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Polymers Used in Novel Drug Delivery System.

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Abstract:
This review focus on the role of polymers used in novel drug delivery system of therapeutic agents. The polymers are used as carriers for delivery of drug at target site. 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.

Keywords: Polymers, Proteins, Controlled Delivery, Viscoelastic, Macromolecules.

Introduction:

The word "polymer" means "many parts."1-5 A polymer is a large molecule made up of many small repeating units. In the early days of polymer synthesis, little was known about the chemical structures of polymers. Herman Staudinger, who received the Nobel Prize in Chemistry in 1953, coined the term "macromolecule" in 1922 and used it in reference to polymers. The difference between the two is that polymers are made of repeating units, whereas the term macromolecule refers to any large molecule, not necessarily just those made of repeating units. So, polymers are considered to be a subset of macromolecules.

The advancements in polymer science, in amalgamation with pharmaceutical field, have helped for development of novel drug delivery systems, by use of these polymers. This polymeric drug delivery, has used for spatial or temporal delivery of drugs. The natural as well as synthetic polymers have been utilized for design of drug delivery system. With the introduction of first synthetic polymer (polyglycolic acid) drug delivery system, it led to sharp importance in design and synthesis of new biodegradable polymers; it was advantageous over non-degradable polymers. Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation. Transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of a fixed dose at regular intervals, due to which the drug concentration in the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdosing. The limitations of the oral route can be overcome and benefits of intravenous drug infusion such as to bypass hepatic "first pass" hepatic elimination (HEPE) to maintain constant prolonged and therapeutic effective

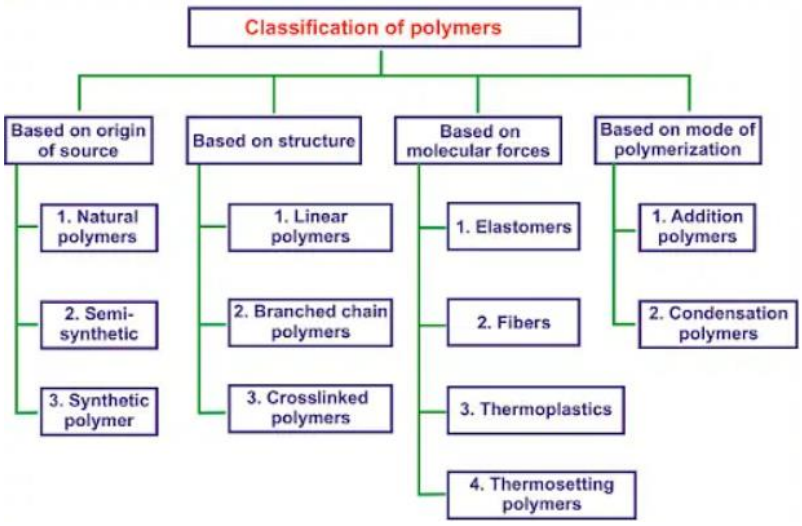
drug levels in the body can be closely duplicated, without its potential hazards, by transdermal drug administration through intact skin. The use of polymers for delivery of medicament is recent area of interest. The controlled drug delivery technology represents one of the frontline areas of medical science for effective delivery of drugs. The drug delivery systems utilize polymer for controlling rate of drug release from these systems. The current chapter highlights different polymer based controlled drug delivery systems along with their applications.

A monomer is a small molecule that combines with other molecules of the same or different types to form a polymer. Since drawing a complete structure of a polymer is almost impossible, the structure of a polymer is displayed by showing the repeating unit (the monomer residue) and an "n" number that shows how many monomers are participating in the reaction. From the structural prospective, monomers are generally classified as olefinic (containing double bond) and functional (containing reactive functional groups) for which different polymerization methods are utilized. If two, three, four, or five monomers are attached to each other, the product is known as a dimer, trimer, tetramer, or pentamer, respectively. An oligomer contains from 30 to 100 monomeric units. Products containing more than 200 monomers are simply called a polymer.(From a thermodynamic perspective, polymers cannot exist in the gaseous state because of their high molecular weight. They exist only as liquids or high solid materials

➢ **Characteristics of Ideal Polymer**

1. Low density.
2. Low coefficient of friction.
3. Good corrosion resistance.
4. Good mould ability.
5. Excellent surface finish can be obtained.
6. Can be produced with close dimensional tolerances.
7. Economical.
8. Poor tensile strength.
9. Low mechanical properties.
10. Poor temperature resistance.
11. Can be produced transparent or in different colours

➢ **Classification of polymers:**



1)Based on origin of source

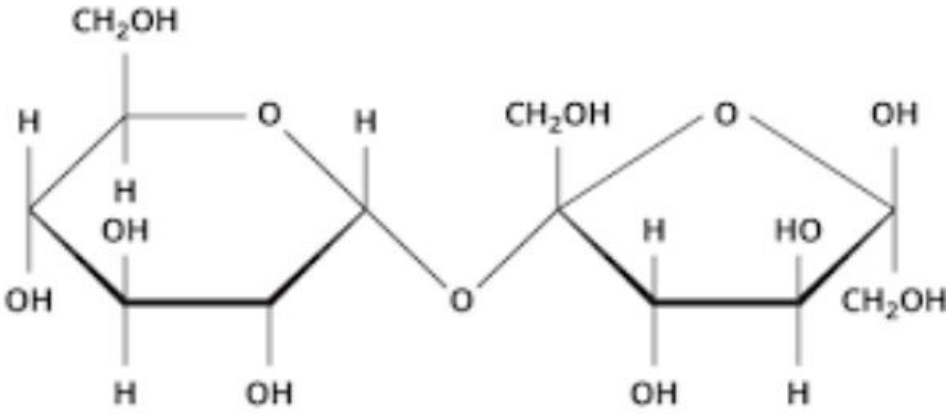
1.1Natural polymers

Natural polymers

Natural polymers are those materials obtained from natural sources. These can be obtained from a wide variety of natural sources such as plants, animals, and microorganisms. Natural polymers have been investigated for biomedical applications such as pharmaceuticals, tissue regeneration scaffolds and drug delivery systems. These polymers offer various advantages like stability, biocompatibility, biodegradability, lack of toxicity, good water holding capacity and low cost. Based on the chemical composition the natural polymers can be classified into various subtypes like polysaccharides, proteins. The natural polymers, especially polysaccharides, have been widely used in the formulation of nanoparticles and controlled drug delivery systems. These occur naturally, found in plants and animals. Examples include - cellulose, starch, hyaluronic acid, alginate, dextran, rubber etc. Even biodegradable polymers called as biopolymers are also included in it. The below table shows properties of some natural polymers.

The few examples of these polymers are Collagen, Albumin, Gelatine, Alginate, Cyclodextrin, Chitosan, Dextran, Agarose, Hyaluronic acid, Starch and Cellulose.

1.2 Semi-synthetic polymers



These are chemically modified natural polymers. These polymers are prepared by grafting synthetic substituents like various functional groups on natural polymers. The examples of these polymers are Carboxy methyl cellulose, Ethyl cellulose, Cellulose acetate, hydroxyl propyl methyl cellulose. These are semisynthetic polymers prepared by modification of naturally occurring cellulose with various functional groups.

These types of polymers are derived from naturally occurring polymers by means of chemical modifications. For e.g. Vulcanized rubber, Gun cotton, Cellulose diacetate, HPMC, etc.

(i) Vulcanized rubber is used in making tyres as the process of vulcanization increases the mechanical strength of natural rubber. Gun cotton which is a cellulose nitrate is used in making explosives. Cellulose on acetylation with acetic anhydride in the presence of sulfuric acid forms cellulose diacetate which is used in production of treads and materials like films glasses

1.3 Synthetic polymers: These are manmade and synthesized in laboratories. These are commercially created by for human necessities. Widely used in diary and industries is the plastic polymer. Example includes nylon-6, 6, polyether's, Polyethylene (used for packaging) or Nylon Fibers (used for clothes, fishing nets etc . These are the material synthesized in laboratory using various monomers. These are also known as human made polymers. The various chemical reactions were investigated for laboratory synthesis of polymers which resulted information of polymers like polyester, polyamides, polyanhydrides and Phosphorous based polymer.

e.g.: polythene

2).Based on structure

2.1 linear polymers: The smallest repeating unit arranged in straight line path is known as Linear polymer. For example: PVC. The polymers contain long and straight chains are similar in structure. Monomers are linked to form long chain. These polymers possess high melting points and are of high density. Example of this is poly-vinyl chloride (PVC) that is used in pharmaceutical industry and is also used for preparation of cables and pipes

2.2 branched chain polymers: Contain linear chains having some branches. Linear polymers, when form branches, then they are termed as branched chain polymers. The monomers are joined to form a long straight chain, but with some branched chains of unlike lengths. For example: low density polymer, Polyethylene, HPLD polyethylene

2.3 cross- linked polymers: In this type, all molecules are chemically bonded together, forming a three-dimensional network. The bonding is usually covalent but other types such as; ionic bond is also possible. Cross-linked polymers are produced from linear and branched polymers or directly from chemical precursor. In these polymers, the monomers are linked together that form a three- dimensional network. The monomers have strong covalent bonds as these are composed of bi-functional and tri-functional in nature. These polymers are brittle and hard. Example include - Melamine, Bakelite (used -electrical insulators). For e.g. Natural rubber, polyacrylamide gels, epoxies, alkyd resins, etc

3)based on mode of polymerization

3.1 addition polymers : Additional polymers are formed by the repeated addition of monomer molecules possessing double or triple bonds. n(CH2=CH2) (CH2-CH2)- Ethylene polyethylene, one form of polymer is converted into another form of polymer by loss of atoms and ions from molecule.

3.2Condensation polymers: Condensation polymers formed by repeated condensation reaction between two different bi-functional or tri- functional monomeric units. For e.g. terylene (dacron),. nylon 6, 6, One polymer can be converted into anther form of polymer without loss of atoms and ions from molecule.

4)based on molecular forces

4.1Elastomers: These are rubber like solids, in which weak interaction forces are present. Example - Rubber

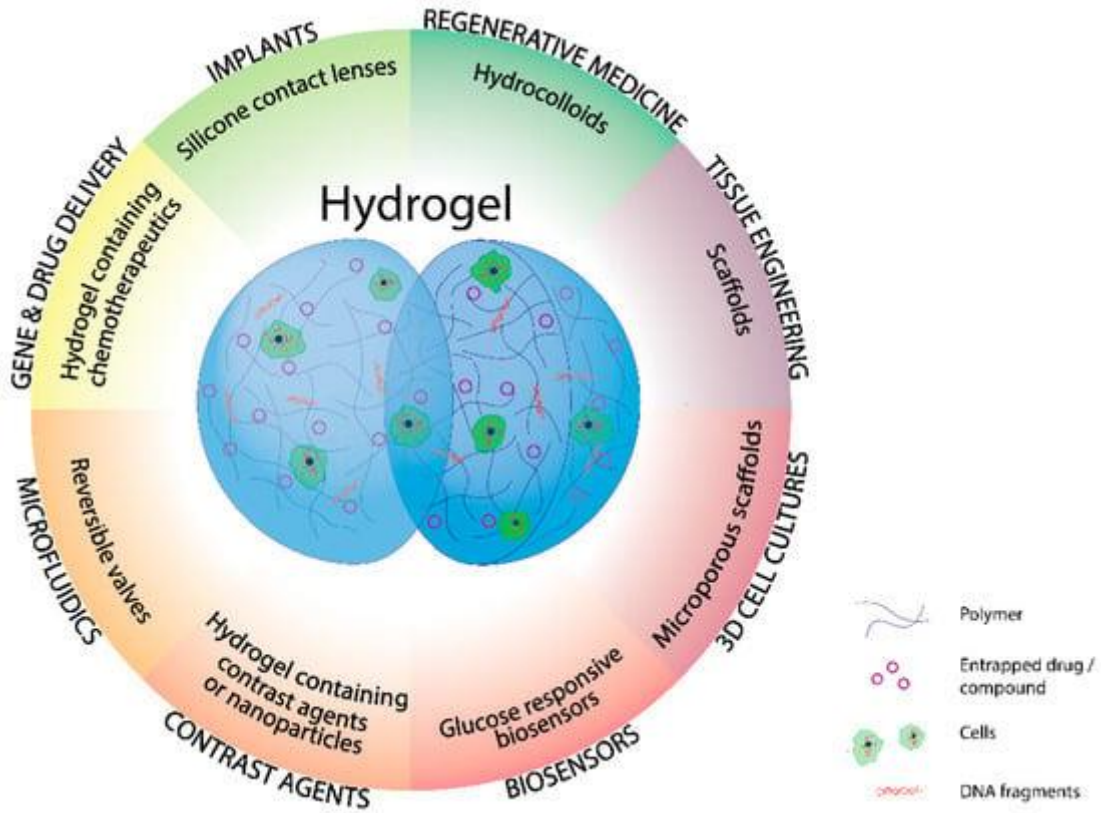
4.2 Fibers: These are strong, with high tensile strength and strong interaction forces. Example Nylon -6,6

4.3Thermoplastics: This when, heated, becomes liquid, so it can be simply produced in preferred shape. These polymers, once cooled, retain the shape. Examples - Polypropylene, Polyethylene, polyvinyl chloride, polystyrene, acrylic etc

4.4Thermosetting polymers: These improve mechanical properties of polymers, with good heat resistance and chemical resistance. Example silicones, epoxy, phenolics etc

- **Recently used polymers in drug delivery system**

1)hydrogels



Introduction: Hydrogels are composed of a large amount of water and a crosslinked polymer network. The high water content (typically 70–99%) provides physical similarity to tissues, and can give the hydrogels excellent biocompatibility and the capability to easily encapsulate hydrophilic drugs. Hydrogels may be prepared from a variety of sources comprising both natural and synthetic systems; they may also be prepared for various applications in separation technology. The hydrogel term came out first time in 1894 as it was employed to explain a colloidal gel.
e.g.: Dextran, Carbomer propylene glycol, Polyethylene glycol, Hyaluronic acid derivative, Carboxymethyl cellulose

stability of hydrogels:
The thermal stability of hydrogel showed two decomposition steps, one in the range of 100–200 °C related to the loss of water and another in the range of 300–400 °C associated with degradation of the collagen structure. Results showed that the GO composite has higher thermal stability than an unfilled hydrogel

Advantages:
hydrogel is crosslinked via electron beams. This is having enough mechanical strength due to crosslinking. The main advantage is that it contains about 90% of water and it has the capability to absorbing and donating water to the wound environment. It also induces the granulation and epidermisation.

- **Evaluation test for hydrogels:**

1)High-performance liquid chromatography (HPLC): High-performance liquid chromatography (HPLC) is used to separate and concentrate the sample before quantification by UV absorbance, and less frequently fluorescence spectrometry , or mass spectrometry. Separation of therapeutic molecules based on their physicochemical properties is performed using two non-miscible phases, a static and a mobile phase, which are chosen depending on the target molecule . The utilization of HPLC allows for selective and sensitive concentration of target molecules , but requires the development and optimization of the HPLC method, which is time-consuming. Additionally, HPLC requires an extraction step either to extract a hydrophobic drug into an appropriate solvent (liquid-liquid separation) , or to remove any impurities, e.g., plasma protein, or potential degradation products from the hydrogels, from the samples (solid-liquid separation) .

The hydrophobic anticancer drug paclitaxel was quantified using HPLC-UV at 273 nm to quantify its release from a Pinus koraiensis polysaccharide-based hydrogel drug delivery system in PBS . Because of the hydrophobic nature of paclitaxel, a liquid-liquid extraction step was added between the sampling and the HPLC-UV analysis. The release medium was lyophilized; then, paclitaxel was solubilized in acetonitrile. Then, a centrifugation step removed insoluble particles, and the supernatant was injected in the HPLC-UV for quantification . Zhao et al. also used HPLC to quantify paclitaxel from their PLGA nanoparticle embedded in a photopolymerizable polyethylene glycol Di methacrylate (PEG-DMA) hydrogel to treat Glioblastoma multiforme in vivo

2)Mass Spectroscopy:
Mass spectrometry is an analytical technique that detects and quantifies molecules with a high degree of sensitivity and selectivity. It can detect small molecules, as well as peptides, proteins, oligosaccharides,

and DNA fragments . The technique is based on the fragmentation of the molecule of interest into ions that are characteristics of that molecule since every molecule has a unique fragmentation pattern. The ratio of the mass and charge of the detected ion is determined, and thus the technique provides as outputs a retention time and a mass/charge spectra for the target molecule that is used, for comparison with a standard to provide a definite quantification . Mass spectrometry is usually coupled with a molecule separation and concentration unit like HPLC. Then, the separated compounds enter the ion source where they are ionized via electrospray ionization (ESI) or matrix-assisted laser desorption/ionization (MALDI) . The ion(s) mass and charge are detected and quantified. The other advantage of the technique is that it is high throughput owing to embedded auto sampling in most current machines.

This technique is the most selective and sensitive and can detect a wide range of molecules. Yet, its usage remains limited in the drug hydrogel delivery field because the technique requires the appropriate expertise to develop and validate the method as well as being expensive .

3)Quantitative Polymerase Chain Reaction:

The polymerase chain reaction is the gold standard technique for the detection of DNA . The technique is composed of three steps: DNA denaturation, annelation, and extension. Double-stranded DNA is denatured to obtain single-stranded DNA. Then in the annealing phase, the forward and reverse primer hybridize specifically and selectively to a target sequence of the DNA molecule. In the third and last phase, a DNA polymerase enzyme carries out the extension of the primer-target DNA complex. In quantitative PCR (qPCR), also known as real-time qPCR, the quantity of DNA present at each cycle is measured via a fluorescence signal coming either from a specific hydrolysis probe or a non-specific dye that binds to double-stranded DNA following the extension step. This technique is inherently sensitive and very effective but also quite expensive. Real-time (RT)-qPCR was used by Peng et al., who developed a hydrogel to co-deliver resveratrol and a plasmid DNA coding for the VEGF growth factor for the application of wound healing . They characterized the expression of VEGF as a protein in vitro via ELISA assay, but, in vivo, they used RT-qPCR to detect and quantify the presence of mRNA encoding for VEGF. They found that the drug-treated groups were expressing more VEGF compared to the untreated groups and that the increase was incremental over time . This was an indirect way of measuring the release of plasmid DNA by measuring its translation in mRNA hence its efficacy but not an absolute quantitation

- **Evaluation Test Methods for Polymers:**

1 Physicochemical stability and acid/alkali solubility tests

1. Particle size of the test substance Pulverize the test substance into grains as small as possible. 60-80 mesh is recommended.
2. pH range of the test liquid Adjust the pH to 4.0, 7.0, 9.0 and 1.2, as adopted in 111 "Hydrolysis as a Function of pH" in The OECD (Organization for Economic Co-operation and Development) Guidelines for the Testing of Chemicals (OECD Council Decision [C(81)30 Final Appendix 1]).
3. Testing temperature 40±2°C.
4. Light Indoor light.
5. Air Stir the test liquid to facilitate its contact with air.
6. Testing period Two weeks, except for the testing period for pH 1.2, which is 24 hours, considering the retention time in digestive organs.

7. Test concentration of the test substance Set the concentration within the range of 102 -104 mg/l in accordance with the properties of the test substance (1,000 mg/l is recommended).
8. Number of repetitions n=2
9. Analysis Analyse as many of the following parameters as possible at the beginning and end of the test to detect any chemical change. Dissolved oxygen concentration (DOC), weight, molecular weight, infrared absorption spectrum, etc.

2 Solubility in water and organic solvents

(1) Test solvents (1.1) As indices for lipophilicity n-octanol, n-heptane. (1.2) As general solvents Toluene, 1,2-dichloroethane, Isopropyl alcohol, THF (Tetrahydrofuran), MIBK (Methyl isobutylketon), DMF (Dimethyl formamide). (1.3) Water

(2) Testing conditions

2.1:Temperature Stir at 35-40°C and subsequently cool to 25±2°C to achieve equilibrium.

2.2: Testing period Twenty-four hours.

2.3 Test concentrations of the test substance Test at two concentrations, i.e., 200 mg/l and 2,000 mg/l.

2.4 Particle size of the test substance Pulverize the test substance into grains as small as possible. 60- 80 mesh is recommended.

2.5 Number of repetitions Two repetitions.

2.6 Stirring Constantly stir or shake the test liquid to facilitate contact between the test substance and the solvent.

2.7 Analysis Perform a gravimetric analysis. For water, also perform a total organic carbon (TOC) analysis. Perform as many instrumental analyses as possible for other organic solvents depend on the properties of the test substance.

3 Evaluation of solubility

As a general rule, confirm the insolubility of the test substance in nine solvents. If the test substance has been confirmed to be soluble in one of the nine solvents, the remaining eight solvents do not necessarily need to be tested. However, it is recommended that solubility data on at least one solvent from each of the categories 2(1)(1) to (3) are submitted

- **Properties of polymers:**

Physical Properties: The strength and flexibility of polymer depends on properties like Chain length - The polymer is stronger, when the chain length is long.

Cross-linking- The polymer chains are linked together by covalent bonds, and polymer is hard due to this, but takes time to melt

Side groups-the polymer is strong, when polar side groups are present.

Branching-it can be straight branched or unbranched. The unbranched chains pack closely than the branched chains.

Mechanical Properties

Depending on their structure, molecular weight, and inter- molecular forces, polymers resist differently when they are stressed. They can resist against stretching (tensile strength), compression (compressive strength), bending (flexural strength), sudden stress (impact strength), and dynamic loading (fatigue). With

increasing molecular weight and hence the level of intermolecular forces, polymers display superior properties under an applied stress. As far as structure is concerned, a flexible polymer can perform better under stretching whereas a rigid polymer is better under compression. A polymer is loaded and its deformation is monitored to measure its strength.

Crystalline and Amorphous Polymers

Polymers display different thermal, physical, and mechanical properties depending on their structure, molecular weight, linearity, intra- and intermolecular interactions. If the structure is linear, polymer chains can pack together in regular arrays. For example, polypropylene chains fit together in a way that intermolecular attractions stabilize the chains into a regular lattice or crystalline state. With increased temperature, the crystal cells (crystallites) start to melt and the whole polymer mass suddenly melts at a certain temperature. Above the melting temperature, polymer molecules are in continuous motion and the molecules can slip past one another. In many cases, the structure of a polymer is so irregular that crystal formation is thermodynamically infeasible. Such polymers form glass instead of crystal domains. A glass is a solid material existing in a noncrystalline.

Viscoelastic Properties

Mechanical properties of a given polymer are generally measured at a fixed rate of loading, certain temperature or relative humidity, and so on and so forth. Polymers are neither a pure elastic nor a pure fluid material. They have the ability to store energy (display elastic behaviour) and to dissipate it (display viscous behaviour). For this reason, most polymers are viscoelastic materials. For example, poly (vinyl chloride) has a glass transition temperature of about 100°C. This means, it behaves like a solid at temperatures below its T and like a fluid at temperatures above its T. Since a typical PVC product is generally used at room temperature, its T is supposed to be well above the temperature of the environment in which it is expected to serve. In other words, a PVC product behaves like a solid or glass at any temperature (including its service temperature) below its T. Now, assume that your PVC product is expected to serve under a certain load (thermal, mechanical, etc.) and at certain temperature below its T, but for various periods of time. Such a loaded polymer, which originally behaves as a solid, or elastic may change its behaviour upon a long-term loading. Over time, the polymer intermolecular forces will essentially become weaker and hence, the polymer becomes softer. This can be seen in the glass windows used in the old churches as they show different thicknesses from top to the bottom. There are generally two methods to evaluate the viscoelasticity in polymers; the creep test and the stress relaxation test. With the former, the polymer is first loaded with a certain weight and its deformation is then monitored over the time. With the latter, the polymer is first deformed to a certain extent, and then its stress relaxation (internal stress) is monitored with the time.

Conclusion:

Polymers can important role in novel drug delivery system in formulating various doses form in it. Polymers have been used as a main tool to control drug release rate from formulations. They are also increasingly used as taste-masking, stabilizing, and protective agents in oral drug delivery. Polymers can bind the particles of a solid dosage form and also change the flow properties of a liquid dosage form. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials. Polymers are macromolecules

having very large chains, Understanding the basic concepts of polymers provides a foundation for further understanding of drug products and designing of better delivery systems. This review can serve as a valuable source of information for those with little or no background in polymers, researchers in the polymer, pharmaceutics and biomedical areas, as well as pharmacy students.

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