Review Article

POLYMERS IN PHARMACEUTICAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The current review article focuses on polymers in pharmaceutical drug delivery of therapeutic agents. These dosage forms include tablets, patches, tapes, films, semisolids and powders. Polymers are the backbone of a pharmaceutical drug delivery system as they control the release of the drug from the device. Biodegradable polymers attracts the attention of its use as they can be degraded to non-toxic monomers and most important, a constant rate of drug release can be achieved from a biodegradable polymer based controlled release device. Natural polymers can be used as the means of achieving predetermined rates of drug delivery and their physico-chemical characteristics with the ease of availability provide a platform to use it as a polymer for drug delivery systems. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. In the biomedical area, polymers are generally used as implants and are expected to perform long term service. These improvements contribute to make medical treatment more efficient and to minimize side effects and other types of inconveniences for patients. The main role of polymer is to protect drug from physiological environment and prolong release of drug to improve its stability. The drug is release from polymer by diffusion, degradation and swelling. In addition to this review presents characteristics and behaviours of plant derived and mucoadhesive polymers which are currently used in drug delivery.

Keywords: Polymers, excipients, synthetic polymer, natural polymer, sustained release, control release, mucoadhesion.

INTRODUCTION

Over the past decades research at the level of molecular biology has unveiled the molecular basis for many diseases. New important technologies and concepts such as recombinant DNA and gene therapy have provided tools for the creation of pharmaceuticals and methods designed to specifically address such diseases. However progress towards the application of these medicines outside of the laboratory has been considerably slow principally due to the lack of effective drug delivery systems that is mechanisms that allow the release of the drug into the appropriate body compartment for the appropriate amount of time without seriously disrupting the rest of the organism functionality. The application of the polymeric materials for medical purposes is growing fast. Polymers have found applications in diverse biomedical fields such as drug delivering systems, developing scaffolds in tissue engineering, implantation of medical devices and artificial organs, prosthesis, ophthalmology, dentistry, bone repair, and many other medical fields.[1] Polymers have been used as a main tool to control the drug release rate from the formulations. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which have not been attained by any other materials. Advances in polymer science have led to the development of several novel drug delivery systems. A proper consideration of surface and bulk properties can aid in the designing of polymers for various drug delivery applications.[2] These newer technological development include drug modification by chemical means carrier based drug delivery and drug entrapment in polymeric matrices or within pumps that are placed in desired compartments. These technical development in drug delivery/targeting approaches improve the efficacy of drug therapy thereby improve human health.[3] Polymer chemists and chemical engineers, pharmaceutical scientists are engaged in bringing out design predictable, controlled delivery of bio active agents.[4]

Extensive Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. In the biomedical area polymers are generally used as implants and are expected to perform long term service. These improvements contribute to make medical treatment more efficient and to minimize side effects and other types of inconveniences for patients.[5]

The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise/mask the unpleasant taste of a drug, to enhance 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. Monolithic delivery devices are systems in which a drug is dispersed within a polymer matrix and released by diffusion. The rate of the drug release from a matrix product depends on the initial drug concentration and relaxation of the polymer chains which overall displays a sustained release characteristic.[6, 7]

Simple manipulation of the water solubility of polymers, by increasing their chain length through cross-linking or by hydrophobising or hydrophilizing them with

copolymers and other groups yields a wealth of materials with a wide spectrum of possible application. The resulting materials are capable of a variety of drug-enhancing functions.[8]

Polymers are able to:

• Prolong drug availability if medicines are formulated as hydrogels[9] or microparticles.[10]

• Favourably alter bio distribution, if formulated into dense nanoparticles.

• Enable hydrophobic drug administration if formulated as micelles.

• Transport a drug to its usually inaccessible site of action if formulated as gene medicines.

• Make drugs available in response to stimuli.

HISTORY

The use of polymers in the medical field is not a novelty - natural polymers have been used as components of herbal remedies for centuries. When it comes to synthetic polymers however the situation is very different. Because polymer science is a relatively recent area of research synthetic water-soluble polymers as macromolecular drugs or as part of drug delivery systems related to inoculation can be considered a modern achievement. The first polymer-drug conjugates appeared around 1955, being mescaline-N-vinylpyrolidine conjugate one of the first.

About ten years later Frank Davis and Abraham Abuchowski were able to foresee the potential of conjugating poly(ethylene glycol) (PEG) to proteins causing the birth of a technique called PEGylation. PEGylation consists in the covalent bond of poly(ethylene glycol) polymer chains to another molecule usually a drug or a protein with therapeutic effects.

In 1994, the first synthetic polymer-drug conjugate (as shown in figure 1b) designed to treat cancer was clinically tested. It consisted on an HPMA (N-(2-hydroxypropyl) methacrylamide) copolymer conjugate of doxorubicin. Targeted release of anticancer agents can also be made using block copolymer micelles which have the ability to entrap the drug or to covalently link to it.

In the 2000s, two polymer-protein conjugates,(as shown in figure 1a) PEG-interferon-α (an antiviral drug intended to treat chronic hepatitis C and hepatitis B) and PEG-GCSF (PEG granulocyte colony-stimulating factor) were placed in the market and five years later the first therapeutic nanoparticles (albumin-entrapped paclitaxel) was approved as a treatment for metastatic breast cancer. All the above achievements and researches were the core element that led to the development of polymer based pharmaceuticals namely polymeric drugs, polymer-drug conjugates and polymer-protein conjugates. The clinical trials of these new technologies eventually lead to the resolution of many other unexpected challenges that quickly appeared, such as the manufacturing of the polymers at an industrial scale and the quick and total solubilization of the pharmaceuticals for safe inoculation. The optimization of these clinical tests (in terms of dosage and frequency) is still being evaluated today for a large variety of products.[11]

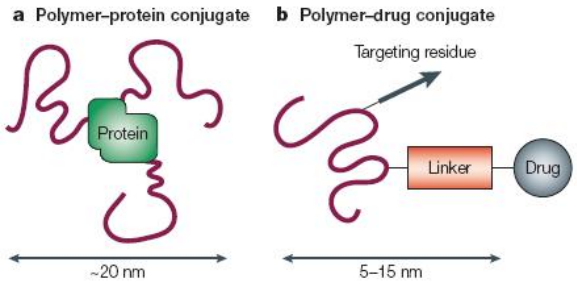

Figure 1: The families of polymer constructs called polymer therapeutics.

ROLE OF POLYMER IN PHARMACEUTICAL DRUG DELIVERY[8]

■ Immediate release dosage forms

• Tablets

Polymers have been used for many years as excipients in conventional immediate-release oral dosage forms, either to aid in the manufacturing process or to protect the drug from degradation upon storage. Microcrystalline cellulose is often used as an alternative to carbohydrates as diluents in tablet formulations of highly potent low-dose drugs. Starch and cellulose are used as disintegrants in tablet formulations, which swell on contact with water, resulting in the tablet "bursting," increasing the exposed surface area of the drug and improving the dissolution characteristics of a formulation. Polymers including polyvinyl-pyrrolidone and hydroxypropyl methylcellulose (HPMC) also find uses as binders that aid the formation of granules that improve the flow and compaction properties of tablet formulations prior to tableting. Occasionally, dosage forms must be coated with a "non-functional" polymeric film coating in order to protect a drug from degradation, mask the taste of an unpalatable drug or excipients, or improve the visual elegance of the formulation without affecting the drug release rate. [12]

• Capsules

Capsules are used as an alternative to tablets, for poorly compressible materials, to mask the bitter taste of certain drugs, or sometimes to increase bioavailability. Many of the polymeric excipients used to "bulk out" capsule fills are the same as those used in immediate-release tablets. Gelatine has been used almost exclusively as a shell material for hard (two-piece) and soft (one-piece) capsules. HPMC has recently been developed and accepted as an alternative material for the manufacture of hard (two-piece) capsules.

■ Modified-release dosage forms

It is now generally accepted that for many therapeutic agents drug delivery using immediate release dosage

forms results in suboptimal therapy and/or systemic side effects. Pharmaceutical scientists have attempted to overcome the limitations of conventional oral dosage forms by developing modified release dosage forms.

- **Extended release dosage forms**

The therapeutic effect of drugs that have a short biological half-life may be enhanced by formulating them as extended or sustained release dosage forms. Extended and sustained release dosage forms prolong the time that systemic drug levels are within the therapeutic range and thus reduce the number of doses the patient must take to maintain a therapeutic effect thereby increasing compliance**.** The most commonly used water-insoluble polymers for extended-release applications are the ammonium ethacrylate copolymers (Eudragit RS and RL), cellulose derivatives ethylcellulose, cellulose acetate, and polyvinyl derivative, polyvinyl acetate. Eudragit RS and RL differ in the proportion of quaternary ammonium groups, rendering Eudragit RS less permeable to water, whereas ethylcellulose is available in a number of different grades of different viscosity, with higher-viscosity grades forming stronger and more durable films.

- **Gastroretentive Dosage Forms**

Gastroretentive dosage forms offer an alternative strategy for achieving extended release profile, in which the formulation will remain in the stomach for prolonged periods, releasing the drug in situ, which will then dissolve in the liquid contents and slowly pass into the small intestine. Unlike a conventional extended release dosage form, which gradually releases the drug during transit along the gastrointestinal tract, such a delivery system would overcome the problems of drugs that are absorbed preferentially from specific sites within the gastrointestinal tract (for example, many drugs are absorbed poorly from the distal gut, where an extended-release dosage form may spend the majority of its time), producing nonuniform plasma time profile delivery systems do not relay on polymers present, to achieve gastroretention mucoadhesive[13-17] and low-density[18,19] polymers have been evaluated, with little success so far, for their ability to extend gastric residence time by bonding to the mucus lining of the stomach and floating on top of the gastric contents respectively.

TYPES OF POLYMER DRUG DELIVERY SYSTEM[8]

Polymers for Drug Delivery in Tissue Engineering

Several strategies have been developed in order to regenerate functional tissue, the majority of which involve the use of polymer scaffolds specifically designed to direct tissue growth. The cell transplantation method is one of the most commonly used in cartilage and bone formation.[20] Polymer matrices both natural and synthetic can play a vital role in the delivery of protein growth factors and cytokines to aid angiogenesis and tissue reconstruction procedures. These molecules are essential to tissue growth as they control a number of vital cellular processes including proliferation and differentiation. It has been shown that by careful selection of the polymer and the processing method, controlled-release matrices, incorporating proteins and growth factors that induce and enhance tissue growth can be produced. The future use of gene therapy as a way of regenerating tissue is an exciting area, and despite still being in its infancy, it may yet provide a solution to the challenge of delivering drugs and proteins more effectively in all areas of medicine.

Poly (lactic-co-glycolic acid) Microspheres

The term microsphere refers to a small sphere with a porous inner matrix and variable surface from smooth and porous to irregular and nonporous. The drug when encapsulated is dispersed throughout the inner matrix. The size range of microspheres is typically 1 to 500 µm in diameter. Poly (lactic-co-glycolic acid) microspheres have increasingly become the focus of research efforts in the scientific community and pharmaceutical industry. Their application as drug delivery vehicles has risen in line with the expanding biotechnology sector and the promise of new drugs discovered in the wake of the human genome project and proteomics.

Polymeric Nanoparticles as Drug Carriers

Certain chemical entities are either rapidly degraded and/or metabolized after administration (peptides, proteins, and nucleic acids). This is the reason the idea that nanotechnologies may be employed to modify or even to control the drug distribution at the tissue, cellular, or sub cellular levels has emerged. Among the technologies utilized for drug targeting are polymer-based nanoparticles, which have been developed since the early 1980s, when progress in polymer chemistry allowed the design of biodegradable and biocompatible materials. Nanoparticles may be defined as being submicron (<1 µm) colloidal systems generally composed of polymers. Thus, nanoparticles are colloidal systems with a size 7 to 70 times smaller than the red cells. They may be administered intravenously without any risk of embolization. Depending on the method used in the preparation of nanoparticles, either nanospheres or nanocapsules can be obtained. Nanospheres are matrix systems in which the drug is dispersed within the polymer throughout the particle. On the contrary, nanocapsules are vesicular systems, which are formed by a drug-containing liquid core (aqueous or lipophilic) surrounded by a single polymeric membrane.

Polymeric Micelles as Pharmaceutical Carriers

Polymeric micelles demonstrate many attractive properties as pharmaceutical carriers. They are stable both in vitro and *in vivo*, can be loaded with a wide variety of poorly soluble pharmaceutical agents, effectively accumulate in pathological body areas with compromised vasculature (infarcts, tumors), and can be targeted by attaching various specific ligands to their surface. Both therapeutic and diagnostic micelles can be

easily produced in substantial quantities. It appears that micellar carriers have a promising future.

Polymeric Vesicles

Polymeric vesicles may be fabricated from a variety of macromolecular amphiphile architectures, which include: block copolymers, random graft copolymers, and polymers bearing hydrophobic low-molecular-weight pendant or terminal groups. These tough particles, which reside in the nanometre and micrometer size domains, may be used for drug targeting, the preparation of responsive release systems, and other drug delivery applications.

Polymer Drug Conjugates

Current research in the field of polymer anticancer drug conjugates is directed towards the identification of the mechanism of action of free and polymer-bound drugs at the cellular and subcellular levels. Newer applications for polymer–drug conjugates are also being explored[21]. Inflammatory diseases are characterized by an increase in the vascular permeability (similar to tumors). Though there may be lesser amounts of retention as the lymphatics are not blocked, there may be a therapeutic advantage offered by the conjugation of drugs to polymer backbones. These represent new and exciting avenues of research for polymeric drug delivery scientists.

Polymers Used for the Delivery of Genes in Gene Therapy

A number of polymers by virtue of possessing a cationic charge at physiological pH have been found to be suitable candidates for the transfer of genes across the various biological barriers outlined in the preceding text. An ideal gene delivery system has to be able to shuttle the gene safely to the nuclei of its target tissue with the travelling gene having limited encounters with degradative influences.

POLYMERS IN PHARMACEUTICAL APPLICATIONS[22-24]

Water-Soluble Synthetic Polymers

- Poly (acrylic acid) Cosmetic, pharmaceuticals, immobilization of cationic drugs, base for Carbopol polymers.
- Poly (ethylene oxide) Coagulant, flocculent, very high molecular-weight up to a few millions, swelling agent.
- Poly (ethylene glycol) *M*w <10,000; liquid (*M*w <1000) and wax (*M*w >1000), plasticizer, base for suppositories.
- Poly (vinyl pyrrolidone) Used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation.
- Poly (vinyl alcohol) Water-soluble packaging, tablet binder, tablet coating.

Cellulose-Based Polymers

- Ethyl cellulose Insoluble but dispersible in water, aqueous coating system for sustained release applications.
- Carboxymethyl cellulose Super disintegrant, emulsion stabilizer.
- Hydroxyethyl and hydroxypropyl celluloses Soluble in water and in alcohol for tablet coating.
- Hydroxypropyl methyl cellulose Binder for tablet matrix and tablet coating, gelatin alternative as capsule material.
- Cellulose acetate phthalate enteric coating.

Hydrocolloids

- Alginic acid Oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions; binder and disintegrants.
- Carrageenan Modified release, viscosifier.
- Chitosan Cosmetics and controlled drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms.

Water-Insoluble Biodegradable Polymers

- (Lactide-co-glycolide) polymers Microparticle–nanoparticle for protein delivery.

Starch-Based Polymers

- Starch Glidant, a diluent in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder.
- Sodium starch glycolate super disintegrant for tablets and capsules in oral delivery.

Plastics and Rubbers

- Polyurethane Transdermal patch backing, blood pump, artificial heart, and vascular grafts, foam in biomedical and industrial products.
- Polyisobutylene Pressure sensitive adhesives for transdermal delivery.
- Polycyanoacrylate Biodegradable tissue adhesives in surgery, a drug carrier in nano- and microparticles.
- Poly (vinyl acetate) Binder for chewing gum.
- Poly (vinyl chloride) Blood bag, and tubing.
- Polyethylene Transdermal patch backing for drug in adhesive design, wrap, packaging, containers.
- Poly (methyl methacrylate) Hard contact lenses.
- Poly (hydroxyethyl methacrylate) Soft contact lenses.

CLASSIFICATION POLYMERS

Basis on interaction with water

- Non-biodegradable hydrophobic Polymers:- E.g. Polyvinyl chloride,
- Soluble Polymers:- E.g. HPMC, PEG
- Hydro gels:- E.g. Polyvinyl pyrrolidine

Based on polymerisation method

- Addition Polymers:- E.g. Alkane Polymers
- Condensation polymers:- E.g. Polysterene and Polyamide

Based on polymerization mechanism

- Chain Polymerization
- Step growth Polymerization

Based on chemical structure

- Activated C-C Polymer
- Inorganic polymers
- Natural polymers

Based on occurrence

- Natural polymers:- E.g. 1. Proteins-collagen, keratin, albumin, cellulose
- Synthetic polymers:- E.g. Polyesters, polyamides

Based on bio-stability

- Bio-degradable
- Non Bio-degradable

Characteristics of an ideal polymer

- It should be versatile and possess a wide range of mechanical, physical, chemical properties.
- It should be non-toxic and have good mechanical strength and should be easily administered.
- It should be inexpensive and easy to fabricate.
- It should be inert to host tissue and compatible with environment.

Criteria followed in polymer selection

- The polymer should be soluble and easy to synthesis.
- It should have finite molecular weight.
- It should be compatible with biological environment.
- It should be biodegradable.
- It should provide good drug polymer linkage.

General mechanism of drug release from polymer

There are three primary mechanisms by which active agents can be released from a delivery system namely

Diffusion

Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues its rate normally decreases with this type of system since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.[25]

Degradation

Biodegradable polymer degrades within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds.[26] For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system

Swelling

They are initially dry and when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. [27]

POLYMERS IN PHARMACEUTICAL DRUG DELIVERY SYSTEM

Rosin

Rosin a film-forming biopolymer and its derivatives have been extensively evaluated pharmaceutically as film-coating and microencapsulating materials to achieve sustained drug release. They are also used in cosmetics, chewing gums, and dental varnishes. Rosin has been used to prepared spherical microcapsules by a method based on phase separation by solvent evaporation. Rosin combination with polyvinyl pyrrolidone and dibutyl phthalate (30 % w/w) produces smooth film with improved elongation and tensile strength.[28-30]

Chitin and Chitosan

Chitin a naturally abundant muco polysaccharide and consist of 2-acetamido-2- deoxy-b-D-glucose. Chitin can be degraded by chitinase. Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-

D glucosamine (acetylated unit). The most important property of chitosan with regards to drug delivery is its positive charge under acidic conditions. This positive charge comes from protonation of its free amino groups. Lack of a positive charge means chitosan is insoluble in neutral and basic environments.[27]

Zein

Zein an alcohol-soluble protein contained in the endosperm tissue of *Zeamais,* occurs as a by-product of corn processing. Zein has been employed as an edible coating for foods and pharmaceuticals for decades. Zein is an inexpensive and most effective substitute for the fast-disintegrating synthetic and semi synthetic film coatings currently used for the formulation of substrates that allow extrusion coating.[31]

Collagen

Collagen is the most widely found protein in mammals and is the major provider of strength to tissue. It not only has been explored for use in various types of surgery, cosmetics and drug delivery, but in bioprosthetic implants and tissue engineering of multiple organs.

Starches

It is the principal form of carbohydrate reserve in green plants and especially present in seeds and underground organs. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species, as is also the ratio of the content of the principal constituents, amylose and amylopectin. A number of starches are recognized for pharmaceutical use. These include maize (Zea mays), rice (Oryza sativa), wheat (Triticum aestivum), and potato (olanum tuberosum). To deliver proteins or peptidic drugs orally, microcapsules containing a protein and a proteinase inhibitor were prepared. Starch/bovine serum albumin mixed-walled microcapsules were prepared using interfacial cross-linking with terephthaloyl chloride. The microcapsules were loaded with native or amino-protected aprotinin by incorporating protease inhibitors in the aqueous phase during the cross-linking process. The protective effect of microcapsules with aprotinin for bovine serum albumin was revealed in vitro.

Polycaprolactone

Polycaprolactone (PCL) is biodegradable polyester with a low melting point of around 60°C and a glass transition temperature of about −60°C. PCL is prepared by ring opening polymerization of ε-caprolactone using a catalyst such as stannous octanoate. The most common use of polycaprolactone is in the manufacture of speciality polyurethanes. Polycaprolactones impart good water, oil, solvent and chlorine resistance to the polyurethane produced.

Polyorthoesters

These materials have gone through several generations of synthetic improvements to yield materials that can be polymerized at room temperature without production of condensation by-products. These materials are hydrophobic with hydrolytic linkages that are acid-sensitive, but stable to base. They degrade by surface erosion and degradation rates may be controlled by incorporation of acidic or basic excipients.

POLYMERIC PLANT-DERIVED EXCIPIENTS IN DRUG DELIVERY SYSTEM[32]

Polymers have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose but the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, capable of chemical modifications, potentially biodegradable and with few exceptions also biocompatible.

Cellulose

The polysaccharides of the plant cell wall consist mainly of cellulose, hemicelluloses and pectin used in pharmaceutical applications such as filler in tablets, it is microcrystalline cellulose that represents a novel and more useful cellulose powder.[33] Microcrystalline cellulose is mainly used in the pharmaceutical industry as a diluent/binder in tablets for both the granulation and direct compression processes.[32] Microcrystalline cellulose is partially depolymerised cellulose prepared by treating high quality cellulose with hydrochloric acid to produce free flowing non-fibrous particles. It was further found that the hydroxypropylmethylcellulose matrix systems have a stronger gel structure than those made of Molecules polyethylene oxide, which may provide superior in vivo performance in terms of matrix resistance to the destructive forces within the gastrointestinal tract.[34]

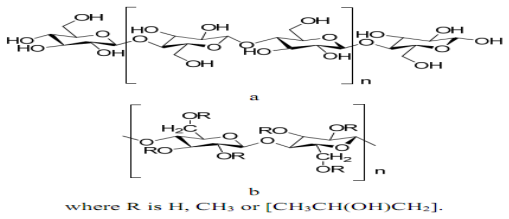

Figure 2: Chemical structure of a) powdered cellulose (n ≈ 500) or microcrystalline Cellulose (n ≈ 220) and b) hydroxyl propyl methyl cellulose.

Pectin

Pectin is a family of complex polysaccharides present in the walls that surround growing and dividing plant cells It is also present in the junctional zone between cells within secondary cell walls including xylem and fiber cells in woody tissue.[35, 36] Pectin has been investigated as excipients in many different types of dosage forms such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, microparticulate delivery systems for ophthalmic preparations and matrix

type transdermal patches. The composition of pectin can vary based on the botanical source, for example pectin from citrus contains less neutral sugars and has a smaller molecular size compared to pectin obtained from apples.[37-39]

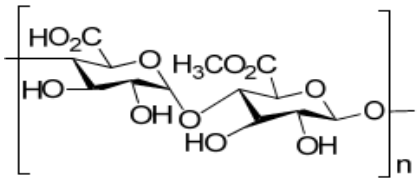

Figure 3: Chemical structure of pectin.

Inulin

Inulin is resistant to digestion in the upper gastrointestinal tract, but is degraded by colonic microflora. Inulin with a high degree of polymerisation was used to prepare biodegradable colon-specific films in combination with Eudragit® RS that could withstand break down by the gastric and intestinal fluids. It was shown in another study where different Eudragits® were formulated into films with inulin that when a combination of Eudragit® RS and Eudragit® RL was mixed with inulin it exhibited better swelling and permeation properties in colonic medium rather than other gastrointestinal media.[40, 41]

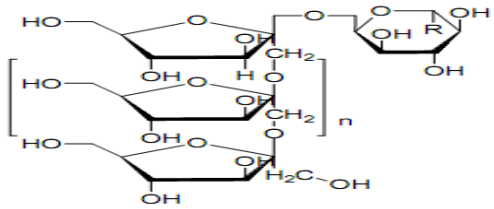

Figure 4: Chemical structure of inulin.

Alginates

Alginates have been used and investigated as stabilizers in emulsions, suspending agents, tablet binders and tablet disintegrants.[42] The gelling properties of alginate's guluronic residues with polyvalent ions such as calcium or aluminium allow cross-linking with subsequent formation of gels that can be employed to prepare matrices, films, beads, pellets, microparticles and nanoparticles.[43, 44]

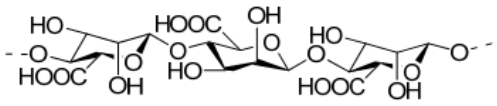

Figure 5: Chemical structure of alginates.

Carrageenans

Carrageenans is the generic name for a family of high molecular weight sulphated polysaccharides obtained from certain species of red seaweeds belonging to the class Rhodophyceae, especially Chondrus crispus, Euchema spp, Gigartina stellata and Iridaea spp. Carrageenan extracted from seaweed is not assimilated by the human body and provides only bulk but no nutrition. There are three basic types of carrageenan: kappa (κ), iota (ι) and lambda (λ). The λ-type carrageenan results in viscous solutions but is non-gelling, while the κ-type carrageenan forms a brittle gel. The ι-type carrageenan produces elastic gels.[45]

Hydrogel beads were prepared from a mixture of cross-linked κ-carrageenan with potassium and cross-linked alginate with calcium and they exhibited a smoother surface morphology than that of the one-polysaccharide network beads. The carrageenan parts of the hydrogel pronouncedly enhanced the thermostability of the polymeric network. These beads were introduced as novel carriers for controlled drug delivery systems.[46]

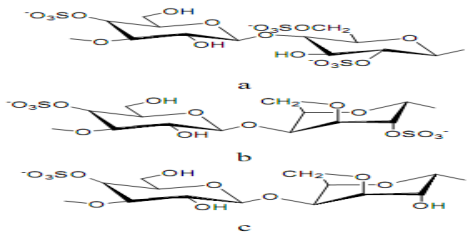

Figure 6: Chemical structure of a) λ-carrageenan, b) ι-carrageenan and c) κ-carrageenan.

Guar gum

Guar gum has recently been highlighted as an inexpensive and flexible carrier for oral extended release drug delivery.[47] Guar gum is particularly useful for colon delivery because it can be degraded by specific enzymes in this region of the gastrointestinal tract. It is also used as thickener for lotions and creams, as a tablet binder and as an emulsion stabilizer.[48]

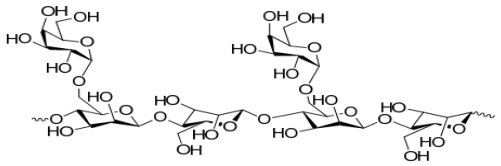

Figure 7: Chemical structure of guar gum.

NOVEL MUCOADHESIVE POLYMERS[49]

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time.[50]

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effective in terms of therapeutic action and patent protection. The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug. The use of acrylate polymers for the development of mucoadhesive formulations have increased many-fold, various authors have investigated

the mucoadhesive properties of different polymers with varying molecular architecture.[51]

The use of a mucoadhesive polymer that attach to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal etc. This system of drug delivery is called as mucoadhesive drug delivery system. The various mucoadhesive polymers used for the development of buccal delivery systems include cyanoacrylates, polyacrylic acid, sodium carboxymethylcellulose, hyaluronic acid, hydroxypropylcellulose, polycarbophil, chitosan and gellan.[52, 53]

Lectins

Lectins are proteins which have the ability to reversibly bind with specific sugar / carbohydrate residues and are found in both animal and plant kingdom in addition to various microorganisms.[54-56] Lectins extracted from legumes have been widely explored for targeted delivery systems. The various lectins which have shown specific binding to the mucosa include lectins extracted from Ulex europaeus I, soybean, peanut and Lens culinarius.[57] The use of wheat germ agglutinin has been on the rise due to its least immunogenic reactions, amongst available lectins, in addition to its capability to bind to the intestinal and alveolar epithelium and hence could be used to design oral and aerosol delivery systems.[58]

Thiolated polymers

These are the special class of multifunctional polymers called thiomers which are modified existing polymers by the addition of thiol group. These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Thiomers are capable of forming intra- and interchain disulphide bonds within the polymeric network leading to strongly improved cohesive properties and stability of drug delivery systems such as matrix tablets. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhesive properties of all so far tested polymeric excipients via thioldisulphide exchange reaction and an oxidation process. Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly(acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.[59]

Poloxomer

Poloxomer gels have been investigated as they are reported to show phase transitions from liquids to mucoadhesive gels at body temperature and will therefore allow in-situ gelation at the site of interest.

MECHANISMS OF MUCOADHESION[60]

The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. The mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (shown in figure 8)

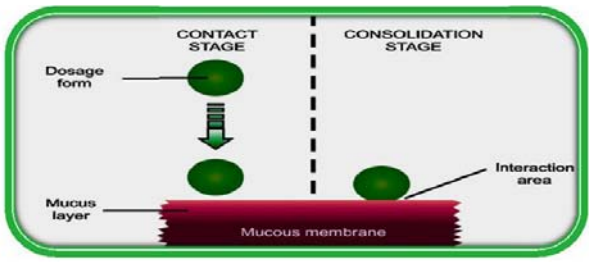

Figure 8: The two steps of the mucoadhesion process

FUTURE TRENDS

Despite the excessive use of synthetic polymers the need for natural biodegradable polymers to deliver drugs continues to be area of active research. Natural polymer has numerous advantages over synthetic ones as being readily available relatively inexpensive, natural products of living organisms, possibilities of chemical modifications. The most exciting opportunities in polymer drug delivery lie in the arena of responsive delivery systems, with which it will be possible to deliver in response to a measured blood level or to deliver a drug precisely to a targeted site. Much of the development of novel materials in controlled drug delivery is focusing on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features.

Such systems include:

- Copolymers with desirable hydrophilic/hydrophobic interactions.
- Complexation networks responding via hydrogen or ionic bonding.
- Polymers as nanoparticles for immobilization of enzymes, drugs, peptides, or other biological agents.
- New biodegradable polymers.
- New blends of hydrocolloids and carbohydrate-based polymers.

Design and synthesis of novel combinations of polymers will expand the scope of new drug delivery systems in the future. This will obviously require assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials. There is an increasing movement of scientists and engineers who are dedicated to minimizing the environmental impact of polymer composite production. Life cycle assessment is of paramount importance at every stage of a product's life, from initial synthesis through to final disposal and a sustainable society needs environmentally safe materials and processing methods.[61, 62]

CONCLUSION

Polymer-based pharmaceuticals are starting to be seen as key elements to treat many lethal diseases that affect a great number of individuals such as cancer or hepatitis. Although excipients have traditionally been included in formulations as inert substances to mainly make up volume and assist in the manufacturing process, they are increasingly included in dosage forms to fulfil specialized functions for improved drug delivery because many new drugs have unfavourable physicochemical and pharmacokinetic properties. The synthetic polymers can be designed or modified as per requirement of the formulation by altering polymer characteristics and on the other hand natural pharmaceutical excipients are biocompatible, non toxic, environment friendly and economical. Several polymers have been successfully used and others are being investigated as excipients in the design of dosage forms for effective drug delivery.

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