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Review Article

# APPLICATIONS OF BIODEGRADABLE NATURAL POLYMERS AS DRUG DELIVERY SYSTEMS: A REVIEW

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## ABSTRACT

In order to achieve controlled release of drug and their targeting sites, many approaches have been investigated. Synthetic and naturally occurring absorbable polymers in the form of matrix (monolith) devices, hydrogels, microspheres, nanoparticles, films, and sponges are finding increasing use in drug delivery systems. They hold the promise of providing better drug efficacy, reducing toxicity, and improving patient compliance. The desirable characteristics of polymer systems used for drug delivery, whether natural or synthetic are minimal effect on biological systems after introduction into the body; in vivo degradation at a well-defined rate to nontoxic and readily excreted degradation products; absence of toxic endogenous impurities or residual chemicals used in their preparation. Natural polymers remain attractive primarily because they are natural products of living organisms, readily available, relatively inexpensive, and capable of a multitude of chemical modifications. The present review suggests the naturally available polymers and their application in the controlled release of drugs.

**Keywords** Biodegradable, Natural Polymers, Drug delivery, Gelatin and Alginate

## INTRODUCTION

New technological advances have brought many innovative drug delivery systems to the market and others to the brink of commercialization. A variety of approaches have been investigated for the controlled release of drugs and their targeting to selective sites: polymeric prodrugs, drug conjugates, liposomes, monoclonal antibodies, and microcapsules[1-3]. Synthetic and naturally

occurring absorbable polymers in the form of matrix (monolith) devices, hydrogels, microspheres, nanoparticles, films, and sponges are finding increasing use in drug delivery systems[4]. They hold the promise of providing better drug efficacy, reducing toxicity, and improving patient compliance.

The use of natural biodegradable polymers to deliver drugs continues to be an area of active research despite the advent of synthetic biodegradable polymers[5-12]. The desirable characteristics of polymer systems used for drug delivery, whether natural or synthetic are minimal effect on biological systems after introduction into the body; in vivo degradation at a well-defined rate to nontoxic and readily excreted degradation products; absence of toxic endogenous impurities or residual chemicals used in their preparation. Natural polymers remain attractive primarily because they are natural products of living organisms, readily available, relatively inexpensive, and capable of a multitude of chemical modifications.

A majority of investigations of natural polymers as matrices in drug delivery systems have centered on proteins (e.g., collagen, gelatin, and albumin) and polysaccharides (e. g., starch, dextran, inulin, cellulose, and hyaluronic acid)[13]. Most protein-based delivery systems have been formulated as solid crosslinked microspheres in which the drug is dispersed throughout the polymer matrix, although one recent report describes the preparation of an enzyme-digestible disc made from an albumin-crosslinked hydrogel[14]. The formulation of proteins into microspheres has been dictated to a great extent by considerations related to their mechanical strength, dimensional and conformational stability in biological fluids and conditions under which processing is possible.

Collagen, because of its unique structural properties, has been fabricated into a wide variety of forms including crosslinked films, meshes, fibers, and sponges. Starch is usually derivatized by the introduction of acrylic groups, prior to polymerization and manufacture into microspheres. Poly (acryl) starch microspheres, as they are referred to, are an example of a semisynthetic polymer system.. In addition to starch, dextran, inulin, and cellulose have frequently been used as drug carriers by covalently bonding the drugs, antibiotics, and enzymes to reactive derivatives of available functional groups [15-22].

Hyaluronic acid is a linear polysaccharide found in the highest concentrations in soft connective tissues where it fills an important structural role in the organization of the extracellular matrix[23,24]. It has been used in ophthalmic preparations to enhance ocular absorption of

timolol, a beta blocker used for the treatment of glaucoma[25], and in a viscoelastic tear formulation for conjunctivitis [26].

The covalent binding of adriamycin and daunomycin to sodium hyaluronate to produce water-soluble conjugates was recently reported[27]. Partially deacetylated chitin, a cellulose-like biopolymer consisting predominantly of N-acetyl-D-glucosamine chains, in the form of films or crosslinked hydrogels has been used for the delivery of drugs [28,29]. The suitability of chitin as a vehicle for the sustained release of drugs was examined using indomethacin and papaverine hydrochloride as model drugs [30].

## CLASSIFICATION OF POLYMERS

Polymers are mostly classified as:

1. Based on degradability: Figure 1 shows the classification and examples of polymers based on degradability
2. Based on nature : Figure 2 shows the classification and examples of polymers based on nature
3. Based on source : Figure 3 shows the classification and examples of polymers based on source of the polymers
4. Based on polymerization : Figure 4 shows the classification and examples of polymers based on the polymerization type.

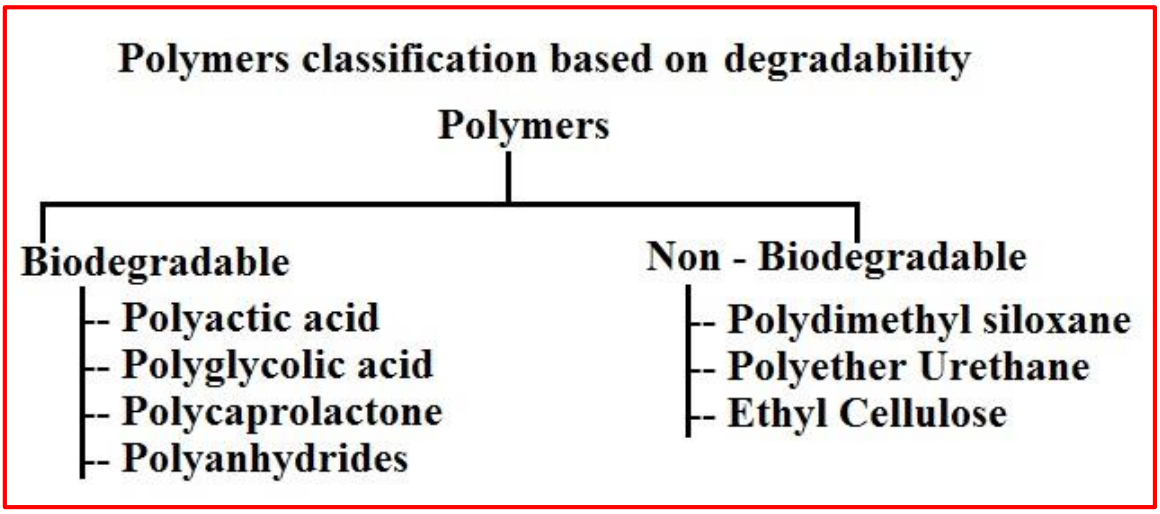


**Figure. 1 Polymeric classification based on degradability**

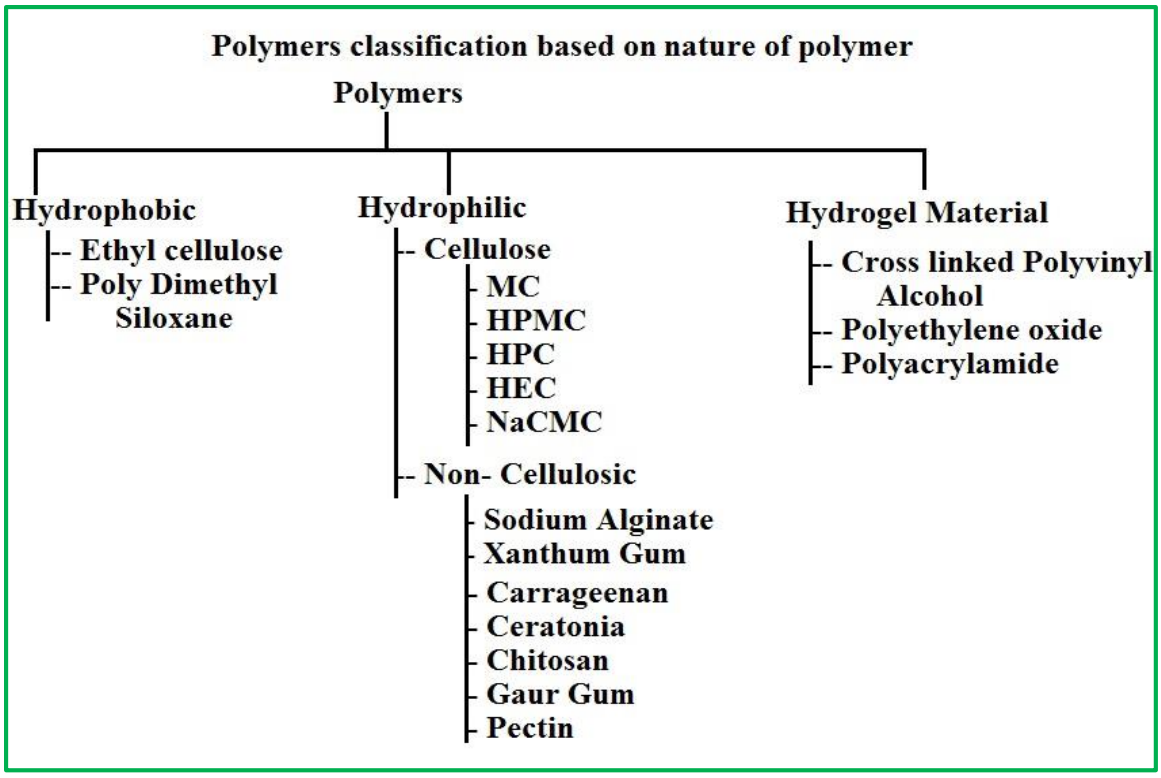


**Figure. 2 Classification of polymers based on nature of the polymer**

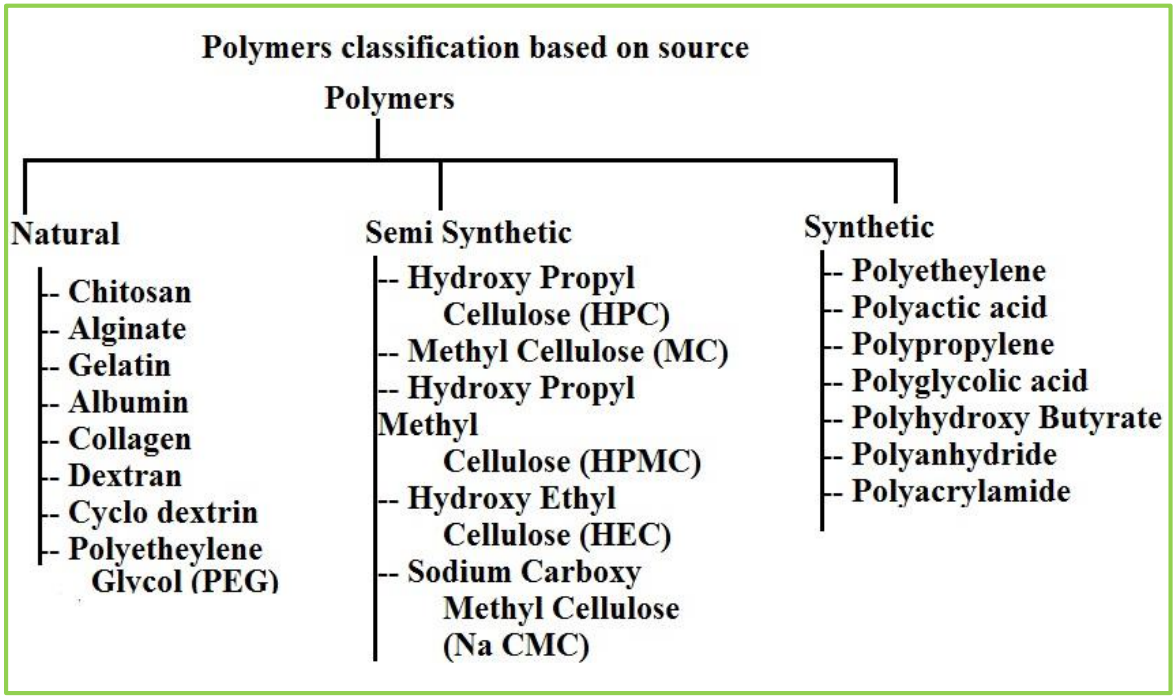


**Figure. 3 Classification of polymer based on the source of polymer**

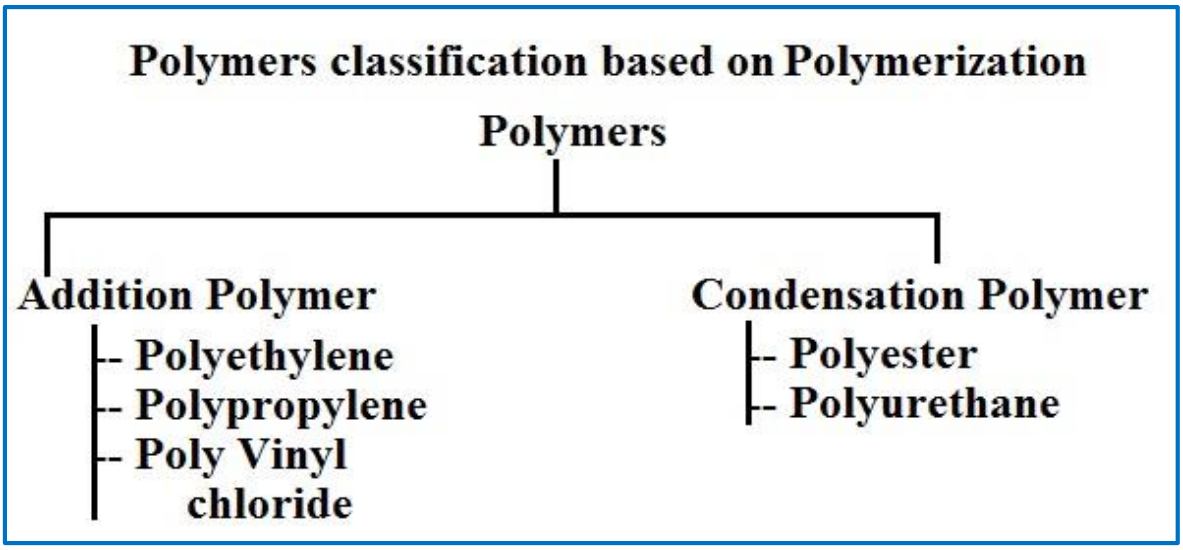


**Figure. 4 Classification of polymer based on polymerization**

**COLLAGEN**

Collagen is a major structural protein found in animal tissues. It is usually present as aligned fibers in tissues such as skin and tendons, and serves to limit tissue deformation and to prevent mechanical failure. Because of its unique structural properties, collagen has been used in a wide variety of biomedical applications as homeostatic fleece, absorbable sutures, sponge wound dressings, composite tissue tendon allografts, injectables for facial reconstructive surgery, and as drug delivery vehicles [31].

Its characteristics as a biomaterial offer several advantages:

- It is biocompatible and nontoxic in most tissues[32]
- It is readily isolated and purified in large quantities
- It has well-documented structural, physical, chemical, and immunological properties [33,34]
- It can be processed into a variety of forms.

However, certain properties of collagen have adversely influenced its use as a drug delivery vehicle like

- Poor dimensional stability due to swelling in vivo
- Poor in-vivo mechanical strength and low elasticity
- Occurrence of an antigenic response
- Tissue irritation due to residual aldehydes crosslinking agents

- Poor patient tolerance of ocular inserts
- Variability in drug release kinetics

**A. FILMS**

In 1973, Rubin et a1. first described the ocular delivery of pilocarpine from a collagen film [35]. Bloomfield et a1. demonstrated that the antibiotic gentamicin could be delivered from a soluble succinylated collagen ocular insert [36]. Slater et a1. used an insoluble collagen film crosslinked by glutaraldehyde to release gentamicin for the treatment of infectious bovine keratoconjunctivitis[37]. The effect of various chemical modifications on the mechanical properties of reconstituted collagen and the diffusion rates of the steroid medroxyprogesterone was investigated[38]. Formaldehydetreated films, which are heavily crosslinked, have high moduli and low rates of drug release. Films treated with chrome quickly become hydrated in solution and have low moduli and very rapid drug release characteristics.

In vitro studies[39] further elucidated the parameters controlling drug release from collagen films. In those studies, collagen gel prepared from beef hide was rendered soluble by succinylation followed by air-drying to produce a film. Films with different dissolution rates were produced by crosslinking with buffered formaldehyde of varying concentrations. Insoluble films were prepared by exposing samples to ammonia and glutaraldehyde.

Shell [40] contends that besides avoiding pulse delivery in case of ocular drug delivery; side effects, sustained release will improve patient compliance and allow for around-the-clock therapy, considered important for the treatment of glaucoma. Succinylated soluble collagen (SSC) and insoluble collagen (lC) films with procaine penicillin, erythromycin, or erythromycin estolate were prepared and their in vitro release rates measured[41]. Results showed that procaine penicillin was not released from IC, probably due to inactivation by the ammonia vapor or gluteraldehyde used during the film preparation. Differences in release of drugs from the two different collagen preparations were thought to be related to ionic repulsion and solubility factors.

**B. SPONGES**

Collagen sponges have been used to deliver steroid hormones[42], the anticancer drugs trans retinoic acid (TRA)[43,44], and 5-fluorouracil (5-FU)[45], and antibiotics[46]. The effects of progesterone and several other steroids delivered from a collagen matrix as a means for

preventing allograft skin rejection in mice and rats was reported[42]. Results showed that the half-life of both progesterone and estradiol preparations was about 7 days, and about 90% of all steroid present was absorbed in 15-30 days.

All-TRA, delivered via a collagen sponge fitted into a cervical cap, has been used in the treatment of intraepithelial cervical dysplasia, a precancerous lesion[44]. The release kinetics of tetracycline, incorporated into a collagen sponge device prepared from acid-swollen collagen paste and alkaline collagen paste showed that the Basic preparations released significantly higher amounts of the antibiotic than acidic preparations and All sponges effectively inhibited growth, indicating that antibacterial activity was not lost during the preparation

5-Fluorouracil (5-FU) and bleomycin have been shown to be effective in preventing fibroblast proliferation following ophthalmic surgery, Both drugs were incorporated into a crosslinked sponge made from purified bovine skin collagen[45]. Results showed that A chronic inflammatory reaction was elicited by the sponge, even in the absence of drug, but had no adverse effect on treatment outcome.

**C. PEPTIDE AND PROTEIN DELIVERY**

Water-soluble protein fractions, isolated from extracts of bone matrix, were incorporated into a collagen matrix and shown to induce bone[47,48] and cartilage formation both in vitro and in vivo [49,50].

**NON-COLLAGENOUS PROTEINS**

Noncollagenous proteins, particularly albumin and to a lesser extent gelatin, in the form of microspheres and nanoparticles continue to be exploited as drug delivery systems.

**A. Albumin Microspheres**

Albumin is a major plasma protein constituent, accounting for about 55% of the total protein in human plasma. albumin microspheres have been extensively investigated in controlled release systems and as vehicles for the delivery of therapeutic agents to local sites[51]. Albumin microspheres have been used extensively in diagnostic nuclear medicine for the evaluation of organ function and circulatory studies following administration by a variety of routes[52]. The exploitable features of albumin include its reported biodegradation into natural products [53-55], its lack of toxicity and nonantigenicity[56,57], and its ready availability. The delivery of drugs from albumin microspheres showed that exposure of microspheres to proteolytic enzymes such

as trypsin, papain, and protease resulted in significant weight loss and surface topographic changes[58,59,60]. Studies reported that human serum albumin (HSA) microspheres have been used to deliver more drug types, also the incorporation of drug into microspheres influences the routes available for microsphere manufacture; the appearance, size, and surface charge of the microspheres; and the extent of swelling in vivo[60-68]. the major application of albumin microspheres is in the area of chemotherapy, there have been studies reporting the release of such varied compounds as 1-norgestrel[69], insulin[70], and hematoporphyrins[71] from bovine serum albumin, and the antibacterial sulfadiazine from ovalbumin[72]. Corticosteroid drugs show a high incidence of adverse side effects. To minimize these effects, intraarterial therapy was investigated[73]. Rabbit serum albumin (RSA) microspheres containing corticosteroids injected into rabbit knee joints were evaluated for the treatment of rheumatoid arthritis[74,75]. The in vitro and in vivo release characteristics of microspheres, prepared using both chemical crosslinking and heat denaturation, were determined. With respect to prednisolone, high glutaraldehyde content resulted in rapid drug release, while low content exhibited slower release. Diffusion of drug through the swelled microsphere was considered to be the rate-controlling step.

**B. Magnetic albumin microsphere**

The technique entails the incorporation of ultrafine particles of magnetite, Fe304 into the microspheres, making them responsive to an externally applied magnetic field. The application of a magnetic field on the target site, such as a tumor, followed by the intraarterial injection of the magnetically responsive albumin microspheres (MRAMs) containing drug results in the microspheres concentrating in the target site and releasing the drug. This system of site specific delivery eliminates the adverse side effects associated with systemic drug delivery[76-82]. The in vivo kinetics of radiolabeled, magnetically targeted drug carriers including albumin microspheres revealed that the efficacy of magnetic targeting should be very low for drugs with long half-lives in the systemic circulation[83-85].

**C. Caesin Microspheres**

Casein microspheres containing adriamycin were produced by dispersing casein in heated phosphate buffer and then adding the drug which was in a 2% *w/v* solution with lactose as excipient.

**D. Gelatin Microspheres**

Gelatin is obtained by the partial hydrolysis of collagenous animal tissue, which converts the tough fibrous Gollagen into an unoriented water-soluble protein[86]. Gelatin offers the advantages of ready availability, relatively low antigenicity, and a good history in parenteral formulations. By comparison with albumin, gelatin offers several advantages in drug delivery systems: weaker binding to drugs, less potential for drug degradation because of low temperature preparation techniques, and lower antigenicity. Gelatin is generally used as a coating material to microencapsulate drugs and as a matrix, usually in the form of microspheres. The microspheres, used to deliver chemotherapeutic agents including mitomycin C, adriamycin, 5-fluorouracil, and bleomycin, have been manufactured using emulsification[87-92], desolvation[93-95] and reverse micellization [96]. Magnetically responsive gelatin microspheres, prepared using
methods adopted from albumin preparations[97], were evaluated as a delivery system for the antineoplastic drug aclarubicin[98].

**E. Fibrinogen Microspheres**

Fibrinogen, a soluble plasma protein of molecular weight 340,000, is commonly used as a coagulant. Microspheres were prepared from bovine blood fibrinogen by an emulsification technique followed by thermal denaturation at either 90 or 160°C for the delivery of anti-cancer agents[99-101].

## 5. Application of polymers in various novel drug delivery systems

Applications of different natural polymers obtained from different sources are shown in table 1 below.

**Table. 1 Application of polymers in various novel drug delivery systems**

| S No. | Name of polymer | Source | Application | Modification to the polymer in NDDS |
|---|---|---|---|---|
| 1. | Chitosan | Obtained from the N-deacetylation of chitin with strong alkali | Muco adhesive oral absorption enhancer and used in protein and gene delivery | - Inhalable powders<br>- Matrix tablet<br>- Transdermal films<br>- Microparticles<br>- Nanoparticles<br>- - microspheres for oral delivery of Insulin<br>- Mucoadhesive vaginal gels |
| 2. | Alginate | marine algae such as *Laminaria hyperborea*, *Ascophyllum* | Thickener, emulsion stabilizer | - Alginate combined with chitosan, thiolated alginate<br>- albumin nanoparticles,<br>- Alginate–poloxamer microparticles, |

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|---|---|---|---|---|
| | | *nodosum* and *Macrocystis pyrifera* | | - Hydrated thiolated alginate,<br>- alginate-poly (lactic-co-glycolic acid) nano/micro hydrogel matrices,<br>- chitosan-Ca-alginate microspheres,<br>- alginate modified by microenvironmental interaction with calcium ion, polyethylene glycol–anthracene<br>- modified alginate- photocrosslinked heparin<br>- alginate hydrogels,<br>- alginate guargum hydrogel,<br>- Micelles/sodiumalginate |
| 3. | Gelatin | derived from the collagen inside animals skin and bones | as coating agent, film-forming agent, gelling agent, suspending agent, tablet binder, viscosity-increasing agent | - matrix material in implantable delivery system.<br>– for microencapsulation of drugs<br>- PEGylatedgelatin nanoparticles - fluoride anion-modified gelatin nanogel system for ultrasound-triggered drug release,<br>- antibody modified gelatin nanoparticles as drug carrier system for uptake in lymphocytes,<br>- thiolmodified gelatin nanoparticles for intracellular DNA delivery<br>- DNA-loaded gelatin nanoparticles |
| 4. | Albumin | Human plasma | stabilizing agent in parentral formulation | - microspheres and microcapsules for controlled drug delivery system |
| 5. | Dextran | by fermentation of media containing sucrose by Leuconostoc mesenteroides. | | - hydrogel implants,<br>- microspheres for scaffolds<br>- For stabilized enzyme preparation |
| 6. | Cyclodextrin | derived from starch | solubilizing agent and stabilizing agen | - to mask the unpleasant taste of active materials<br>- convert a liquid substance into a solid material<br>- enhanced solubility and bioavalability in formulations |
| 7. | PEG | additional reaction of Ethylene Oxide with Monoethylene Glycols or Diethylene Glycol | Plasticizer | - plasticizer in aqueous film coating<br>- combination of Microcrystalline Cellulose and Polyethylene Glycol for maximum protection from the damage of Potassium Chloride microcapsules |
| 8. | Gelatin | collagen inside | gelling agent | - PEGylatedgelatin nanoparticles, |

| | | | | |
|---|---|---|---|---|
| | | animals skin and bones. | | - fluoride anion-modified gelatin nanogel system for ultrasound-triggered drug release<br>- antibody modified gelatin nanoparticles as drug carrier system for uptake in lymphocytes<br>- thiolmodified gelatin nanoparticles for intracellular DNA delivery<br>- hydrophobic hexanoyl anhydrides grafting to the amino groups of primitive gelatin<br>-,DNA-loaded gelatin nanoparticles<br>- modified gelatin microspheres impregnated collagen scaffold |
| 9. | Guar Gum | The guar seeds are dehusked,milled and screened to obtain the guar gum | | - carboxymethyl guar films for the formulation of transdermal delivery systems<br>- yttrium crosslinked guargum-g acrylamide gel systems<br>- Phosphated cross linked guar gum<br>- pulsatile release capsule of valsartan for chronotherapeutic drug delivery for early morning surge in boold pressure by using guar gumand sodiumalginate<br>- metronidazole by using various polysaccharides or by graft copolymerisation using methacrylic acid (MAA) with guar gum.<br>- hydrocortisone hydrogels by using guar gumCrosslinked with tri sodiumtrimetaphosphate |
| 10. | Pectin | extracted from cell walls of most plants | | - self-assembling pectin–liposome nanocomplexes<br>- novel pectin–4-aminothiophenole conjugate microparticles<br>- metronidazole-containing microparticles based on a pectin–4-aminothiophenol conjugate for colonspecific drug delivery.<br>- enteric-coated calcium pectinate microspheres (MS) for colon drug delivery, |
| 11. | Xanthum gum | fermentation of the bacterium *Xanthomonas campestris* | Thickening agent Emulsifying agent Suspending | - starch–xanthan gum hydrogel system<br>- xanthan gum with Konjac glucomannan to producematrix tablets of Cimetidine<br>- 5-FU Compressed coated |

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|---|---|---|---|---|
| | | | agent | tablets with a mixture of xanthum gum and boswellia gum<br>- sustained release floating tablets of diltiazem HCl using xanthan gum for the treatment of angina and hypertension |

## CONCLUSION

Natural polymers, particularly in the form of microspheres, have an important role in the controlled release of drugs and their targeting to selective sites. Yet there remain many issues to be addressed before they will have widespread use in clinical situations. Among these issues are better understanding of the kinetics of drug release; more effective ways to control burst phenomena; greater understanding of drug-polymer interactions and their effect on shelf life stability; additional animal studies to determine local tissue response, biodegradation rates, and metabolic fate; and, most importantly, as it relates to cancer chemotherapy, well-designed clinical studies to assess efficacy in relation to current therapies.

In the area of drug targeting, there needs to be continuing emphasis on understanding the interaction between polymeric particles and biological systems such as blood components, cell types (e.g., phagocytes), and cell receptors. For ocular drug delivery, much progress has been made in developing and commercializing novel drug delivery systems. Ocular delivery will gain greater acceptance as progress.

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