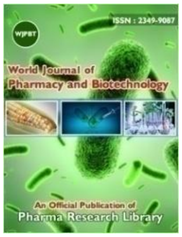

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A Review on polymers used in controlled drug delivery system

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A b s t r a c t

Polymers have played an integral role in the advancement of drug delivery technology by providing controlled release of therapeutic agents in constant doses over long periods, cyclic dosage, and tunable release of both hydrophilic and hydrophobic drugs. From early beginnings using off-the-shelf materials, the field has grown tremendously, driven in part by the innovations of chemical engineers. Modern advances in drug delivery are now predicated upon the rational design of polymers tailored for specific cargo and engineered to exert distinct biological functions. In this review, we highlight the fundamental drug delivery systems and their mathematical foundations and discuss the physiological barriers to drug delivery. Hierarchical progress in modern drug delivery begins with the use of polymer carriers to elicit spatiotemporal release of therapeutics in both pulsatile dose delivery products and implanted reservoir systems. Although conventional drug delivery formulations have contributed greatly to the treatment of disease, the emergence of potent and specific biological therapeutics has escalated the impetus for intelligent delivery systems. Tremendous progress has been made as a result of the exploration of diffusion-controlled and solvent-activated formulations in drug delivery. Hydrogels and other polymer-based carriers have been developed to provide safe passage for pharmaceuticals through inhospitable physiological regions. Polymers of controlled molecular architecture can be engineered to give a well-defined response to external conditions as a result of a solid understanding of the underlying mechanisms and the nature of behavioral transitions. Polymers incorporated with therapeutics can be bioactive to provide their own therapeutic benefit or can be biodegradable to improve release kinetics and prevent carrier accumulation. Pharmaceutical agents have been conjugated to polymers to modify transport or circulation half-life characteristics as well as to allow for passive and active targeting.

Keywords: Polymers, controlled molecular, biological therapeutics, Pharmaceutical agents, conventional drug delivery.

A r t i c l e I n f o

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C o n t e n t s

1. Introduction

Controlled drug delivery system:

Controlled releases are drug delivery system which maintains constant level of drug in blood and tissue for extended period of time. It implies a predictability and reproducibility in drug release kinetics. In other words, the rate and duration are designed to achieve a desired concentration. Examples include Plendil ER (Felodipine), Agon SR (Felodipine), Kapanol (Morphine sulphate) and Slow-K (Potassium chloride). TIMERx is a CR product based on agglomerated hydrophilic matrix consisting of xanthum gum and locust bean gum1-5.

Different types of controlled drug delivery systems:

- Oral (through the mouth)
- Topical (skin)

- Trans- mucosal (nasal, bucal, sublingual, vaginal, ocular, rectal)
- Parenteral (injection into systemic circulation)
- Inhalation routes.

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner.

Polymers:

The word polymer is derived from two Greek words poly means many mer means unit. In basic terms, a polymer is a long-chain molecule that is composed of a large number of repeating units of identical structure. These identical structures, we understand as a unit made up of two or more molecules, join together to form a long chain. Polymers are becoming increasingly important in the field of drug delivery. 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 the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. The review focuses on the significance of pharmaceutical polymer for controlled drug delivery application. Sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of the medicines they need to fight a variety of human ailments, including cancer. Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing. Polymers are playing important role in pharmaceuticals. They are used as binders in tablet, increases solubility of poorly soluble drugs, used as film coatings on drugs to disguise their taste and enhances their stability.

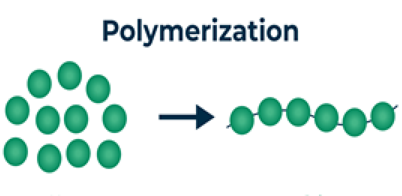

Fig.1

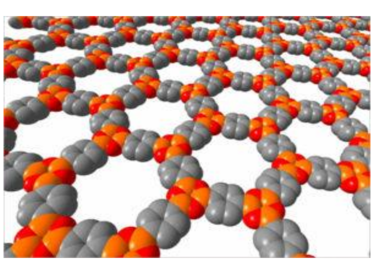

Fig.2

History of polymers:

A polymer is a large molecule, or macromolecule, composed of many repeated subunits. Because of their broad range of properties, (Painter et al 1997) both synthetic and natural polymers play an essential and ubiquitous role in everyday life. Polymers range from familiar synthetic plastics such as polystyrene to natural biopolymers such as DNA and proteins that are fundamental to biological structure and function. Polymers, both natural and synthetic, are created via polymerization of many small molecules, known as monomers. Their consequently large molecular mass relative to small molecule compounds produces unique physical properties, including toughness, visco elasticity, and a tendency to form glasses and semi crystalline structures rather than crystals.

The term was coined in 1833 by Jöns Jacob Berzelius, though with a definition distinct from the modern IUPAC distinction. The modern concept of polymers as covalently bonded macromolecular structures was proposed in 1920 by Hermann Staudinger, who spent the next decade finding experimental evidence for this hypothesis. Historically, products arising from the linkage of repeating units by covalent chemical bonds have been the primary focus of polymer science; emerging important areas of the science now focus on non-covalent links. Poly isoprene of latex rubber and the polystyrene of Styrofoam are examples of polymeric natural/biological and synthetic polymers respectively. In biological contexts, essentially all biological macromolecules i.e., proteins (polyamides), nucleic acids (poly nucleotides), and polysaccharides are purely polymeric, or are composed in large part of polymeric components e.g., iso prenylated lipid modified glycol proteins, where small lipid molecule and oligosaccharide modifications occur on the polyamide backbone of the protein respectively. In biological contexts, essentially all biological macromolecules i.e., proteins (polyamides), nucleic acids (poly nucleotides), and polysaccharides are purely polymeric, or are composed in large part of polymeric components e.g., iso prenylated lipid modified glycol proteins, where small lipid molecule and oligosaccharide modifications occur on the polyamide backbone of the protein[6-10].

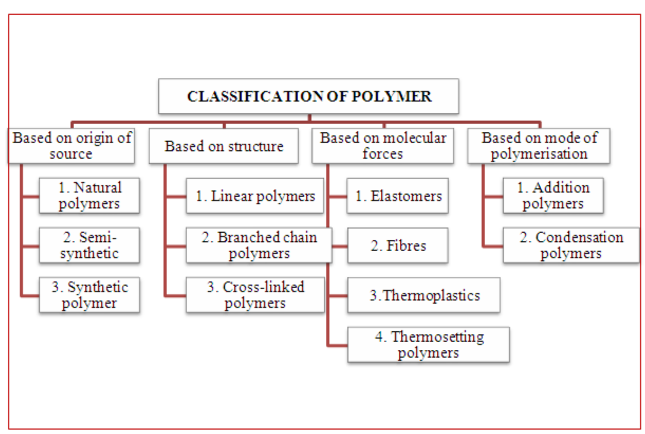

Fig.3

2. Classification

The first classification of polymers is based on their source of origin, Let's take a look.

Natural polymers:

The easiest way to classify polymers is their source of origin. Natural polymers are polymers which occur in nature and are existing in natural sources like plants and animals. Some common examples are Proteins (which are found in humans and animals alike), Cellulose and Starch (which are found in plants) or Rubber (which we harvest from the latex of a tropical.

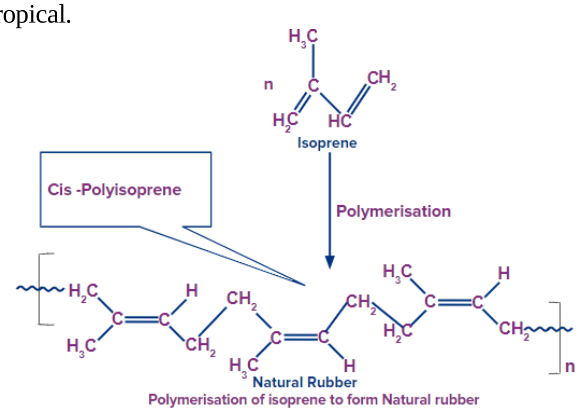

Fig.4

Synthetic polymers:

Synthetic polymers are polymers which humans can artificially create/synthesize in a lab. These are commercially produced by industries for human necessities. Some commonly produced polymers which we use day to day are Polyethylene (a mass-produced plastic which we use in packaging) or Nylon Fibers (commonly used in our clothes, fishing nets etc.)For example-Polyethylene, Polypropylene, Buna-S, and Nylon-6,6.

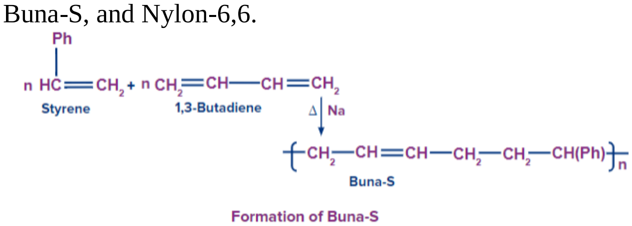

Fig.5

Semi-synthetic polymers:

Semi-Synthetic polymers are polymers obtained by making modification in natural polymers artificially in a lab. These polymers formed by chemical reaction (in a controlled environment) and are of commercial importance. Example: Vulcanized Rubber (Sulphar is used in cross bonding the polymer chains found in natural rubber) Cellulose acetate (rayon).

Classification based on structure of polymers:

Classification of polymers based on their structure can be of three types:

Linear polymers: These polymers are similar in structure to a long straight chain which identical links connected to each other. The monomers in these are linked together to form a long chain. These polymers have high melting points and are of higher density. A common example of this is PVC (Poly-vinyl chloride). This polymer is largely used for making electric cables and pipes.

Branch chain polymers:

As the title describes, the structure of these polymers is like branches originating at random points from a single linear chain. Monomers join to form a long straight chain with some branched chains of different lengths. As a result of these branches, the polymers are not closely packed together. They are of low density having low melting points. Low-density polyethene (LDPE) used in plastic bags and general-purpose containers is a common example.

Cross linked (or) network polymers:

In this type of polymers, monomers are linked together to form a three-dimensional network. The monomers contain strong covalent bonds as they are composed of bi-functional and tri-functional in nature. These polymers are brittle and hard. Ex:- Bakelite (used in electrical insulators), Melamine etc.

Classification based on polymerization: Polymerization is the process by which monomer molecules are reacted together in a chemical reaction to form a polymer chain (or three-dimensional networks). Based on the type of polymerization, polymers can be classified as11-13;

Addition polymers:

These type of polymers are formed by the repeated addition of monomer molecules. The polymer is formed by polymerization of monomers with double or triple bonds (unsaturated compounds). Note, in this process, there is no elimination of small molecules like water or alcohol etc (no by-product of the process). Addition polymers always have their empirical formulas same as their monomers. Example: ethene n(CH2=CH2) to polyethene -(CH2-CH2)n-.

Example: Polyethylene Polystyrene

Condensation polymers:

These polymers are formed by the combination of monomers, with the elimination of small molecules like water, alcohol etc. The monomers in these types of condensation reactions are bi-functional or tri-functional in nature. A common example is the polymerization of Hexamethylenediamine and adipic acid. to give Nylon – 66, where molecules of water are eliminated in the process.

Example: cellulose, starch

Classification based on molecular forces:

Intramolecular forces are the forces that hold atoms together within a molecule. In Polymers, strong covalent bonds join atoms to each other in individual polymer molecules. Intermolecular forces (between the molecules) attract polymer molecules towards each other. Note that the properties exhibited by solid materials like polymers depend largely on the strength of the forces between these molecules. Using this, Polymers can be classified into 4 types:

Elastomers:

Elastomers are rubber-like solid polymers that are elastic in nature. When we say elastic, we basically mean that the polymer can be easily stretched by applying a little force. The most common example of this can be seen in rubber bands (or hair bands). Applying a little stress elongates the band. The polymer chains are held by the weakest intermolecular forces, hence allowing the polymer to be stretched. But as you notice removing that stress also results in the rubber band taking up its original form. This happens as we introduce crosslinks between the polymer chains which help it in retracting to its original position, and taking its original form. Our car tyres are made of Vulcanized rubber. This is when we introduce sulphur to cross bond the polymer chains14-19.

Thermplastic polymers:

Thermoplastic polymers are long-chain polymers in which inter-molecules forces (Van der Waal's forces) hold the polymer chains together. These polymers when heated are softened (thick fluid like) and hardened when they are allowed to cool down, forming a hard mass. They do not contain any cross bond and can easily be shaped by heating and using moulds. A common example is Polystyrene or PVC (which is used in making pipes).

Thermosetting polymers:

Thermosetting plastics are polymers which are semi-fluid in nature with low molecular masses. When heated, they start cross-linking between polymer chains, hence becoming hard and infusible. They form a three-dimensional structure on the application of heat. This reaction is irreversible in nature. The most common example of a thermosetting polymer is that of Bakelite, which is used in making electrical insulation.

FIBRES:

The classification of polymers, these are a class of polymers which are a thread like in nature, and can easily be woven. They have strong inter-molecules forces between the chains giving them less elasticity and high tensile strength. The intermolecular forces may be hydrogen bonds or dipole-dipole interaction. Fibres have sharp and high melting points. A common example is that of Nylon-66, which is used in carpets and apparels.

Advantages of polymers in controlled drug delivery system:

Polymers used in colloidal drug carrier systems, consisting of small particles, show great advantage in drug delivery systems because of optimized drug loading and releasing property

- A polymer (natural or synthetic) is aggregated with a drug in controlled drug delivery and hence it gives a effective and controlled dose of dug avoiding overdose
- The degradable polymers are ruptured into biologically suitable molecules that are assimilated and discarded from the body through normal route.
- Reservoir based polymers is advantageous in various ways like it increase the solubility of incompetently soluble drugs and it lowers the antagonistic side effects of drugs
- Magneto-optical polymer coated and targeted nanoparticles are multimodal (optical and MRI detection) while Quantum Dots are only optically detectable.
- In controlled release, some of the polymers like polyurethanes for elasticity, poly siloxane for insulating ability are used for their intended non-biological physical properties.
- Current polymers like Poly 2-hydroxy ethyl methacrylate, polyvinyl alcohol, Polyethylene glycol are used because of their inert characteristics and also they are free of leachable impurities
- Biggest benefit of utilizing polymers in drug delivery is their control (manipulation) on their properties (e.g. linkers and molecular weight) to modify to the need of drug delivery systems.
- Polymers are more resistant to chemicals than their metal counterparts.
- Polymer parts do not require post-treatment finishing efforts, unlike metal.
- Polymer and composite materials are up to ten times lighter than typical metals.
- Polymer materials handle far better than metals in chemically harsh environments. This increases the lifespan of the aircraft and avoids costly repairs brought about by corroding metal components.
- Polymers are naturally radar absorbent as well as thermally and electrically insulating.
- In medical Facilities polymer and composite materials are easier to clean and sterilize than metal.

Disadvantages of polymers in controlled drug delivery system:

- Cannot withstand very high temperature as all plastics melt down very soon as compared to metals.
- The strength to size ratio of polymer is less while for metals is more.
- Cannot be machined easily and limited speed for machining for it.
- Heat capacity of polymer is very less so cannot be used in heat applications.
- Heavy structure cannot be made by polymer as the structural rigidity is very less.
- The disposal becomes an issue as some polymer cannot be recycled but all metals can be recycled.
- It is not an easy task to remove the organic solvents totally as mostly they are toxic and there should be a regulation on the concentration of residual solvents in the microsphere.
- A crucial limitation in the development of biodegradable polymer microspheres for controlled-release drug delivery applications is the difficulty of specifically designing systems that exhibit precisely controlled release rates.
- Core-shell microparticles are significantly more difficult to manufacture than solid microspheres
- Handling and fabricating the microspehre's architecture is not easy as its shell and core must be immiscible.

3. Types of polymers in CDDS

The most commonly use of polymers in drug delivery system are:

- Poly lactic
- Poly carpolactone
- Poly anhydrides
- Polyorthoesters
- Cellulose

- Starches
- Collagen
- Pectin

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. Microcrystalline cellulose is mainly used in the pharmaceutical industry as a diluent/binder in tablets for both the granulation and direct compression processes. 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 hydroxyl propyl methylcellulose 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.

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 (Oryzasativa), wheat (Triticumaestivum), and potato (olanumtuberosum). 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.

Polyorthoester:

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

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 apples20-21.

Polylactic acid:

Polylactic acid, also known as PLA, is a thermoplastic monomer derived from renewable, organic sources such as corn starch or sugar cane. Using biomass resources makes PLA production different from most plastics, which are produced using fossil fuels through the distillation and polymerization of petroleum

Polyanhydrides:

Currently are used mainly in the medical device and pharmaceutical industry.2 the generalized structure of an anhydride polymer and two polyanhydrides that are used to encapsulate certain drugs. The poly (biscarboxyphenoxypropane) (pCCP) is relatively slow to degrade. The poly (sebacic anhydride) (pSA) is fast to degrade. Separately neither of these materials can be used, but if a copolymer is made in which 20% of the structure is pCCP and 80% is pSA, the overall properties meet the needs of the drug. Polyanhydrides are now being offered for general use.

Role of Polymer in Pharmaceutical Drug Delivery

Immediate release dosage forms are:

1) 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.

2) 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.

3) Modified-release dosage forms

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

4) 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.

5) Gastro retentive Dosage Forms

Gastro retentive 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-density18,19 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.

Applications of Polymers in Formulation of Controlled Drug Delivery System:

- Osmotic Pressure-Controlled GI Delivery System
- Gel Diffusion Controlled GI Delivery System
- Mucoadhesive GI Delivery System
- Transdermal Drug Delivery System
- Ocular Drug Delivery System
- Other Applications

Osmotic Pressure-Controlled GI Delivery System

A semi-permeable membrane is made from biocompatible polymers. E.g. cellulose acetate

Examples of such type of system include Acutrim tablet which contains Phenylpropanolamine as a drug22-27. In this device, an osmotic agent is contained within a rigid housing and is separated from an active agent compartment-b, a movable partition. One wall of the rigid housing is a semipermeable membrane so that when the pump is exposed to an aqueous environment, water will be driven osmotically across the membrane, the increased volume within the osmotic compartment will force the active agent out of the device through the delivery orifice. A major application is for gastro-intestinal drug deliveries because the delivery rate is pH-independent.

Gel Diffusion Controlled GI Delivery System

Diffusion and Dissolution-Controlled Release System:

- The drug is encased in a partially soluble membrane.
- Pores are created due to the dissolution of parts of the membrane.
- It permits entry of aqueous medium into core and drug dissolution.
- Diffusion of dissolved out of the system.
- Example: Ethylcellulose and PVP mixture dissolves in water and creates pores of insoluble ethylcellulose membrane.

3) Mucoadhesive GI Delivery System:

The new generation mucoadhesive polymers for buccal drug delivery with advantages such as; increase in the residence time of the polymer, penetration enhancement, site-specific adhesion, and enzymatic inhibition, site-specific mucoadhesive polymers will undoubtedly be utilized for the buccal delivery of a wide variety of therapeutic compounds. The class of polymers has enormous potential for the delivery of therapeutic macromolecules.

4) Transdermal Drug Delivery System:

TDDS is defined as, self-contained, self-discrete dosage forms, which when applied to the intact skin, deliver the drug at a controlled rate to the systemic circulation. In this, polymer matrix plays a major role. It releases the drug from the device to the skin. Advantages of Transdermal.

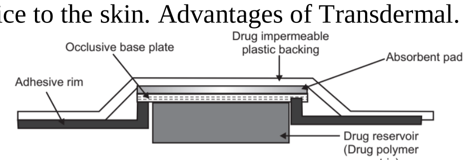

Fig.6

Drug Delivery System:

They permit easy removal and termination of drug action in situations of toxicity. Problems encountered with oral administration like; degradation, gastric irritation, etc. are avoided.

Ocular Drug Delivery System: It allows prolonged contact of the drug with the corneal surface of the eye. An example of ODDS is pilocarpine in the treatment of glaucoma. In this, mucoadhesive polymers are used as barriers to control the drug release. E.g. Polyacrylic acid, Copolymers of acetate vinyl, and ethyl.

6) Other Applications

Drug Delivery and the Treatment of Diabetes: Here the polymer will act as a barrier between the bloodstream and insulin. E.g. Polyacrylamide or N, N-Dimethyl amino ethylmetha acrylate.

Drug Delivery of Various Contraceptives and Hormones

It consists of a drug saturated liquid medium encapsulated in a polymeric layer which controls the concentration and release of drugs into the bloodstream. E.g. Medoxy progesterone acetate, Progestasert, Duromine, etc.

Drug Delivery of Various Contraceptive and Hormones

Recent Advances of Polymers in CDDS:

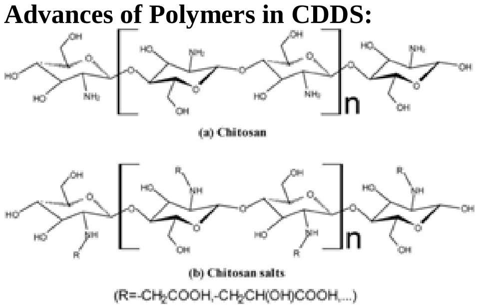

Fig.7

Polymeric drug delivery system has defined as a formulation or a device that enables the introduction of a therapeutic substance into the body. It improves its safety and efficacy by controlling the rate, time, and place of release of drugs in the body. Drug delivery has achieved great development in the last two decades, but it remains a difficult task to regulate drug entry into the body such as brain. However, recent progress in studies of the carrier-mediated transportation of nano-drug delivery system across the blood-brain barrier is beginning to provide a rational basis for controlling drug distribution to the brain. The transport systems at the blood-brain barrier are the uptake transporters for natural nutrients such as amino acid, peptide, hexose, mono-carboxylate and stem cells. The present paper has been reviewed for the polymeric drug and gene delivery systems of natural and synthetic polymers to formulate drugs into the backbone structures in various cases. The future prospects of the research for practical applications has been also proposed for the development in the fields.

Natural polymers for drug delivery

Arginine derivatives: Arginine, also known as L-arginine, is α-amino acid that uses in the biosynthesis of proteins [12]. It contains α-amino group, α-carboxylic acid group, and a side chain consisting of a 3-carbon aliphatic straight chain ending in a guanidino group. At physiological pH, the carboxylic acid is deprotonated (−COO−), the amino group is protonated (−NH3+), and the guanidino group is protonated to give the guanidinium form (−C-(NH2)2+), making arginine a charged aliphatic amino acid.

Chitosan derivatives

Chitosan is one of cationic polysaccharides derived from the natural chitin. As a cationic polymer with favorable property, it has been widely used to form polyelectrolyte complexes with polyanions for drug delivery. Chitosan is a linear copolymer composed by glucosamine and N-acteyl glucosamine units, via β-(1, 4) linkages, namely 2-amino-2-deoxy-β-d-glucan. Chitosan is the product of the deacetylation reaction of chitin (2-acetamido-2-deoxy-β-d-glucan). It has favorable biological properties such as nontoxicity, muco-adhesiveness, biocompatibility and the biodegradability. The aqueous derivatives of chitosan such as chitosan salts zwitterionic chitosan, and chitosan oligomers have drawn increasing attention due to their water-solubility for biomedical applications

Cyclodextrin derivatives

Cyclodextrin is a family of cyclic oligosaccharides composed of α (1,4) linked glucopyranose subunits. Cyclodextrin is useful molecular chelating agent. There are three types of cyclodextrins in the nature. Those are named α (6 units), β (7 units) and γ-cyclodextrins (8 units β-Cyclodextrin is ideal for drug delivery due to the cavity size, efficiency drug complexation and loading, availability and relatively low cost .An example of cyclodextrin in drug delivery system is 2-hydroxylpropyl derivate, which is a powerful solubilizer, and has a hydrophilic chain outside and a hydrophobic chain inside. They are able to prevent the drug degradation and to improve the drug stability and solubility resulting on a higher bioavailability. Those are very useful for polymeric drug delivery systems for practical applications.

The chemical structure of the three main types of cyclodextrin (CD) for polymeric drug delivery systems Poly (glycolic acid), poly (lactic acid), and hyaluronic acid Glycolic acid is a useful intermediate for organic synthesis, in a range of reactions, including oxidation-reduction, esterification, and long chain polymerization. It has used as a monomer in the preparation of polyglycolic acid and other biocompatible copolymers. Two molecules of lactic acid have dehydrated to the lactone lactide. In the presence of catalysts, lactides polymerize to either atactic or syndiotactic polylactide which are biodegradable polyesters. Glycolic acid and lactic acid have employed in pharmaceutical technology to produce water-soluble glycolate and lactate from otherwise-insoluble active ingredients. They have found further to use in drug delivery, topical preparations, and cosmetics to adjust acidity and for its disinfectant and keratolytic properties. Hyaluronic acid, which is a natural polymer, has the ability to target the CD44 over expressing cancer cells.

Polysaccharides

Natural polymers have been in use for many years with the aim of facilitating the efficiency of drugs and their delivery. Biodegradable polymers are widely being studied as a potential carrier material for specific drug delivery because of their non-toxic, biocompatible nature. Natural polysaccharides have investigated for application in drug delivery industry as well as in biomedical fields. Modified polymer has found its application as a support material for gene delivery, cell culture, and tissue engineering. Nowadays, natural polymers have modified to obtain novel biomaterials for controlled drug delivery applications.

Polysaccharides are long chains of carbohydrate molecules, specifically polymeric carbohydrates composed of monosaccharide units bound together by glycosidic. This carbohydrate can react with water-hydrolysis using amylase enzymes at catalyst, which produces constituent sugars (monosaccharides or oligosaccharides). Natural saccharides are generally of simple carbohydrates called monosaccharides with general formula (CH2O)n where n is three or more. Examples of monosaccharides are glucose, fructose, and glyceraldehyde. Those natural polymers have used as biomaterials for drug delivery systems. Starch is a glucose polymer in which glucopyranose units have bonded by alpha-linkages. It has made up of a mixture of amylose and amylopectin. Amylose consists of a linear chain of several hundred glucose molecules and amylopectin is a branched molecule made of several thousand glucose units. Amylose is a linear polymer of glucose mainly linked with α ($1 \rightarrow 4$) bonds. It is one of the two components of starch polymer

Synthetic polymers for drug delivery systems

Poly (2-hydroxyethyl methacrylate):

Poly(2-hydroxyethyl methacrylate) [poly (HEMA)] is a polymer that forms a hydrogel in water or aqueous solution Poly (PHEMA) hydrogel for intraocular lens material was synthesized by solution polymerization using 2-hydroxyethyl methacrylate (HEMA) as raw material, azobisisobutyronitrile (AIBN), ammonium persulfate or sodium pyrosulfite (APS/SMBS) as catalyst, and ethylene glycoldimethacrylate(EGDMA)triethylene,glycoldimethacrylate (TEGDMA) as cross-linking additive Poly (HEMA) is commonly used to coat cell culture flasks in order to prevent cell adhesion and induce spheroid formation, particularly in cancer research. Older alternatives to pHEMA include agar and agarose gel.

Equilibrium swelling, structural characterization and solute transports in swollen poly (HEMA) gels cross-linked with tripropyleneglycoldiacrylate (TPGDA) were investigated for a wide range of TPGDA concentrations for drug delivery systems. The physical and chemical properties of pilocarpine from poly (HEMA) hydrogels were investigated to elucidate the mechanism of drug–polymer interaction and the effect on drug release behavior of controlled release polymeric devices. Poly (HEMA) hydrogels are widely used for biomedical implants. The extreme hydrophilicity of poly (HEMA) confers resistance to protein fouling, making it a strong candidate coating for ventricular catheters

Poly (N-isopropyl acrylamide)s

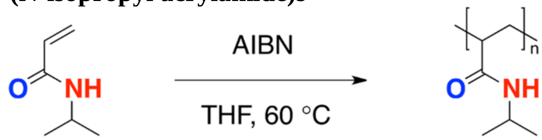

Fig.8

Aqueous solution of poly (N-isopropyl acrylamide) (PNIPAAm) shows a lower critical solution temperature (LCST). The temperature-responsive polymer has investigated in the 1960’s. They have established 32 C as the LCST of thermos-sensitive poly (N-isopropyl arylamide). The thermodynamic property of the system has evaluated from the phase diagram and the heat absorbed during phase separation by entropy effect. The process of free radical polymerization for a single type of monomer, in this case of N-isopropyl-acrylamide, find to form the polymer known as a homo-polymerization. The initiator of azobisisobutyronitrile (AIBN) has commonly used in radical polymerization.

Thermo-responsive polymers have attracted much attention because of their potential biological and medical applications such as drug and gene delivery. The swelling of cross-linked poly(N, N′-alkyl substituted acrylamides) in water was studied in relation to temperature changes. The thermo-sensitivity of water swelling has attributed to the delicate hydrophilic/hydrophobic balance of polymer chains and has affected by the size, configuration, and mobility of alkyl side-chain groups.

The cell culture surface of the polymer has readily prepared by the technique reversibly into hydrophilic and hydrophobic coatings of PNIPAAm-grafted polymers. Temperature/pH sensitive hydrogels were prepared by copolymerizing N-isopropyl acrylamide (NIPAAm) and acrylic acid (AAc). The influence of polyelectrolyte on the LCST of temperature/pH sensitive hydrogels had investigated in the pH range of swelling ratio. The swelling ratio of the hydrogels in the presence of poly (allyl amine) (PAA) as a polyelectrolyte was also measured at the same conditions. It has briefly discussed about the tumor micro-environmental responsive nano-particles in situ stimuli responsive such as pH, redox responsive, hypoxia sensitive, etc.

Poly (ethyl enimine)

Linear poly (ethyl enimine)(PEI) is soluble in hot water, at low pH, ethanol or chloroform. They are insoluble in cold water, acetone, benzene, and ethyl ether. Branched PEI has synthesized by the ring opening polymerization of aziridine Linear PEI is available by post-modification of other polymers like poly (2-oxazolines) or N-substituted polyaziridines Linear PEI was synthesized by the hydrolysis of poly (2-ethyl-2-oxazoline).

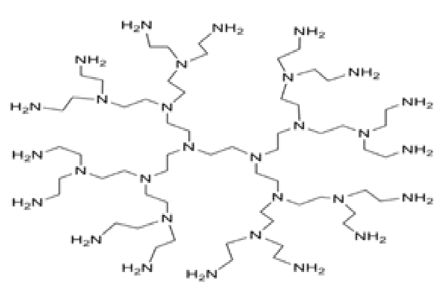

Fig.9

The chemical structure of poly (ethylenimine)s for polymeric drug delivery:

Poly (N-(2-hydroxypropyl) methacrylamide)s Degradable diblock and multiblock (tetrablock and hexablock) N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-gemcitabine (GEM) and -paclitaxel (PTX) conjugates had synthesized by reversible addition-fragmentation chaintranster (RAFT) copolymerization followed by click reaction for preclinical investigation. Poly (HPMA) copolymer-cytarabine and GDC-0980 conjugates were synthesized. In vitro studies demonstrated that both conjugates had potent cytotoxicity and their combination showed strong synergy, suggesting a potential chemotherapeutic strategy .Telechelic water-soluble HPMA copolymers and HPMA copolymer-doxorubicin (DOX) conjugates had synthesized by RAFT polymerization mediated by a new bi-functional chain transfer agent that contained an enzymatically degradable oligopeptide sequence

Dendritic polymers

Dendritic polymers are highly branched polymers with controllable structures, which possess a large population of terminal functional groups, low solution or melt viscosity, and good solubility. Their size, degree of branching and functionality can be controlled and adjusted through the synthetic procedures. The research of dendrimer has increased on the design and synthesis of biocompatible dendrimer and its application to many areas of bioscience including drug delivery, immunology and the development of vaccines, antimicrobials and antivirals. The dendrimers are the members of a versatile, new class of polymer architectures, dendritic polymers after traditional linear, cross-linked, and branched types. The dendrimer type of bio-reducible polymer for efficient gene delivery had been also investigated.

The schematic design of divergent synthesis of dendrimers for drug delivery

The chemical structures of dendrimer and dendron for drug delivery

Biodegradable and bio-absorbable polymers

Bio-absorbable drug delivery systems are a better choice for the application of drug carriers where only the temporary presence of the implant is needed. Among the synthetic and biodegradable polymers, aliphatic polyesters such as poly (glycolic acid), poly (lactic acid), poly (caprolactone) and polydioxanone, are most commonly used and applied to drug delivery systems. The several classes of polymers such as poly (esters), poly (ortho esters), polyanhydrides, and biodegradable polycarbonates have also been introduced as potential implant materials for drug delivery. Biodegradable polymers with representative monomer units for polymeric drug delivery. Biodegradable polymers commonly used include the α-hydroxy acids, polyanhydrides, poly (amides), poly (ester amides), poly (phosphoesters), poly (alkyl cyanoacrylates), poly (hyarulonic acids) and natural sugars such as chitosan, in addition to many other types of degradable polymers Synthetic biodegradable polymers are favored in drug delivery systems, as they have immunogenicity as compared to biodegradable polymers from natural polymers

4. 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 hepatitis28-30. 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 unfavorable 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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