Role of Polymers in Exploring Modified and Sustained Release for Intradermal Drug Delivery

Ritika Puri\textsuperscript{1*}, Chandan Sharma\textsuperscript{1}, Dr. Manish Goswami\textsuperscript{1}
University Institute of Pharma Sciences, Chandigarh University, Gharuan (Punjab)

Abstract
Biodegradable polymers have an extensive history in Pharmaceutical field. Polymer being macromolecules possess long chains, a number of functional groups, blend of low molecular and high molecular weight substances and could be customized for various applications depending upon the chemical structure of the monomers. Polymers exhibit unique properties which cannot be attained with any another material till date. Biopolymers such as cellulose, chitosan are used in drug formulations with extended and sustained drug release. The objective of sustained release system is to deliver the drug at a predetermined rate to a specific site, reduction in dosing frequency, minimization of side effects and enhanced patient compliance. In this review, there is major highlight on origin of polymers and various biodegradable polymers used in intradermal drug delivery systems and their major characteristics.

Keywords: Biodegradable, Sustained release, Targeted drug delivery


Introduction
Oral intake of the drug is considered to be the simplest mode of administration. However, its limitations include low bioavailability mainly because of the first pass metabolism and enzymatic degradation of the drug. Certain biomolecules that include peptides, vaccines, and proteins are the large constituents of the newer drugs and are promising for the future of therapeutics. \cite{1,2} If most of the biotherapeutics are taken by injections in the skin that usually causes pain and might even lead to infections in severe cases. Another option is the intradermal drug delivery that is made using biodegradable polymer needles.

The impact of polymers on the society is wide ranging. In 1845, the first semisynthetic polymers guncotton was made by Christian F. Schonbein. With time, the polymer experienced change in its manufacturing process because of its poor properties like processability, explosivity, and solubility. As a result of changes made in the manufacturing process, a variety of different polymers were formed. These include Parkesine, cellulose acetate which is cellulose treated with acetic acid, celluloid that is plasticized cellulose nitrate, and hydrolyzed cellulose acetate that is soluble in acetone. Another durable and strong polymer, Bakelite which is based on phenol and formaldehyde was formed in 1872. Later on, many synthetic polymers were invented; these are poly (vinyl chloride)
in 1933, polyamide in 1935, synthetic rubbers in 1942, polyethylene in 1933, polystyrene in 1933, and Teflon in 1938. The use of Polyethylene was made for the making of radar equipment for airplanes. Also, the use of polyethylene was made by British Air Force to ensure the insulation of electrical parts in the radar of the airplanes. Also, with the duration of formation of synthetic rubbers as almost 1 hr in comparison to 7 years in case of natural rubbers, it was used in the making of tires and other military supplies. Also, for the separation of hot isotopes from Uranium, Teflon is used. Moreover, silk that was initially imported from Japan was replaced in the making of parachutes with Nylon. [3]

With the advancement in technology, the plastic revolution in the 20th century has opened many newfields in the biomedical and pharmaceutical sectors. The use of the polymers is recently done to make devices to control the drug delivery and also for the process that includes the replacement of natural human organs failed. In case of oral delivery of medicines, these polymers are used in various forms that include binders, protective agents, drug release controlling agents, coatings, taste maskers, and drug carriers.

For the drug that requires to be targeting at the lower areas of the gastrointestinal tract for instance the large or the small intestine, polymers have been used for the protection of such drugs from the harsh environment in the stomach during its passage. Polymers are used in transdermal patches as adhesives, backings, and drug carriers for membrane products. Also, biodegradable polymers are made use of during the controlled delivery of proteins and peptides. After the insertion in the skin, the drug is inserted inside the polymer microneedles when the biocompatible polymer dissolves easily for the release of encapsulated cargo without the requirement of any removal and without leaving behind of any biohazardous sharps.

**Polymers for Pharmaceutical Applications**

Polymers are used as tablet binders for the binding of tablets excipients in the traditional pharmaceutics area. Also, advanced pharmaceutical dosage forms make use of polymers for the taste making, controlled release, drug protection, increase drug bioavailability and targeted delivery.

The liquid dosage form of the polymers is used as rheology modifiers other than the usual solid dosage forms. They have found their usage in the controlling of viscosity of an aqueous solutions or stabilizing suspensions. This can also be used for granulation step included in the formation of solid dosage forms. The polymers are used in the current pharmaceutical field, majorly for the controlled release of the drugs. Also, these polymers are used as implants in the biomedical area, for providing long term services. And in order to use them on a long term basis, it is made sure that the polymers used are unique in the properties as compared to their general applications.
Biodegradable Polymers:

Natural biodegradable polymers

The natural biopolymers occur naturally during the growth cycles of organisms. Various reactions of enzyme chain polymerization of activated monomers are involved in the synthesis of polymers. Their formation is a result of complex metabolic processes within the cells.

Figure 1: Classification of Biodegradable Polymers

1) Cellulose:

Cellulose consists of a polymer chain comprising unbranched β (1, 4) linked D-glucopyranosyl units. The source of the cellulose is the deciding factor for the β (1, 4) glucan chain length. It is one of the main constituents of the cell wall, found in the secondary wall. Inter and intra-molecular hydrogen bonds are formed by the presence of three – OH groups present at C2, C3, and C6 positions. As a result of the strong tendency of inter and intramolecular hydrogen bond formation, bundles of cellulose molecules come together to form microfibrils, that are responsible for the formation of less ordered (amorphous), and highly ordered (crystalline) regions.

However, cellulose makes the major component of the cell wall mainly in the plant containing lignocelluloses, its content largely depend on the factors like the growing environment, plant species, maturity, growth, and the position. In general, lingo-cellulosic plant contain around 23 to 53% of cellulose content which is relatively less than the cotton; comprising up of cellulose purely comprising of fibers. Although, this highly crystalline polymer with higher molecular weight, cellulose is not fusible as well as not soluble in all the solvents, but certain solvents that are insistent mostly in breaking hydrogen bonding such as N-methylmorpholine-N-oxide can dissolve it to some extent.

http://doi.org/10.36295/ASRO.2020.231546
extent. As a consequence of the insolubility and infusibility properties of cellulose, it can be easily converted into its various derivatives in order to make them more processable. The presence of more than three hydroxyl group in each repeating unit of glucopyranoside gives cellulose as an important derivative.\([5]\)

![Structure of Cellulose](image)

![Structure of Chitosan](image)

Figure 2: Structure of Natural Polymers

Table 1 showing Cellulose based Polymers:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymer</th>
<th>Brand Name</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cellulose</td>
<td></td>
<td>Insoluble in water due to the presence of hydrogen bonding</td>
</tr>
<tr>
<td>2</td>
<td>Ethylcellulose</td>
<td>Ethocel(^\text{®})</td>
<td>Insoluble in water; has applications in sustained release formulations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aqualon(^\text{®})</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Hydroxyethyl cellulose</td>
<td>Natrasol(^\text{®})</td>
<td>Soluble in aqueous (water) and organic solvent such as alcohol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tylose(^\text{®})</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Hydroxypropyl cellulose</td>
<td>Nisso HPC(^\text{®})</td>
<td>Water soluble. Useful in film coating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Klucel HPC(^\text{®})</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Hydroxypropylmethyl cellulose</td>
<td>Walocel(^\text{®}), Hydrocel(^\text{®})</td>
<td>Water soluble at a temperature less than 60 degrees. It exhibits gelling properties.</td>
</tr>
<tr>
<td>6</td>
<td>Carboxymethyl cellulose</td>
<td>Akkucel(^\text{®})</td>
<td>Soluble in water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depramin(^\text{®})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bermocell(^\text{®})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabroil(^\text{®})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staflo(^\text{®})</td>
<td></td>
</tr>
</tbody>
</table>
2. Chitosan

A polysaccharide, that is found in the shell of shrimps, crabs, and other insects is also called as Chitin and it can also be generated by various fungal fermentation processes. Deacetylated derivative of chitin is termed as Chitosan. Also, chitosan form the basic constituent of the exoskeleton in various arthropods. Chitosan is considered as a polysaccharide which is linear and consisting of β (1-4) linked with D-glucosamine exhibiting N-acetylglucosamine groups at random locations largely depending on the extent of de-acetylation taking place in the polymer. However, water soluble chitosan is insoluble in its native form. Due to the solubility of Chitosan in weekly acidic solutions, cationic polymers with high charge density are formed. Moreover, they can even form polyelectrolyte complexes with variety of anionic polymers.

In the pharmaceutical industries, various chitosan-based polymeric drug carriers are being utilized for the delivery of proteins/peptides, antibiotics, anticancer agents, growth factors, and other drugs. In addition to this, they are used as strategy in gene therapy as well as vaccine delivery.

In vitro degradation of Chitosan is done by using the enzymes like lysozyme, chitosanase, and papain. Lysozyme results in the in vivo degradation of chitosan that happens when the acetylated residues undergo hydrolysis. The degree of crystallization and acetylation of the polymer is contrariwise proportional to the rate of degradation of chitosan. Lower degradation rates are exhibited by the highly deacetylated forms that can last for several months in vivo.

Other than this, the solubility and the degradation rate can be significantly affected by the chemical modification of the chitosan and the same process is responsible for the production of materials with a variety of mechanical and physical properties.

Synthetic Biodegradable Polymers:

This class of polymers is expansively considered because of its synthetic versatility and diversity of the biodegradable polymers. This makes use of a large variety of monomers. The routes for the development of synthetic polyesters are many butpolycondensation of the bifunctional monomers low molecular weight polymers can be yielded preferentially. Polymerization by ring opening is preferential if high molecular weight polymers are required.

Also, biodegradable polymers formed as a result of polymerization by ring opening reactions involves lactones. The reason behind the extensive investigation of the aliphatic polyesters is that they are the only biodegradable compounds exhibiting high molecular weight which are made biodegradable by their hydrolysable ester bonds.

a) Polyglycolic Acid(PGA):

PGA is the polyester which is aliphatic in nature and is prepared by the ring opening polymerization of glycolide, and cyclic lactone. PGA is insoluble in most of the solvents which are organic in nature because of its highly crystalline nature and crystallinity of 45-55%. The glass transition temperature of PGA is 35-40 °C and its melting point is as high as 220-225 °C.
In spite of excellent mechanical properties, it has limited biomedical applications. The yielding of acidic products is a result of its lower solubility and higher extent of degrading. As a consequence of which, glycolide is copolymerized with trimethylene, lactide or caprolactone are prepared for use in medical devices. [13][14]

b) Polylactic acid (PLA):
PLA is gained from lactide via its ring opening polymerization; which is a lactic acid cyclic dimer of or from polycondensation of D- or L-lactic acid. Also, it is available in two optical forms that are L-lactide and D-lactide, where the L-lactide is the natural isomer and the DL-lactide is the synthetic mixture. Because of the presence of methyl groups in the side chain, PLA is a hydrophobic polymer. It also results in steric shielding effect and thus PLA offers more resistance to hydrolysis than PGA. Representative commercial PLA has a typical glass transition temperature as 63.8 °C.[15]

Also, the physical properties and biodegradable nature of the PLA can be attained and regulated by racemization of D- and L- isomers or by engaging a hydroxy acid co-monomer component.[16]

To favor the crystallization and improve the chain mobility PLA can be plasticized. However, the poor thermal stability and the brittleness add to the disadvantages of PLA.[17]

c) Poly Lacticglycolic Acid (PLGA):
The use of DL-lactide (L) and L-lactide has been done for polymerization with glycolic acid monomers (G). Different ratios of poly(lactide-co-glycolide) are developed on commercial levels such as 50:50, 85:15 and 75:25 under the brand names Expansorb® and Resomer®. With the increase in the ratio of monomer L/G, the rate of degradation of copolymer decreases.

d) Polycaprolactone (PCL):
PCL is a comparatively cheaper cyclic monomer. In the presence of catalyst tin octoate semi-crystalline polymer having linear structure is obtained via ring-opening polymerization of ε-caprolactone.[18]

Wide range of solvents can easily dissolve PCL into them. The melting point of PCL is 60 – 65 °C and it has a very low glass transition temperature that is -60 °C.

The tensile strength of PCL is as low as 23 MPa. Also, PCL occurs as a less rigid material at the room temperatures, with its modulus ranging from low as well as high density polyethylene. PCL majorly finds its usage in polyurethane formulations as a compatibilizer.

As PCL can be easily biodegraded with fungi and enzymes,[19], several copolymers with glycolide or lactide have been prepared for improving the degradation rate.[14]

e) Polybutylene Succinic Acid (PBSA):
PBSA is a member of poly (alkenedicarboxylate) family. It is formed as a result of polycondensation reactions of ethylene glycol or 1,4- butanediol with certain aliphatic dicarboxylic acids.[20]
PBSA is formed with the addition of adipic acid. The molecular weight of this can range from many tens to hundreds of thousands. However, the molecular weight can be further increased by the addition of small amounts of coupling agents which can be used as chain extenders. \[21\]

The rate of biodegradation and the properties of the copolymers are largely influenced by the nature of diols and diacids used \[22\][20]. The melting point of PBS, which is a white crystalline thermoplastic is around 90 – 120 °C. The glass transition temperature of PBS lies between the Tgs of polyethylene and polypropylene and is -45 °C to -10 °C. \[23\][24] With its mechanical properties resembling polypropylene or polyethylene PBS suffers from insufficient bioactivity for medical applications, and biocompatibility.

Plasma treatment is used to amend the surface of PBS. \[25\] With the addition of secondary component (adipate) the tensile strength of the polyester decreases, showing a affinity comparable to that of the other physical properties. It has been observed that PBS shows the highest tensile strength, while its different copolymers PBSA(60/40) and PBSA (80/20) show improved elongation. \[26\]

\[f\] Poly(p-dioxanone) (PPDO):

This is aliphatic polyester that has excellent physical properties. PPDO is semi crystalline formed as a result of the ring opening polymerisation of \(p\)-dioxanone. Moreover, its glass transition temperature is very low ranging between -10 °C to 0 °C. \[27\]

With the investigation of properties of PPDO with different molecular weights, it was inferred that the increase in the molecular weight improved the thermal stability of this aliphatic polyester. As per the rheological tests results, PPDO shows shear-thinning behaviour. Also, with the increase in the molecular weight, the modulus and the tensile strength of PPDO increased. And because of the presence of polyester chains and ester bonds it has ultimate biodegradable properties.

As many of the microorganisms in nature can degrade PPDO, this can be put to great use. Moreover, with the chain extension of PPDO with PBS newer biodegradable polyester was prepared with the use of Toluene diisocyanate as chain extender. Both polymers used in the process have good compatibility. \[28\]

**Aromatic copolyesters**

Although, variety of copolyesters and polyesters have been developed making the use of with aliphatic monomeric units of various sizes there mechanical properties are comparatively lower than the non biodegradable polymers.

Other than this, these aromatic polyesters have resistance to microbial and enzymatic attack other than hydrolytic degradation and for the same reason of their improvement and aliphatic-aromatic copolyesters were made.

These contain a mixture of aromatic and aliphatic monomers. These Aliphatic-aromatic copolyesters are usually based on terephthalic acid. \[29\]
Table 2: Example of Aromatic Copolyesters:

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>poly(butylene adipate-co-terephthalate)</td>
<td>Ecoflex®</td>
<td>BASF, Germany</td>
</tr>
<tr>
<td></td>
<td>Easter Bio®</td>
<td>Eastman Chemicals, USA</td>
</tr>
<tr>
<td>Poly (ethylene terephthalate)</td>
<td>Biomax®</td>
<td>Dupont, USA</td>
</tr>
</tbody>
</table>

a) Polyamides and polyesteramides
The amide bond present in the Polyamides is similar to that of polypeptides. However, they contain strong chain interactions and have high crystallinity making their rate of biodegradation comparatively lower than the polypeptides.\(^{[30]}\)

The degradation of the low molecular weight oligomer is possible due to the microorganisms and the enzymes. With the help of copolymerization to introduce side groups like benzyl, hydroxyl and methyl biodegradation can be increased to some extent.

Copolymers that contain amide and ester groups can be readily degraded. And as the ester content increases in the copolymer molecule, the rate of its degradation increases. The synthesis of Aliphatic polyesteramides is done by 1,6-hexanediol, glycine and diacids with −CH\(_2\) groups varying from 2 to 8 in number\(^{[31]}\). Highly crystalline polymers are formed as a result.

Another series is formed using adipic acid, 1,2-ethanediol, and amino acids that include phenylalanine and glycine\(^{[32]}\).

However, in all these cases, high susceptibility to enzymatic degradation was shown.\(^{[33]}\) Also, the rate of degradation can be controlled by the modification of phenylalanine:glycine ratio. A polyesteramide blend that is based on phenylalanine or leucine is Cameo.

In 1995, Bayer (Germany) introduced first commercial polyester amide, Bak 1095®. However, its production was halted in the year 2001.

The mechanical and thermal properties of Bak 1095® are similar and quiet close to polyethylene.\(^{[34]}\) It is based on butanediol, caprolactam, and adipic acid. Some other characteristic of Bak 1095® are its tensile strain at break and high toughness. Bak 1095® possesses 125 °C and its crystallization temperature is 66 °C. With the low crystallization rate it is not suitable for use in the injection moulding. So, another grade was launched in 1997 that is Bak 2195®, developed specifically for use in the injection moulding. The melting point of Bak 2195®, is 175 °C and its crystallisation temperature is 130°C.\(^{[35]}\)
b) Polyurethanes

With multiple applications of physical and chemical properties, Polyurethane is extensively designed and formulated in a way to meet the ever changing demands of modernized technologies. These include adhesives, foams, coatings, fibre and various thermoplastic elastomers. Three constituents are used for the preparation of Polyurethanes, these include, a polyol, a diisocyanate, and any chain extender. The formation of segmented polymers with alternating hard and soft segments is formed by the reaction of these components together.

When polyether polyols and polyester polyols form the soft segments, the hard segments are formed from the chain extender and the diisocyanate. Also, the chemical nature of the segments plays a major role in determining the biodegradation of polyurethanes.

However, the calculated appropriate choice of soft segment can tailor the degradation process. The Polyether-based polyurethanes do not undergo biodegradation. However, in case the polyol is a polyester, polyurethanes get readily biodegraded.

PLA, PGA, and PCL are some of the biodegradable polyesters used in the process. It has been assumed that the degradation rate largely depends on the soft segments located at the esters bounds. It is not easy to hydrolyze the urethane bound located in hard segment. Therefore, the need for the synthesis of the Novel biodegradable poly(ester urethane)s was felt. It consisted of poly(butylene succinate) and poly(Lactic acid) blocks. The preparation is the result of a chain extension reaction of PBS prepolymer and dihydroxyl terminated PLLA. The chain extender used for the preparation is Toluene-2,4-diisocyanate. PBS Segment caused the crystallization of the copolymer. Also, the incorporation of the PBS segment improved the extensibility of PLLA.

The second preparation uses chitin /1,4-butane diol blends. The preparation starts with the synthesis of 4,4-diphenylmethane diisocyanate and prepolymer of poly(ε-caprolactone). The extension of the prepolymer was done through 1,4-butane diol and chitin. The variations have been made in the mass ratio of these two extenders. The mechanical properties of the prepolymer were considerably improved with the increase in the content in chitin. However, the recent studies have shown that the biodegradability of the prepolymer are influenced by the nature of the change extender.

Also, one can expect easy degradation of the hard segment of the polyurethane with the introduction of chain extender with hydrolysable ester linkage.

The reason behind the introduction of aliphatic biocompatible diisocyanates was the toxic nature of most of the common isocyanates. The preparation of Poly(ester urethane)s can be accredited to the reaction of lysine diisocyanate with polyester diols based on ε-caprolactone or lactide.

Also, with the replacement of polyl with renewable sources, like vegetable oils for the synthesis of waterborne urethane materials, environmental protection can be ensured. A newly synthesized waterborne polyurethane made
use of rapeseed oil as a soft segment.[^44] The oil has attained a widespread use, including its end products from refined biodiesel fuel to margarine and from meals for livestock to environmentally friendly lubricants. Another vegetable oil that can be used for the formation is the castor oil. This resulted in excellent mechanical properties like elongation at break [520 (±20%)] and tensile strength [9.3G (±1.5 MPa)]. Later on these waterborne polyurethane helped in the modification of plasticized starch for the preparation of high performing novel biodegradable materials.[^44][^45]

c) **Polyvinyl pyrrolidine (PVP)**

PVP is used as the structural material for micro needles of parenteral drug delivery system for many reasons. Firstly, the vinyl pyrrolidone monomer in its chemical backbone structure contains a ring. This ring is responsible for providing mechanical strength to the polymer by increasing the intramolecular rigidity. This rigidity is responsible for the insertion of microneedle in the skin. Secondly, the high water solubility of PVP ensures its rapid dissolution after it is inserted in the skin. Thirdly, PVP has been used as a blood plasma expander since long.[^46][^47] Also, due to the liquid form of vinyl pyrrolidone monomer at ambient conditions the processing can be done even at mild temperatures. This processing does not require any organic solvent for the filling of microneedle mold.

**Conclusions:**

The therapeutic efficiency of the drug has experienced a significant improvement in the sustained drug delivery system. The key performers of the sustained drug delivery system are the drug release retarding polymers. Specific and successful investigation has been made with the polymers to employ them in various forms of solid, liquid, and semi-solid dosages. Moreover, they are considered to be very useful in the targeted drug delivery system. In such situations desire the use of biodegradable polymers as they degrade in the body to more compatible and biologically inert molecules. By incorporating the drug in biodegradable polymers, helps in the release of the drug over a prolonged time period. In review contains a thorough investigation of both the synthetic and natural for controlled, sustained and modified release formulations in the modern era.

**References**

[^45]: Oct 2020 Vol. 23 Issue 15
[^46]: http://doi.org/10.36295/ASRO.2020.231546
[^47]: Annals of Tropical Medicine & Public Health