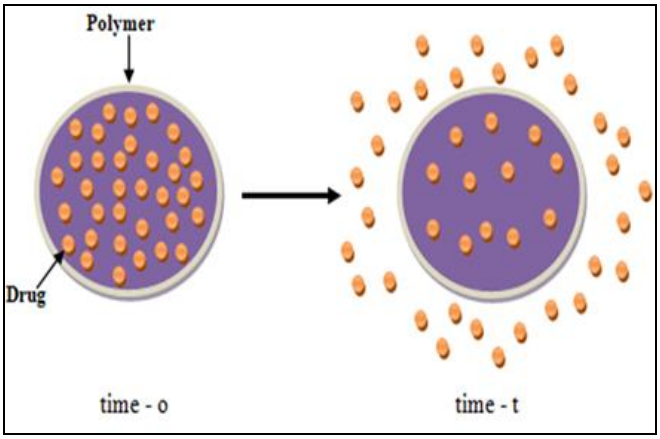


Figure 5B: Mechanism of Drug Release Through Diffusion

Swelling

Swelling is the ability to absorb aqueous fluid or water and get swell. When any drug

substance is placed inside body as such it is in dry form but after absorbing water or other hydrous body fluid it swells, swelling increases water content in drug product, polymer mesh size and release of drugs from formulation (Shown in **Figure 5C**).

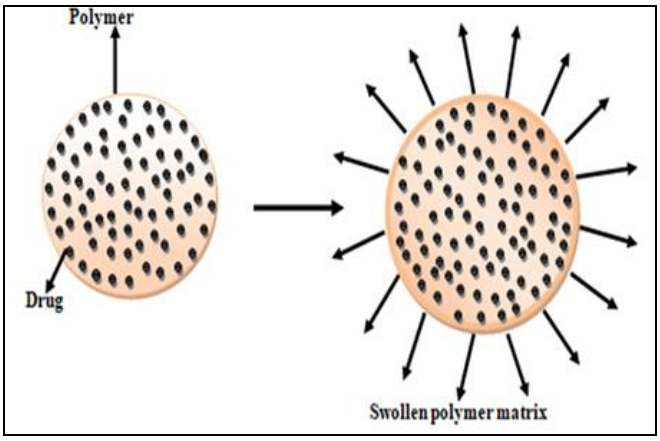


Figure 5C: Release of Drug from Swollen Matrix

Various Nanocarriers Development Using Smart Polymers

Smart polymers are the polymers which show change based on change in environmental circumstances. These are the stimuli responsive polymer and their properties are changes with change in environmental and biological situation. The numbers of different stimuli are pressure, pH, temperature, magnetic field, electric field, change in concentration and ionic strength etc. [67] The response due to change in such stimuli are conformational changes, precipitation and change in lipophillic and lipophobic properties of gastrointestinal tract affect the release profile of drugs, in case of cancer there is extreme changes in pH occur and it affects drug release profile. Poly (methacrylic acid) with PEG had used for the delivery of protein orally [24]. Temperature also affects the response of polymer change their lipophilicity and aqueous solubility hence thermo responsive polymers such as PNIPAAm are generally used. Stimuli responsive polymers are micelles, polyplexes and polymer drug conjugates.

By modification of surface with stimuli responsive polymer changes the physiochemical properties of polymer and makes it susceptible in response to change in environmental condition. Stimuli responsive polymers have the ability to go through lower critical solution temperature (LCST) phase alteration in hydrophilic solution. Smart polymers play a very vital role in development of different types of nanocarriers like nanogels, nanocapsules, micelles, liposomes, polymeric nanoparticles and niosomes etc.

Liposomes

Liposome is spherical bilayer vesicle composed of amphiphilic lipid mainly phospholipid that provide drug loading properties. The size of liposomal formulation is 0.025-10µm in diameter. Now days thermo sensitive polymers are used enormously due to its higher drug loading capacity, controlled drug release profile, greater inner side volume as well as tendency to influence permeability and the most important things is about its respond to peripheral stimuli with an on-off switch mechanism [69, 70, 71].

In recent era liposomal formulation are prepared by using poly (N-isopropylacrylamide) (PNIPAAm) a biocompatible polymer having thermo-responsive property. When liposomal formulation undergoes heating process, the phospholipid bilayer shows an endothermic conversion at a particular temperature (Tc) that is lesser than melting point. Below Tc the phospholipid layer behaves as gel state and above Tc it show liquid crystalline nature [72]. But due to the complex processing and greater manufacturing cost the synthetic liposome is little of use, whereas in case of natural liposome the main drawback is that it does not show defined transition temperature.

The PNIPAAm is a synthetic thermo-sensitive polymer having lower critical solution temperature (LCST) of 32 °C in aqueous medium. In water, it gets wet and swells below the LCST, whereas in non-aqueous or lipophillic environment it crumpled at temperatures higher than the LCST. This show that at lesser temperature than LCST, the intermolecular hydrogen bonding between PNIPAAm and water molecule occur due to which PNIPAAm chain accept hydrophilic coiled arrangements [73].

Polymeric Nanoparticles

Polymeric nanoparticles refer to the formulation of nanoparticles by incorporating drug into polymer using direct polymerization technique. Both natural polymers such as gelatin, chitosan and albumin and synthetic polymer such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), PLGA (poly lactic-glycolic acid) and PCL (poly (Ɛ-caprolactone)) are used extensively because of their biocompatible and biodegradable

nature. PEGylation of nanoparticles improve their surface property by imparting hydrophilicity to surface. These PEGylated nanoparticles does not undergo RES uptake by macrophages and phagocytes thus its blood circulation time improved and it retain in blood circulation for longer period of time and therefore prolongs the duration of action of drug. In some instances the active drug is directly placed over the surface of nano formulations to enhance the bioavailability of medicament [74, 75].

Nanogels

Nanogels prepared by using polymeric materials are three- dimensional hydrogels with nano size range, that are generally made by physical or chemical cross linking of polymers. Now days, nanogels formulation create much more curiosity in the field of controlled drug delivery system due to their structural property as well as in-situ stability. Calcium-cross linked dioctyl sodium sulfosuccinate (aerosol OT formulation, AOT)-alginate nanogels loaded by toluidine blue (TB) for the photodynamic therapy (PDT) of the biofilm-mediated infections of chronic wounds.

Various advantages of nanogels provide new concepts of research in drug delivery system as well as in diagnostic, biosensing and bioengineering [76]. Nanogels formulation is advantageous over polymeric nanomicelles the major problem with polymeric nanomicelles is that it shows stability only above CMC (critical micelle concentration) and below CMC it get separate into single polymer chain so, its drug holding capacity decreases but nanogels formulation does not possess this drawbacks hence, used widely in drug delivery system [77].

Polymeric Micelles

Polymeric micelles are nanosized range amphiphilic polymers and show colloidal dispersion in hydrophilic solvent. Inner side is lipophillic in nature and acts as drug pool and outer surface is made up of lipophobic or aqueous polymer having extended blood circulation time as well as higher aqueous solubility. The skeleton of polymeric micelle is similar to that of biological membrane of human physiology having miniature size, exclusive core shell arrangement and unreliable surface chemistry [78]. Various thermo responsive polymer used are poly (N-alkylacrylamide) s poly (NIPAM), poly (methyl vinyl ether) PMVE, poly (N- vinyl caprolactam) PVC, poly (N-ethyl oxazoline) PEtOx etc.

Hydrogels

Hydrogel is bio-polymeric three- dimensional systems having ability to soak up greater amount of water and get swell but as it is insoluble in aqueous medium. The cross- linking of polymeric chain in hydrogel arises by the help of covalent bonding, hydrogen bonding and Vander- walls interaction and this leads to the formation of three-dimensional structures. The purpose of formulating hydrogel by the use of biodegradable and pH responsive polymer is to control the drug delivery in retort to particular stimulus [66, 79, 80]. The principle behind hydrogel working is, hydrogel is a puffy ionic structure with either acidic or basic suspended groups that helps in development of charge on polymer matrix. (As shown in **Figure 6**) it explains the swelling and deswelling nature of hydrogel with respect to alteration in temperature and pH. Hydrogel have smooth and flexible surface i.e. similar to that of human tissue and this made hydrogel an efficient carrier for drug delivery system. Poly (lactic-glycolic acid) is used as smart polymer in hydrogel-based drug delivery system.

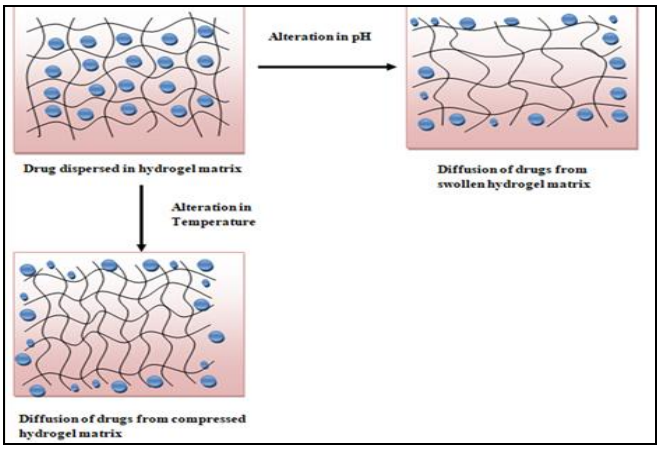


Figure 6: Sweeling and Deswelling Nature of Hydrogel with Respect to Alteration in Temperature and Pressure

Toxicity and Biodegradable Aspects of Polymers

Natural polymers have numerous drawbacks over synthetic polymers such as-

- Batch to batch deviation- synthetic polymer is manufactured in proscribed procedure with predetermined quantity of ingredients, while the natural polymers manufacturing is generally reliant on

environmental and seasonal factors hence, show batch variation.

- Microbial contamination- in case of natural polymer the chances of microbial contamination is more because natural polymers like gums and mucilage contain moisture content more than 10% and their structural backbone are carbohydrates hence during manufacturing it shows microbial growth but this problem is solved in case of synthetic polymers [31].

- Uncontrolled rate of hydration- natural polymers have variation in their chemical constituents because of deviation in their collection of natural material at a different time interval, as well as differences in their climatic condition and regional differences. Generally in case of gums and mucilage during storage their viscosity increases upon interaction with water during formulation due to their complex nature [52].

- Synthetic polymer solves the entire problems related to natural polymer hence, used efficiently in drug delivery.

Market Status of Various Polymers in Term of Commercial Aspects

Molecularly Imprinted Polymer (MIP)

Molecularly imprinting polymer is the polymer set-up that is created with specific identification for desired model molecule. Functional monomers are preferred that reveal chemical structure intended to interact with desired model molecule via covalent or non-covalent bonds. The monomer molecules are then polymerized and the template is later detached and molecularly imprinted polymer (MIP) with specific binding sites is formed [81].

This system was developed for separation application and recently developed for drug delivery systems. Molecularly imprinted polymer shows zero order drug release profile for prolong period of time and retain drug concentration in its therapeutic range that reduces the requirement of frequent dosing hence, have diverse advantages over conventional drug delivery system. The major application of MIPs is in ocular drug delivery system [24]. It solves the problem such as low bioavailability (~5%), frequent dosing and short-term distress and blurred vision related with conventional drug delivery system (As shown in **Figure 7**).

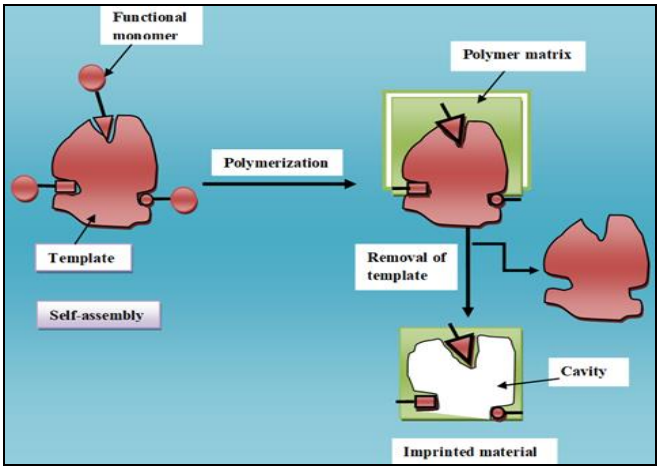


Figure 7: Depict Molecularly Imprinted Polymer

Future Promises and Challenges

The future perspective regarding polymeric drug delivery is basically depending upon biodegradable natural polymer because of its easy availability, lower cost and simply structural modification. Currently, the most exciting researches in polymeric drug delivery system is in the area of responsive delivery system in which it will be possible to deliver the drugs via implantable devices for the measurement of blood level and to deliver the drugs at a particular target site. This type of system includes:

- Water soluble/lipophillic copolymers.
- Block copolymer.
- Dendrimers (**Figure 8**)
- New biodegradable polymer such as, MIPs.

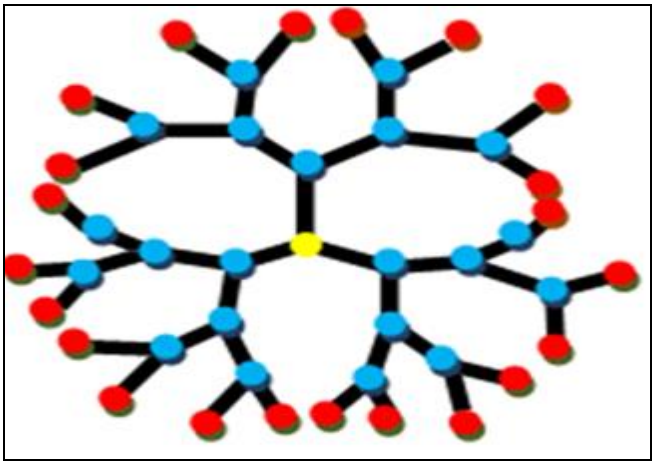


Figure 8: Show Dendrimer

Blends of hydrocolloids and carbohydrate-based polymers. Now day's polymers play vital role in the delivery of drugs in precarious ailments such as cancer. The main aim of controlling drug delivery is to attain more efficient drug release and reduce the possible side effects for both under and overdosing. Future perspective is also based on smart polymer.

CONCLUSION

Application of polymers holds distinctive potency in drug delivery systems which helps in the development of new drug delivery system that improves the way of treatment. Polymer based drug delivery boost drug delivery system by providing various advance research in drug delivery system such as nano and micro-particles, microsphere, dendrimers and micelles. Biodegradable polymers are biocompatible, non-toxic, eco-friendly and cost efficient in nature hence proven as advanced and competent drug delivery system. Current research is based on smart polymeric drug delivery system that supports controlled release of drugs.

Polymers used in targeted drug delivery system overcome the problem related with conventional dosage form as well as prolong the drug release and reduce toxicity by site specific targeting. At nano level the developments of medicine by using polymeric resources to tackle unsolved medical requirements is still required. Currently, several polymers have been efficiently applied and many more are investigated as excipients in development of new dosage form.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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