International Journal of Advanced Multidisciplinary Research and Educational Development
Volume 2, Issue 1 | January - February 2026 | www.ijamred.com
ISSN: 3107-6513

A Review on Polymers in Pharmaceutical Drug Delivery System

Ch. Naga Sowjanya[1], Dr. D Rama Bramha Reddy[2], M. Prasanthi[3]
[1]Assisstant Professor, Pharmaceutics, Nalanda institute of pharmaceutical Sciences, Sattenapalli, Kantepudi, Andhra Pradesh, India
[2]Principal, Phytochemisry, Pharmaceutical Sciences, Sattenapalli, Kantepudi, Andhra pradesh, India
[3]Student, B. Pharmacy, Nalanda Institute of Pharmaceutical Sciences, Sattenapalli, Kantepudi, Andhra pradesh India

Abstract:

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-shell 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. We review the origins and applications of stimuli-responsive polymer systems and polymer therapeutics such as polymer-protein and polymer-drug conjugates. The latest developments in polymers capable of molecular recognition or directing intracellular delivery are surveyed to illustrate areas of research advancing the frontiers of drug delivery.Polymers play a vital role in modern drug delivery systems by controlling drug release, enhancing therapeutic efficacy, improving patient compliance, and providing targeted delivery.

KEYWORDS: controlled release, stimuli-responsive, responsive polymers, recognitive polymers, polymer therapeutics, intracellular delivery.

INTRODUCTION:

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 .These systems must overcome many hurdles before clinical implementation is realized; a truly intelligent delivery system must address the need for specific targeting, intracellular transport, and biocompatibility while integrating elements of responsive behaviour to physiological environments and recognitive feedback control.

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 the polymer chains which overall displays a sustained release characteristic.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.[1-5]

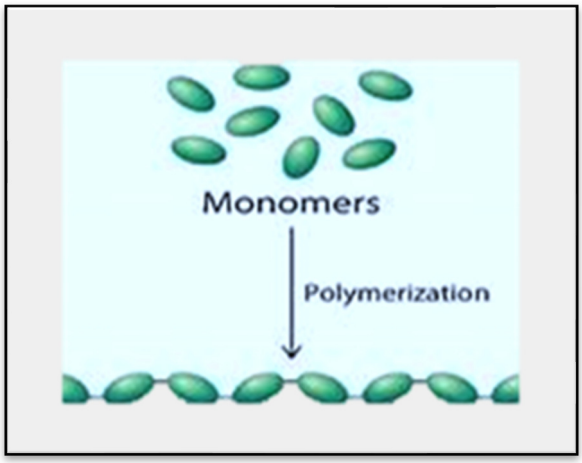

FIG:1: polymer

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 watersoluble polymers as macromolecular drugs or as part of drug delivery systems related toinoculation can be considered a modern achievement. The first polymerdrug conjugates appeared around 1955, being mescalineNvinylpyrolidine c

ISSN: 3107-6513

onjugate one of the first In 1994, the first synthetic polyme rdrug conjugate (as shown in figure 1b) designed to treat ca ncer was clinically tested. It consisted on an HPMA .A prop er consideration of surface and bulk properties can aid in t he designing of polymers for various drug delivery applicat ions. These newer technological development include drug modification by chemical means carrier based drug deliver y and drug entrapment in polymeric matrices or within pu mps that are placed in desired compartments. These techni cal development in drug delivery/targeting approaches imp rove the efficacy of drug therapy thereby improve human h ealth.3 Polymer chemists and chemical engineers, pharmac eutical scientists are engaged in bringing out design predict able, controlled delivery of bio active agents.4 Extensive Biodegradable polymers have been widely used in biomedi cal applications because of their known biocompatibility a nd biodegradability.[6-8]

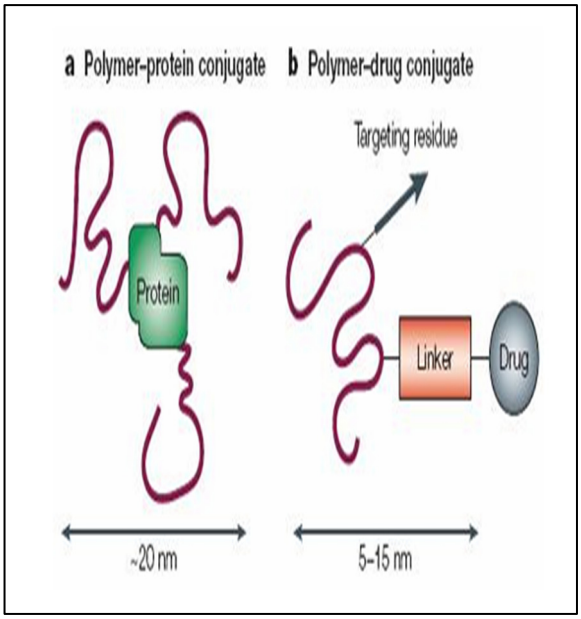

FIG2:The families of polymer constructs called polymer therapeutics.

ROLE OF POLYMER IN PHARMACEUTICAL DRU G DELIVERY

Immediate release dosage forms

Tablets

Polymers have been used for many years as excipients in c onventional immediaterelease oral dosage forms, either to aid in the manufacturing process or to protect the drugfrom degradation upon storage. Microcrystalline cellulose is ofte n used as an alternative to carbohydrates as diluents in table t formulations of highly potent lowdose drugs. Starch and c ellulose are used as disintegrants in tablet formulations, wh ich swell on contact with water, resulting in the tablet "burs ting," increasing the exposed surface area of the drug and i mproving the dissolution characteristics of a formulation.

Capsules

Capsules are used as an alternative to tablets, for poorly co mpressible materials, to mask the bitter taste of certain dru gs, or sometimes to increase bioavailability. Many of the p olymeric excipients used to "bulk out" capsule fillsare the s ame as those used in immediaterelease tablets. Gelatine has been used almost exclusively as a shell material for hard (t wopiece) and soft (onepiece000) capsules. HPMC has rece ntly been developed and accepted as an alternative material

Modified-release dosage forms

It is now generally accepted that for many therapeutic age nts drug delivery using immediate release dosage forms res ults in suboptimal therapy and/or systemic side effects. Pha rmaceutical scientists have attempted to overcome the limit ations of conventional oral dosage forms by developing mo dified release dosage forms.

Extended release dosage forms

The therapeutic effect of drugs that have a short biological halflife may be enhanced by forulating them as extended or sustained release dosage forms. Extended and sustained re lease dosage forms prolong the time that systemic drug lev els are within the therapeutic range and thus reduce the nu mber of doses the patient must take to maintain a therapeut ic effect thereby increasing compliance. The most common ly used water insoluble polymers for extended release applications are the ammonium ethacrylate copoly mers (Eudragit RS and RL), cellulose derivatives ethyl cellulose, cellulose acetate, and polyvinyl derivative.

Gastroretentive Dosage Forms

Gastroretentive dosage forms offer an alternative strategy for achieving extended release profile, in which the formul ation will remain in the stomach for prolonged periods, rele asing 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 graduall y 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 site s within the gastrointestainel tract.[9-12]

IDIAL PROPERTIES OF POLYMERS USED IN PHARMACEUTICALS

An ideal polymer for drug delivery should possess:

Biocompatibility

Biodegradability

Non-toxicity

Chemical stability

Mechanical strength

ISSN: 3107-6513

Ease of formulation

Reproducible drug release behaviour.[13-15]

CLASSIFACTON OF PHARMACEUTICAL POLYMERS

1) Based on origin:

a) Natural polymer: The natural polymers are polymers that result from only raw materials that are found in nature Ex. Protein-collagen, keratin, albumin carbohydrates-starch cellulose, glycogen DNA, RNA.

b) Synthetic polymers: These are the polymers was prepared by laboratory is known as synthetic polymer. Ex. Buna- S, Buna-R, Nylon, Polyesters.

2) **Based on Bio -stability**:

a) Biodegradable polymer: Biodegradable polymers are a special class of polymer that breaks down after its intended purpose by bacterial decomposition process to result in natural by products such as gases, water, biomass, and inorganic salts.

Example: Polyesters, Proteins Carbohydrates etc.

b) Non-biodegradable polymer: The polymers which are not decomposed by the action of microorganisms and are referred to as non-biodegradable polymers. Ex. Ethyl cellulose, HPMC, Acrylic polymers, silicone.

3) On Reaction mode of polymerization:

a) Addition polymers: The monomer molecules bond to each other to each other without the loss of any other atoms. Ex. Alkene monomer.

b) Condensation polymers: Usually two different monomers combine with the loss of small molecules, usually water. Ex. Polyester, Polyamides, nylon 6.

4) On structure a) Linear polymers: The smallest repeating unit arranged in straight-line path is known as linear polymers. Ex. PVC

b) Branched chain polymers: It contains linear chain having some branches. Ex. Low density polymers.

c) Cross linked polymers: Formed from bi- functional and tri-functional monomers and contain strong covalent bond. Ex. Bakelite and monomer.[16-18]

TYPES OF POLYMERS IN PHARMACEUTICAL DRUG DELIVERY:

1. Polymers used as colon targeted drug delivery: Polymers plays a very important role in the colon Targeted drug delivery system. It protects the drug from Degradation or release in the stomach and small Intestine. It also ensures abrupt or controlled release of The drug in the proximal colon.

2. Polymers in the mucoadhesive drug 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 Inhibit on, site specific mucoadhesive polymers will Undoubtedly be uitilized for the buccal delivery of a Wide variety of therapeutic compounds. The class of Polymers has enormous for the delivery of therapeutic Macromolecules.

3. Polymers for sustained release:

Polymers used in the sustain by preparing Biodegradable microspheres containing a new potent Osteogenic compound.

4. Polymers as floating drug delivery system:

Polymers are generally employed in floating drug Delivery systems so as to target the delivery of drug to a Specific region in the gastrointestinal tract i.e. stomach. Natural polymers which have been explored for their Promising potential in stomach specific drug delivery Include chitosan, pectin, xanthan gum, guar gum, gellan gum, karkaya gum, psyllium, starch, husk, starch, alginates etc.

5. Polymers in tissue engineering: A wide range of natural origin polymers with special focus on proteins and polysaccharides might be potentially useful as carriers systems for active biomolecules or as cell carriers with application in the tissue engineering field targeting several biological tissue.[19-21]

MECHANISM OF DRUG RELEASE BY POLYMERS:

Three primary mechanisms for drug release namely:

1) Diffusion

2) Degradation

3) Water penetration (swelling)

Following mechanisms occurs drug release by polymers**-**

1) Drug release from polymers by diffusion:

Rate limiting step is diffusion of the through inert water insoluble membrane barrier**.**

There are two types-

a. Reservoir

b. Matrix

a) Reservoir diffusion system: In membrane-controlled reservoir devices, the drug is contained in a core, which is surrounded by a polymer membrane, and it is released by

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diffusion through this rate controlling membrane Ex. Poly (N-vinyl pyrrolidone), poly (ethylene-co-vinyl acetate).

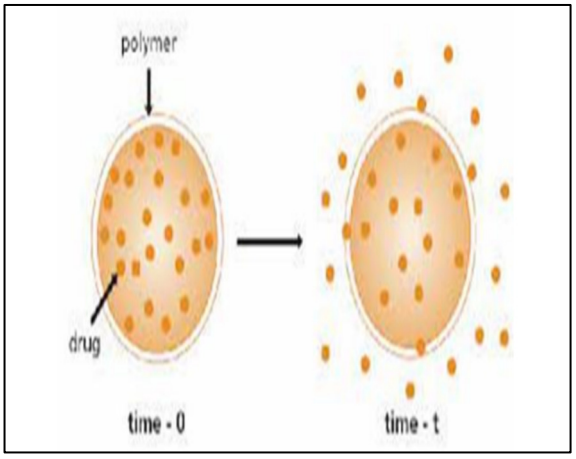

FIG:4 Hydrogel system for polymer administration.

b) Matrix diffusion system:

In these devices, the drug is released either by passing through the pores or between polymer chains, and these are the processes that control the release rate.

Ex. Such as polyethylene, polyvinyl acetate

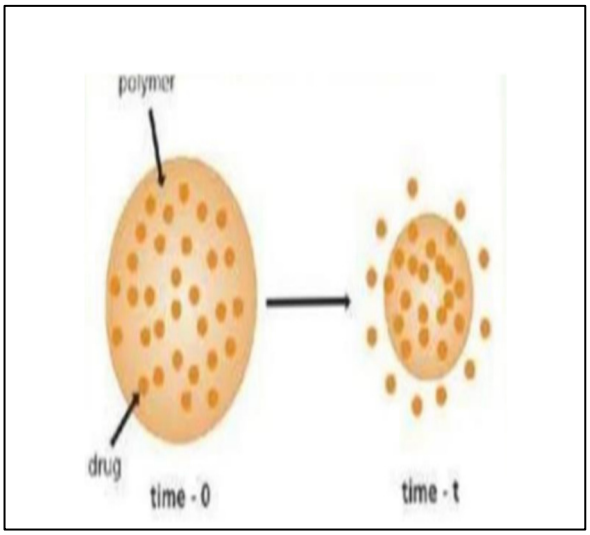

FIG:5 Drug released by polymers by matrix diffusion system.

1) Degradation:

The drug molecules, which are initially dispersed in the polymer, are released as the polymer starts eroding or degrading. The four most commonly used biodegradable polymer in drug delivery systems are poly (lactic acid), poly (lactic-co-glycolic acid),polyanhydrides.

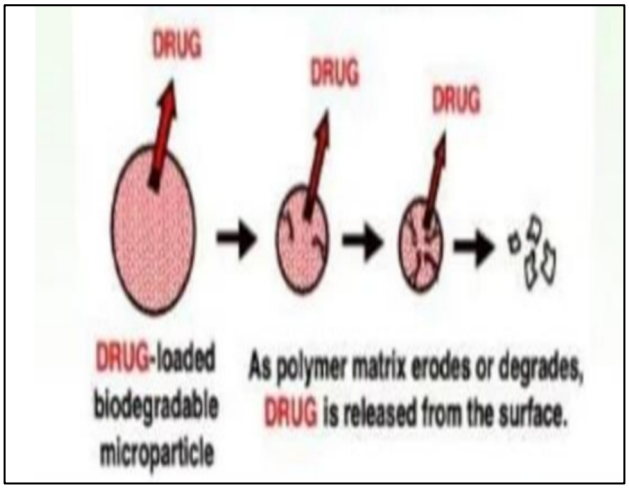

FIG:6 Drug released by polymers by degradation.

2) Water penetration (swelling):

This type of system initially dry and when placed in body, absorb water or other fluid and it swells. Swelling increase diffuse solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into external environment Ex. (N-iso pro-polyacrylamide), Ethylene-vinyl alcohol.[22-24]

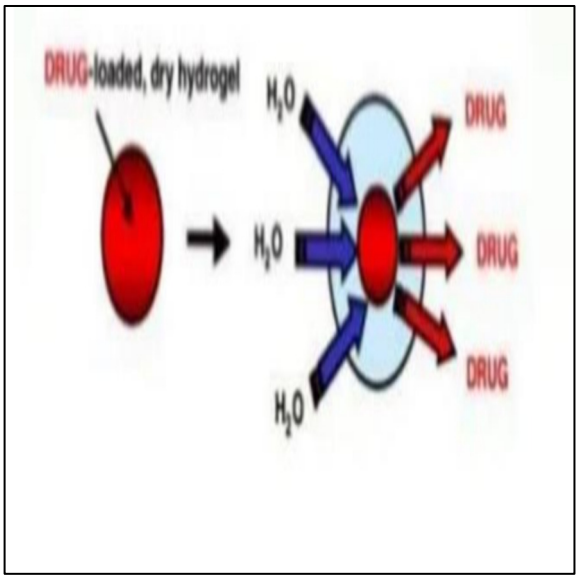

FIG:7 Drug released by polymers by degradation.

Applications of Polymers

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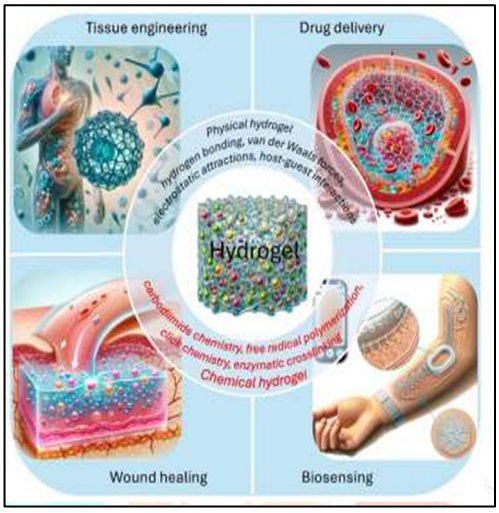

FIG:8 Hydrogel system for polymer administration.

Polymers in Tableting:

Tablet is kind of solid dosage form which is formulated by compressing therapeutically active ingredient with pharmaceutical excipients. Manufacturing polymers mostly used binders and disintegrants. Example of tablet binder are Methyl cellulose (Metho cel), starch, gelatin, PVP, EC and HPMC. Examples of coating agent are Hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC).

Polymers in Capsule:

Capsule are generally containes of gelatin. The composition of gelatin are of different types that are two types in that first one is hard gelatin and second one is soft gelatin. To fill up the volume in capsule Fillers such as MCC and starches are used. To such as starch and sodium starch glycolate are mixed with capsule container

Polymers in disperse system:

It is heterogeneous thermodynamically unstable liquid system in which drugs material sometimes solid or sometimes liquid is dispers in dispersion medium. Suspensions, emulsions, creams, ointments and aerosols are used as pharmaceutical dispersion system. Examples of naturally occurring dispersing agents are Alginates, carrageenan and xanthan gum. And examples of semisynthetic agents are poly (acrylic acid), PVP, PVA and cellulose ethers.

Polymers in gels:

Gel system made up of physical or chemical cross-linked between adjust polymer chain moderate chain mobility. Gel has rheological properties. Cross-linked gels are generally called as hydrogels. They are also called as smart polymers because they gives different gelling properties in different conditions of water. Examples of hydrogels are poly (hydroxyethyl methacrylate), poly (methacry1ic acid) and poly (acrylamide). In pharmaceutical industries cross-linked gels are firstly use to local drug delivery of drugs for skin, oral cavity, vagina and rectum

Polymers in transdermal drug delivery systems (patches):

For delivery of therapeutic agent across skin to systemic circulation transdermal drug delivery system are generally used. System has some applications in pain cure, termination of smoking, heart diseas es and hormonal substitution. In transdermal drug delivery system role of polymer is protective coverings and adhesives. Examples of Adhesives used are acrylates silicones and polyisobutylates.

Polymers in ocuserts:

In treatment of eye disorders like glaucoma ocusert is used. An example of Oxshort is therapeutic agent (Pilochropyin) of 20 grams H-1 or 40 g H-1 for a period of 7 days from implantation. Ocusert is elliptical shape implant having various layers. Poly (ethylene-co-vinyl acetate) is used for preparation of pilocarpinocusert

Polymers in progestasart system:

In controlled drug delivery system medicated implant use for contraceptive purpose example of this is a Progestasart intra-uterine device. The drug release occurs by diffusion from progestasart this polymer act as a rate controlling membrane for drug release. Examples of polymer are used in such system are Polyethylene and poly(ethylene-co-vinyl acetate)

Polymers in colon targeted drug delivery:

Polymers play a very important role in the colon-targeted drug delivery system. It protects from the disorders of the medicine and leaves the stomach and small intestines. It also ensures sudden or controlled release of medicines in the proximal colon

Polymers in the mucoadhesive drug delivery system:

The new generation of mucosidive polymers for drug delivery will increase the time of polymers, increase penetration, site specific adhesion and enzymatic blocks, site specific macrocystic polymers, and can be useful for the treatment of various types of treatment. The polymers class is huge for the distribution of the therapeutic macromolecules.

Polymers in sustained release:

Using polymer builds bio-stimulant microspears and creates it with a new powerful osteogenic compound.

Polymers in floating drug delivery system:

Polymers are generally employed in the floating drug delivery system, so that gastrointestinal tract, which aims to distribute drugs in a particular area in the stomach. The natural polymers discovered for their potential for specific

ISSN: 3107-6513

drug delivery include chitosan, pectin, zanthon gum, guar gum, gallon gum, gram gum, stem, starch, hask, starch, alghen etc.

Polymers in tissue engineering:

A wide range of natural origin polymers with specific targets on proteins and polysaccharides can potentially be useful for active bio-reactants for biological reactors, so that many biological tissues can be concentrated in the field of tissue engineering with the application as a cell carrier.

Polymers in swelling controlled system:

Swelling controlled release systems are physically cross-linked as well as chemically cross-linked. Chemically cross-linked are known as hydrogels. Poly (hydroxyethyl methacrylate) which is used in controlled drug release. HPMC is used as Hydrophilic polymer as well as controlled release hydrogel

Polymers in drug conjugates:

It is one of the approach for enhance the delivery of therapeutic agent. The conjugate of polymer and drug composed of drug that is bound covalently to polymer. Approach of polymer drug chain use primarily in the field of cancer remedy which is called as „polymer therapeutics". Biodegradable polymer areused while non-biodegradable synthetic polymer such as PEG and poly (hydroxylpropyl methacrylate) mostly used.

Polymers in nanoparticles:

Size of nanoparticles in the range of 10-1000nm. The drug is attached, entrapped and dissolve to polymeric matrix this is occur in nanoparticles drug delivery systems. For sustain drug delivery system polymeric nanoparticles are used. Biodegradable and non-biodegradable polymers are used as a diagnostic agent without delivery devices. These biodegradable polymers fall into nonotoxic and biological active substances. These biological active substances can be metabolized and removed from the body in the normal metabolic way. Examples of synthetic biodegradable polymers are poly lactoid, poly (lactoid-co-glyolide), poly-ε-carolacacton and polanhyridide.[25-28]

ADVANTAGES OF POLYMERS

Three benefits can be obtained from polymeric drug delivery products

Localized drug delivery:

By implanting the device exactly where the medication is needed, systemic exposure to the medication can be minimized. Particularly for toxic Medications that have a number of systemic adverse effects.

Drug delivery that lasts:

The medication is given gradually over time, obviating the need for repeated injections. This function can help increase patient compliance, particularly with medications that need to be injected frequently and have chronic indications.

Drug stabilization:

By shielding the medication from the physiological milieu, the polymer can increase the drug's stability in vivo. This characteristic makes the Method appealing for the administration of medications that are labile, such as proteins.[28-29]

POLYMERS IN PHARMACEUTICAL DRUG DELIVERY SYSTEM

1. **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.
2. **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.
3. **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.[30-32]

CHALLENGES AND FUTUR PROSPECTS

Polymeric drug delivery systems have transformed contemporary therapies by providing regulated, targeted, and effective drug release; polymeric drug delivery systems (PDDS) have changed contemporary treatments. However, various obstacles hinder their widespread clinical translation, even with great progress. Safety and biocompatibility are among the primary concerns. To avoid negative consequences, polymers must be nontoxic, non immunogenic, and biodegradable within a reasonable timeframe. Certain synthetic polymers may be broken down into hazardous by-products that cause cytotoxicity, inflammation, or immunological reactions. Variations in

ISSN: 3107-6513

polymer synthesis and batch-to batch discrepancies may also make maintaining regulatory approval and ensuring repeatability challenging. However, large-scale manufacturing and pricing concerns pose significant obstacles. Although PDDS are very successful in laboratories, industrial-scale manufacturing is still complicated and costly. Advanced technology, cleanroom conditions, and precise control over physicochemical characteristics are required for the synthesis of functionalized polymers, encapsulation of pharmaceuticals, and manufacturing of nanoparticles. These factors increase manufacturing costs; therefore, polymeric formulations are less readily available for general therapeutic use.[33-34]

RECENT DEVELOPMENTS IN USE OF POLYMERS FOR DRUG DELIVERY SYSTEMS

Oral drug delivery gadget has been in exercise since a few years because the maximum extensively used root of managementamongst all of the roots that had been hired for the systemic transport of drug through various pharmaceutical merchandise forspecial dosage paperwork. A big of each artificial and natural has been studied for feasible utility in drug transport gadget. Themaximum high-quality belongings of polymers are that they had been maximum extensively used now a days. Two Promisingartificial polymers which had been evolved for biomedical packages are form Polyvinylpyrrolidone and polyethylene glycol acrylateprimarily based totally hydrogels. Both of them are biodegradable and paperwork copolymers with natural macromolecules. On theAlternative side, herbal polymers have the benefit of excessive biocompatibility and less immunogenicity. A unique interest hasbeen shown through the gelatine and collagen which might be herbal Polymers. Other herbal polymers encompass chitosan,alginate, starch pectin, casein and cellulose derivatives. The composites of a number of the above herbal polymers with artificialpolymers provide introduced benefits as providers for pills transport with the aid of using complimenting the homes of every other.Residences of every other. hybrid copolymers of collagen with biodegradable artificial polymers polyethylene glycol 6000 andpolyvinylpyrrolidone had been advanced for the controlled launched of contraceptive a few pills have an optimum variety insidewhich most gain is derived, and concentrations above or underneath this variety may be toxic or produce no healing notion it at all.On the other hand, the very sluggish development with inside the efficacy of the remedy of extreme disease, has cautioned agrowing want for a multidisciplinary technique to the shipping of therapeutics to goals with inside the tissues.[35-36]

Conclusion:

Polymers were correctly hired with inside the system of solid, liquid and semisolid dosage employed and are especially beneficialwithin side the layout of changed launch drug shipping systems. Bothartificial and herbal polymers were investigated significantlyfor this purpose, however the use of herbal polymers for pharmaceutical programs is appealing due to the fact they 'r eeconomical ,comfortably available, non-toxic, and able to chemical modifications, doubtlessly biodegradable and with few exceptions,additionally biocompatible. One of the maximum fantastic and beneficial functions of a polymers swelling capacity manifests itselfwhilst that swelling may be induced through a extrude with inside the surroundings surrounding the shipping system. Polymer-primarily based totally prescription drugs are beginning to be visible as key factors to deal with many deadly sicknesses that havean effect on a wonderful quantity of people including most cancers or hepatitis. Although excipients have historically been blanketed in formulations as inert materials to particularly make up quantity and help with inside the production process, they are an increasing number of blanketed in dosage bureaucracy to fulfil specialized capabilities for stepped forward drug transport due to the fact many new drugs have unfavourable physicochemical and pharmacokinetic properties. The artificial polymers can be designed or changed as in keeping with requirement of the formula through changing polymer traits and on the alternative hand herbal pharmaceutical excipients are biocompatible, nontoxic, surroundings pleasant and economical. Several polymers were successfully used and others are being investigated as excipients in the layout of dosage form for powerful drug transport.

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