METHODS, TYPES AND APPLICATIONS OF PHARMACEUTICAL POLYMERS

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ABSTRACT
The current review article focuses on polymers in pharmaceutical industry which is use for drug delivery and manufacturing of dosage forms. There are various types of polymers which varies in their classification depending on reaction to temperature, chemistry of synthesis and structure. Different polymers in different methods of manufacturing like bulk polymerization, solution polymerization, suspension polymerization and emulsion polymerization. Some polymers are completely eliminate from body with or without metabolism they are called as biodegradable polymer. Most of them shows issues of biocompatibility with tissues. Because of ease of manufacturing property of controlled drug release they are used in tablet coatings. Polyethylene, poly (ethylene-co-vinyl acetate) have widely use in ocuserts and progestarsarts. Hydrogels are kind of smart polymers which shows variation in properties in response to different environments. Most of the cancer therapies are based on polymer drug conjugates by binding polymers with a drug. Poly-e-caprolactone, poly (lactate-co-glycolate) have importance in liposomes and nanosomal drug delivery systems. Polymers have recent application in progestarsarts, ocuserts, nanoparticles and swelling control release system.

KEYWORDS: Biodegradable Polymers, Initiators, Hydrogels, Ocuserts, Monomer.

INTRODUCTION
After Second World War, polymeric material is one of the fastest growing industry in world. About more than third of research dollar spent on polymeric material. The word polymer came from Greek meaning “many membered”, it means large number of smaller unit or
“mers”. Polymers are majorly applied in five areas: 1) plastic 2) rubber or elastomer 3) fibres 4) surface finishes and coatings and, 5) adhesives.\[1\]

Synthetic and natural based polymers have wide applications in pharmaceutical and biomedical industry. Basic understanding of polymers is helpful for developing better drug delivery system as well as formulations. Modern society having wide range of impact of polymer. The first semisynthetic polymer made was “guncotton” made by Christian F. Schonbein in 1845. Manufacturing process changed due to problems like improving poor solubility, processability, and explosivity resulting in a variety of polymers such as Parkesine, celluloid (plasticized cellulose nitrate), cellulose acetate (cellulose treated with acetic acid), and hydrolysed cellulose acetate soluble in acetone. One of a strong and durable synthetic polymer based on phenol and formaldehyde, was invented. Polycondensation based polymeric products such as Bakelite, in 1872.\[2\]

After 20\textsuperscript{th} century polymers have been used to develop devices for controlling drug delivery or for replacing failing natural organs. In pharmaceutical field polymers used for oral delivery, polymers are used as coatings, binders, taste maskers, protective agents, drug carriers, and release controlling agents. In pharmaceutical industry, oral drug delivery system polymers are applied as binder, taste maskers, as coating agent, protective agent, drug carriers and release controlling agent. For transdermal patch polymers are used as a backings, adhesives, or drug carriers in matrix or membrane products.\[2\]

Most of the polymers are linear chain polymers. They are formed by reaction of monomers containing either carbon-carbon double bond or have two active functional group or difunctionality.\[3\] Based on above considerations polymers are synthesized by various methods like 1) condensation polymerization 2) free radicle addition polymerization or chain-growth polymerization 3) non-radicle addition polymerization 4) copolymerization.\[1\]

**Polymers**

A polymer is a macromolecule composed of a combination of many small units that repeat themselves along the long molecule and first unit is called as monomer and other units called repeating units. Degree of polymerization is length of polymer chain which is specified by repeating unit in chains.\[3\]
The brief explanation of above class of polymers is as

1. **Reaction to Temperature**

   Polymers shows different characteristics based on temperature so they are divided as.

   a. **Thermosets**

   These polymers are soften on heating and flow when stress is applied but don not do reversibly. Heating cause cure reaction in such polymers continuous heating of such type of polymers lead to degradation. Natural rubber is one of the example of such type polymer. Curing reaction of rubber with sulphur called vulcanisation.[1]

   b. **Thermoplastic**

   Some polymers are soften on heating and flow when stress is applied. On cooling they reversibly regain their original shape. Nylon is one of the example of thermoplastic polymers.[1]

2. **Chemistry of Synthesis**

   A monomer is unsaturated; its means it may consist double or triple bond but some have functional groups like ester, aldehyde, ketone, carboxyl, amine, they can interact via condensation polymerization.[2]

   a. **Addition Polymerization**

   They are also known as chain polymerization. Radicle generating agent initiate polymerization. Such polymerization has two important characteristics.
   - No splitting of molecule; hence repeated unit has same chemical formula as monomer.
   - Only opening of double bond take place which forms repeated unit.

   Monomers containing C=C bond shows such type of polymerisation. Each radicle have ability to attack double bond. In this manner radicle is transferred to monomer and monomer radicle is produced. Such step is also called initiation. In such way one monomer attached to another monomer and this again attached to another monomer is called as propagation. Example acrylic acid, acrylamide and acrylate salt.[2,4,5,6,7,8]

   b. **Condensation polymerization**

   Two or more monomers having different functional groups react with each other shows condensation polymerization. Most common esterification reaction are condensation
polymerization. Example- when x molecule of diaols react with x molecule of diacid forms condensation polymers. The linkage $\overset{\text{C}}{\text{O}}\overset{\text{C}}{\text{O}}$ characterizes polyester. Where x is degree of polymerization.

Diamine react with diacid gives polyamide or nylon, poly-condensation of amino acid gives lactum.\textsuperscript{[1,2]}

3. Structure
There are three major structural categories of polymers as follows.

1. Linear
This polymer are made up of difunctional monomers, these resulting polymer chains are long, flexible, essentially one dimensional structure.

They are classified as random and block polymers.
- Random polymers- in these polymers having single repeating unit is called homopolymer.
  
  It is represented as–
  
  $\overset{\text{AAAAAAAAAAAAAAAAAA}}{\text{AAAAA}}$

Polymer having two or more repeating unit is called copolymer. It is represented as–

$\overset{\text{AAABABBABABBA}}{\text{AAAAAA}}$

And it is called poly (A co B). Example-pluronic surfactant.

- Block polymer-such linear polymer are form by contagious repeating unit called block polymer.

$\overset{\text{AAAAAAAAABBBBBBB}}{\text{AAAAAA}}$

2. Branched- when the repeating unit grafted on network of linear polymer, resulting polymer is branched or graft polymer.

3. Cross linked – as branching increases the repeating unit with network of polymer chain also increases. A tremendous molecule form by crosslinking network of such repeating unit in three dimensional structure is called cross-linked. Example - Poly (hydroxyethyl methacrylate).\textsuperscript{[1]}
METHODS OF POLYMERISATION
Polymerization methods involves bulk polymerization, solution polymerization, suspension polymerization, emulsion polymerization.

1. Bulk polymerization - bulk polymerization process involves liquid monomer, monomer soluble initiator and perhaps chain transfer agent. Increase in concentration of polymer increases the rate of polymerization as per classical kinetic principle, the process called as auto-acceleration or Tromsdorff effect.¹,⁹

The propagation reaction in such approach involves the approach of small monomer molecule to a growing chain end where in termination ends of two growing chain occur. As concentration of polymer increases it is difficult for growing chain to drag there chain from entangled mass of dead polymer it is difficult for monomer molecule to pass through reaction mass. Thus, rate of termination reaction depends on nature of chemical reaction and reactant can diffuse together. Because of there is no space for heat evolved due to effect of viscosity of polymer mass the overall heat of system increases.¹,⁹

Advantages.¹,⁹
a. Because only monomer, initiator, and chain transfer agent are use that’s why purest possible polymer is obtained.
b. It provides greatest possible polymer yield.

Disadvantages.¹,⁹
a. Reaction is difficult to control.
b. Neat to keep under control, may have to run slowly.
c. It is difficult to get high rates and average chain length polymers.
d. It can be difficult to remove unreacted polymer.

2. Solution Polymerization - inert solvent is use in solution polymerization it reduces tendency of auto-acceleration in free radical addition. The heat of polymerization conveniently and efficiently removed by refluxing the solvent.¹,⁹

Advantages.¹,⁹
a. Easy heat removal and control.
b. As reaction follows known kinetic principle, the design of reactor system is facilitated.
c. Desired polymer solution obtained directly from reactor.
Disadvantages.[1,9]
a. Rate and average chain length are proportional to monomer concentration the use of solvent lowers them.
b. Large amount of flammable expensive and toxic solvent require.
c. Separation of polymer and its recovery requires additional technology.
d. Traces of solvent removal is difficult.

3. Suspension polymerization
In this polymerization monomers is suspended in the form of droplet 0.01 to 1mm in diameter in an inert, non-solvent liquid, because of small droplet size heat removal is not problem.[1,9]

- Monomer phase.
  Monomer (water insoluble).
  Initiator (monomer soluble).
  Chain transfer agent (monomer soluble).

- Water.
- Suspending agent.
  Protective colloid.
  Insoluble inorganic salt.

Protective colloids is water soluble having function to increase the viscosity of continuous water phase. Magnesium carbonate collects at droplet-water interphase by surface tension and prevents coalescence of drops upon collision. About 1/2 and 1/4 monomer water volume ratio of monomer phase is suspended in water.[1,9]

The size of product beads depends on strength of agitation, as well as nature of monomer and suspending system. In between 20-70% conversion agitation critical. Below this range organic phase is still enough to disperse and above this range particles are rigid enough to prevent agglomeration and if that agitation stops or weakens between this limit that sticky particle will agglomerate in large mass so as polymerization is completed.[1,9]

Advantages.[1,9]
a. Heat removal and control becomes easy.
b. It is possible to obtained polymer in a convenient, easily handled and directly useful form.
Disadvantages.[1,9]

a. Per reactor volume yield less.
b. Some less pure polymer than bulk polymerization remain bound to remnants of suspending agent adsorb on particle surface.
c. It cannot used to make condensation type of polymerization or Ziegler-Natta polymerization.

4. Emulsion polymerization

It is in form of latex having particle size in order of 0.05 to 0.15 µm stabilized by soap. Two examples of such polymers are “white glue” and latex paints. The very small size of latex provides short diffusion path for removal of small molecules from polymer. The simplest method for recovery of polymer is spray drying. Latex is cream by adding material like acetone which is less partial for polymer it causes particles to become sticky and causes some agglomeration. The resulting latex is coagulated by adding and sulphuric acid which converts soap to insoluble hydrogen form. Addition of electrolytes salt disrupts stabilizing double layer on particle which causes agglomeration by electrostatic attraction. Emulsion polymerization pretty much restricted to free radicle addition of water insoluble, liquid monomers such as butadiene and vinyl chloride. When hydrophilic monomer disperse in continuous hydrophobic phase produces inverse emulsion polymerization.[1,10]

Advantages.[1,10]

a. Reaction mass viscosity is less than true solution of comparable polymer, the reaction mass is refluxed in which water adds heat capacity therefore viscosity is controlled.
b. High average chain length and high rates of polymerization are obtained by the use of soap and initiate a concentration.
c. Latex is valuable in obtaining uniform compounds through master batching.
d. Small size particles of latex allows low residual monomer level.

Disadvantages.[1,10]

a. Obtaining pure form from such type of polymerization is difficult. The tremendous surface area provides plenty of room for adsorbed impurities.
b. Novel technology is required to recover solid polymer.
c. Water lowers the yield per reactor volume.
d. Emulsion polymerization is not use for making condensation polymers, or ionic or Ziegler-Natta polymerization.
Variety of polymers

1) Biodegradable polymers

These are the polymer which degrade in vivo and in vitro into a products that are normal metabolites of body or products which are completely eliminated from the body with or without metabolic transformations. The basic criteria behind selection of such type of polymer are that its degradation products should be non-toxic and rate of degradation. The biocompatibility of bio degradable polymer is its ability of material to perform host tissue response in a specific application.\(^{[11,12,13]}\)

Biodegradable polymers are broadly classified into natural and synthetic, depending on their original. Natural polymers have excellent biocompatibility so use as choice for biomedical application. They are biodegraded by enzymatic or hydrolytic polymer mechanism. Synthetic polymer have great flexibility that’s why it is possible to develop polymers having wide spectrum of properties and excellent reproducibility.\(^{[13]}\)

A. Synthetic biodegradable polymers

- **Aliphatic polyesters**
  Poly(glycolic acid), poly(lactic acid), poly(L-lactic acid), poly(DL-lactic acid), poly(caprolactone), poly(lactide-co-glycolide), polydioxanone, polyglyconate, BAK, polypropylene fumarate, poly(ester carbonates), poly(ethylene glycol), poly(butylene terephthalate), poly(D-lactic acid).

- **Poly(ortho esters)**
  Poly(ortho ester I), Poly(ortho ester II), Poly(ortho esterIII), Poly(ortho ester IV).

- **Polyanhydrides**
  Poly(sebacic anhydride), poly{(carboxy phenoxy)propane-sebacic acid}, poly(anhydride-co-emide).

- **Poly(alkyl cyanoacrylates)**
- **Poly(amino acids)**
  Poly(imino carbonate).
• Polyphosphazenes
• Polyphosphoestrs
Poly{bis(hydroxylethyl)terephalate-ethyl ortho phosphorylated / terephtaloyl chloride}.

B. Natural biodegradable polymers
• Polysaccharides.
• Cellulose- methyl cellulose, hydroxylpropyl methyl cellulose, hydroxylpropyl cellulose and carboxyl methyl cellulose.
• Starch.
• Alginic acid.
• Hyaluronic acid.
• Chitin and chitosan.
• Collagen.
• Gelatin.
• Albumin.

2) Rubbers
Rubber have unique elongation property, they can be stretch and can be loaded with static and dynamic load under several conditions. Different rubbers have different properties. Examples- isoprene and butadiene offers resiliency. Some are resistant to oil. Examples- chloroprene and nitrile butyl rubber are air impermeable rubber. Silicone rubber is very inert with no affinity to any material. That’s why it is used as an implants.[1,2]

3) Plastics
Plastics has glass transition temperature, which is above the room temperature as to oppose elastomers. Various techniques such as injection moulding, extrusion and thermoforming and use to manufacture plastic in there molten state. Polymer such as polystyrene, polypropylene and polyethylene are used as a packaging materials.[1,2]

4) Fibers
Such type of polymers have very sharp melting point in pharmaceutical industry widely used fibers are cellulose acetate, rayon, polypropylene, polyamide, nylon.[1,2]
5) **Adhesives and coatings**
It has applications in tackiness and adhesiveness. It has mean for adhesive forces should be balance with cohesive forces. Very polar adhesive materials are epoxy and cyanoacrylates. Adhesives are generally use for transdermal patch. Coatings are mostly use for protection purpose. Coating materials are poly(vinyl acetate), acrylates esters, ethyl cellulose.\(^{[1,2]}\)

**Applications of Polymers**

1) **Polymers in Tableting**
Tablet is kind of solid dosage form which is prepare by compressing therapeutically active ingredient with pharmaceutical excipients. Manufacturing polymers most widely used binders and disintegrating agents. Methyl cellulose (Methocel), starch, gelatin, PVP, EC and HPMC are used as tablet binder. Hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) use as a coating agent. Disintegrants initiates disintegration of tablet by increasing surface area of particles. Carboxymethyl cellulose (Ac-Di-Sol), starch, PVP and sodium CMC are use as super disintegrants. MCC enhances compressibility of tablet.\(^{[1,14,15]}\)

2) **Polymers in Capsule**
Capsule are generally composed of gelatin. The composition of gelatin get varied so gelatin are of two types that is hard gelatin and soft gelatin. Fillers such as MCC and starches are used to fill up the volume in capsule. To overcome problem of aggregation various polymers such as starch and sodium starch glycolate are mixed with capsule container.\(^{[1,14,15]}\)

3) **Polymers in disperse system**
It is heterogeneous thermodynamically unstable liquid system in which drugs substances either solid or liquid is disperse in dispersion medium. Example of pharmaceutical dispersion system are suspensions, emulsions, creams, ointments and aerosols. Alginates carrageenan and xanthan gum are naturally occurring dispersing agents, while poly (acrylic acid), PVP, PVA and cellulose ethers are semisynthetic agents.\(^{[1,16,17]}\)

4) **Polymers in gels**
Gel system consist of physical or chemical cross-linked between adjust polymer chain restrict chain mobility. Gel has rheological properties. Cross-linked gels are most commonly known as hydrogels. They are also known as smart polymers because they shows different gelling properties in different environment of water. Most commonly used hydrogels are poly (hydroxyethyl methacrylate), poly (methacrylic acid) and poly (acrylamide). In
pharmaceutical industries cross-linked gels are primarily use for local drug delivery of drugs to skin, oral cavity, vagina and rectum.[14]

5) **Polymers in transdermal drug delivery systems (patches)**

Transdermal drug delivery system generally use for delivery of therapeutic agent across skin to systemic circulation. System has several applications in pain management, cessation of smoking, heart diseases and hormonal replacement. In transdermal drug delivery system polymers are used as protective coverings and adhesives. Adhesives used are acrylates silicones and polyisobutylates.[14,19,20]

6) **Polymers in ocuserts**

Ocusert is use in treatment of eye disorders like glaucoma. The one example of ocusert has been design in release either 20µg h⁻¹ or 40µg h⁻¹ of therapeutic agent (pilocarpin) for the period of 7 days from implantation. Ocusert is elliptical shape implant having several layers. Poly (ethylene-co-vinyl acetate) is used to prepare pilocarpin ocusert.[14]

7) **Polymers in progestasart system**

Progestasart intra-uterine device is the example of controlled drug delivery system medicated implant use for contraceptive purpose. The drug release from progestasart occurs by diffusion polymer act as a rate controlling membrane for drug release. Polyethylene and poly(ethylene-co-vinyl acetate) are used in such system.[14]

8) **Polymers in swelling controlled system**

Swelling controlled release systems are physically cross-linked and chemically cross-linked. Chemically cross-linked are termed as hydrogels example- poly (hydroxyethylmethacrylate) have use in controlled drug release. Hydrophilic polymer example-HPMC. It is also use as a controlled release hydrogel.[1,14,20]

9) **Polymers in drug conjugates**

It is one of the strategy for improved delivery of therapeutic agent. The conjugate of polymer and drug composed of drug that is bound covalently to polymer. Strategy of polymer drug conjugate use especially in the field of cancer therapy which is known as ‘polymer therapeutics’. Biodegradable polymer are preferred although non-biodegradable synthetic polymer such as PEG and poly (hydroxylpropylmethacrylate) preferred mostly. The easiest
way of attaching drug to macromolecule by direct attachment without spacer. HPMA-doxorubicin and HPMA-paclitaxel undergone in clinical trials.\textsuperscript{[14,21]}

10) Polymers in nanoparticles
Nanoparticles have size range of 10-1000nm. In nanoparticle drug delivery system drug is attached, entrapped and dissolve to polymeric matrix. Polymeric nanoparticles are used for sustain drug delivery system. Both biodegradable and nonbiodegradable polymers are used as diagnostic agent apart from delivery devices. This biodegradable polymers degrade into nontoxic and biologically active substances. They are also useful as drug carries in nanoparticle drug delivery system. This biologically active substances may metabolised and removed from the body through the normal metabolic pathway. Example of synthetic biodegradable polymers are poly lactide, poly(lactide-co-glyolide), poly-\(\epsilon\)-caprolactone and polyanhydrides.\textsuperscript{[22,23,24]}

TABLES

Table 1: Classification of Polymers\textsuperscript{[1]}

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Type of Polymer Depending On</th>
<th>Types</th>
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</table>
| 1.     | Reaction to Temperature     | 1. Thermosets  
|        |                             | 2. Thermoplastic |
| 2.     | Chemistry of Synthesis      | 1. Condensation  
|        |                             | 2. Addition |
| 3.     | Structure                   | 1. Linear  
|        |                             | a. Random  
|        |                             | b. Block  
|        |                             | 2. Branched(Graft)  
|        |                             | 3. Cross-linked |

CONCLUSION
Polymers have various beneficial role in preparing pharmaceutical formulation. Care should be taken to properly select polymers in designing drug delivery system. Polymers should be cost effective, biocompatible, less toxic and multifunctional. Bulk polymerization, solution polymerization, suspension polymerization, and emulsion polymerization are cost effective and sophisticated for manufacturing of polymers, because of control release nature, disintegrating, adhering and protective properties polymers are used in different application based on type or nature in tableting, capsule, disperse system, drug conjugates and in nanoparticles.
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