

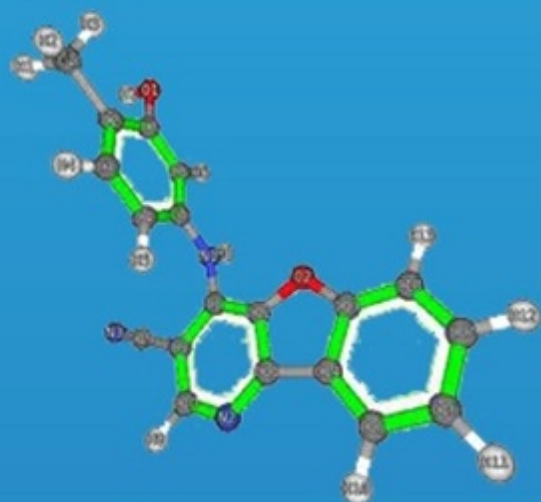
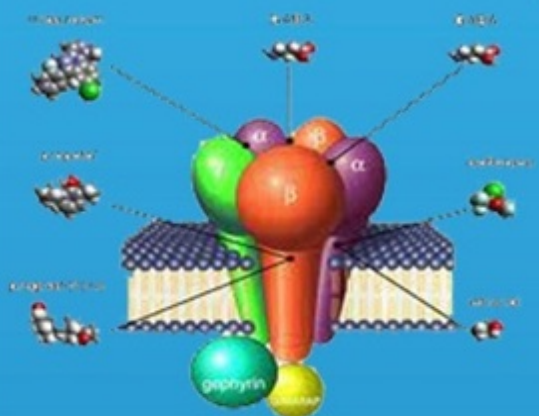
ISSN : 2320-1304



International Journal Of Pharmamedix India.

January 2013. Vol. -I Issue - I.
Research, Review, Survey.

Published by : Pharmamedix.India
www.pharmamedix.in
mail: info@pharmamedix.in



POLYMERS : USED IN DRUG DELIVERY SYSTEMS

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Abstract:

Now -a -days Polymers have extended use in the formulation of tablets and capsules. These are also used in targeted drug delivery systems. These are advantageous in drug targeting by prolonging drug release time. By targeting Pharmaceutical drugs using different polymers makes possible to guarantee local or systemic drug delivery to the site. Mostly, polymers are strongly hydrophilic in nature leading to premature drug release. To overcome this problem some polysaccharides, such as inulin, guar gum, pectin have been chemically modified to increase their hydrophobicity. These polymers play an important role in targeting the drugs to their specific site and used in tablets and capsules. The drug is released by losing strength and tensility of polymers when acted by different polysaccharides. Different microcapsules are also prepared by using selected polymers of cellulose, such as cellulose acetate, cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate. The influence, of different drug, polymer ratios and combination of polymers, on particle size, yield, and release kinetics is imperative. Cellulose acetate is a non-toxic cellulose polymer and it is insoluble in acidic and alkaline fluids and having superior film forming properties. It is extensively used as a coating material and matrix binder for tablets and capsules. It has threshold pH of 6 and expected to use as a carrier in the colonic drug delivery of drugs.

Keywords: Classification, History, Introduction of Polymer, Mechanism of drug delivery. Polymerisation, Properties of polymers.

Introduction:

Polymer is a long chain molecule composed of repeating (at least five) chemical units ('mers') of identical structure joined together like beads on a string. They usually contain more than five monomers and some may contain hundreds or thousands of monomers in each chain. A linear polymer is composed of long chain of monomers. A branched polymer has branches covalently linked to the main chain. Cross-linked polymers have monomers of one chain covalently linked with monomers of another chain. Cross linking results in a three-dimensional network; the whole polymer looks like a giant macromolecule. Elastomers are loosely cross-linked networks while densely cross-linked networks form thermosets. Another classification of polymers is cited on the chemical type of the monomers. Homopolymers consist of the same type of monomers; copolymers have different type of repeating units.¹ Depending on the arrangement of types of monomers in the polymer chain, it can be further classified:

- In random copolymers, there is random distribution of two or more different repeating units.
- Alternating copolymers are made up of different monomers of alternating sequences.
- Block copolymers consist of long sequences of a monomer followed by long sequences of another monomer.

- Graft copolymers are made up of a chain; made from one type of monomers with branches of another type.^{1, 2, 4-6.}

Polymers are extensively used in the development of Solid Dosage forms (SDFs) and serve many purposes. For Immediate Release (IR) SDFs; they are used as binders just to increase the density, flowability and compactibility of bulky Active Pharmaceutical Ingredients (APIs), which would otherwise not process significantly on high-speed tablet press and encapsulation machines. Polymers are used for non-functional (aesthetic) coatings to impart colours and favourable mouth feels to tablets without relying on the time-intensive effect. Polymer-based on functional coatings; such as those used as a barrier for moisture or oxygen can nevertheless be formulated as IR dosage forms, still allowing quick release and absorption of the API. Cross-linked polymers swell extensively in the presence of water and gastrointestinal fluids are used to promote disintegration of tablets and capsule plugs. These are available commercially as powdered form; designed to be readily compatible with encapsulation formulas and tableting processes.

For Modified Release (MR) dosage forms, one use of polymers is in functional enteric coating of tablet dosage forms, which allow a dosage form to pass through the stomach without exposing its internal content to the harshly acidic and enzymatic conditions

present there. This type of formulation is sometimes known as Delayed Release (DR). Other polymers have uses in Controlled Release (CR) coatings and in CR diffusional matrices. Polymers can also be used to enhance the dissolution (solubility enhancement) and bioavailability of the wide array of poorly soluble APIs. These are increasingly common products of current pharmaceutical discovery efforts. The following will represent an overview of polymers used in the more exotic and technically challenging dosage forms which involve MR (enteric) and CR as well as those used for enhancing the dissolution and bioavailability of poorly soluble APIs.^{5, 6}

HISTORY OF POLYMERS

Polymers have a wide-ranging effect on modern society. Polymers are more commonly referred to as “plastics” since people are more familiar with plastic products that they encounter around the house. Plastics have the ability to be molded, cast extruded, drawn, thermoformed or laminated into a final product like plastic parts, films and filaments. In 1845, the first semisynthetic polymer ever made was guncotton (cellulose nitrate) by Christian F. Schonbein. The manufacturing process for this polymer was changed over the years due to its poor solubility, processability and explosivity which results in a variety of polymers such as Parkesine, celluloid (plasticized cellulose nitrate) cellulose acetate (cellulose treated with acetic acid) and

hydrolyzed cellulose acetate and these are soluble in acetone. In 1872, Bakelite, a strong and durable synthetic polymer based on phenol and formaldehyde was invented by Leo Hendrik Baekeland. Polymeric products-based on polycondensation such as; Bakelite and those based on phenoxy, epoxy, acrylic and ketone resins were used as cheap substitutes for many parts in the auto and electronic industries.

Other synthetic polymers had invented later including polyethylene (1933), poly (vinyl chloride) (1933), polystyrene (1933), polyamide (1935), Teflon (1938) and synthetic rubbers (1942) etc. Polyethylene was used to construct radar equipment for airplanes of British air force to insulate electrical parts of the radars. In the 20th century; the plastic revolution advanced technologies has grown and opened new fields of application in the pharmaceutical and biomedical sectors.^{2, 3, 7-10}

POLYMERISATION

This has two basic sections:

1. Addition Polymerisation
2. Condensation Polymerisation^{2, 19}

1. Addition polymerisation

This kind of polymerisation is due to the presence of a carbon – there is carbon double bond in the monomer. A monomer is a small molecule constituting the polymer. Mechanism of addition polymerisation is mainly by a free radical formation. Oxygen is

generates a radical that can proceed to polymerise the alkenes. In addition polymerisation:

- The polymer is the only product.
- Opening out of a double bond.
- Properties of the polymer can be altered by the conditions of the reaction.

Free Radical Polymerization

A free radical is simply a molecule with unpaired electron. The tendency of this free radical to gain an additional electron; in order to form a pair, makes it highly reactive that it breaks the bond by stealing an electron on another molecule, leaving that molecule with an unpaired electron.

Basic Steps in Polymerization

- Initiation: Formation of free radical (active sites)
- Propagation: Combining of monomers to form chains (chain growth)
- Termination: Elimination of free radicals (destruction of active sites)

Polymer configuration

Cis-trans configurations

Stereoisomerism in Addition polymers

Ziegler and Natta discovered an accurate method for controlling the polymerisation process using an aluminium/tin catalyst at 50°C and 1.5atm. Previous to this, only one type of poly (ethene) called LDPE or low density poly ethane could be made. The chains formed a tangled mass. By using this new catalysis method, they could control the process and produce HDPE or high density

poly ethane due to the areas of crystallinity this has a much stiffer structure where the polymer chains are much more ordered. Due to these more ordered regions, HDPE has a much higher boiling point generally used to make plastic bottles. Ziegler and Natta also discovered stereoisomerism in polymers - Isotactic, syndiotactic and atactic.

Stereoisomerism

• Isotactic

This is very regular type of polymer chain. All the methyl groups are on the same side (radicals are linked in the same order). This has an impact on the properties of the polymer.

• Syndiotactic

A slightly less regular but is still very ordered polymer. The methyl groups alternate the side of chain they are on.

• Atactic

This is a completely random allocation of methyl groups along the carbon skeleton. This varying degree of randomness will influence the strength and melting point of the polymer. The less random, the stronger is the polymer and the higher is the melting point because the chains come close together, which impacts on the interactions between the polymeric chains. More ordered side chains means stronger Vander Waals.²⁻⁴

2. Condensation polymerisation

A condensation polymer generally consists of two monomers that have different functional groups. They also involve the elimination of

water or another small molecule. Hence, the term Condensation polymer is known as:

Monomer A + Monomer B = Polymer + small molecule (normally water).

Example of Common condensation polymers include polyesters (the ester linkage) and polyamides (the amide linkage as in proteins).²

POLYMER PROPERTIES

Crystalline and Amorphous Polymers

Polymers show different thermal, physical and mechanical properties; depending on their structure, molecular weight, linearity, intra- and intermolecular interactions. Polymer chains can packed together in regular arrays point; If the structure is linear. For example; polypropylene chains fit together in a way that intermolecular attractions stabilize the chains into a regular lattice or crystalline state. Upon increment in the temperature, the crystal cells (crystallites) begins 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 on one- another.

In many cases, the structure of a polymer is very irregular that crystal formation is infeasible thermodynamically. Such polymers generate glass; instead of crystal domains. A glass is a solid material, exists in non crystalline (i.e. amorphous) state. Amorphous structure is formed due to either rapid cooling

of a polymer melt, in which crystallization is inhibited (by quenching) or due to the lack of structural regularity in the polymer structure. At low temperatures; rotation around single bonds of the polymer chains becomes very difficult during rapid cooling; therefore, the polymer molecules forcedly adopt a disordered (irregular) state and form an amorphous structure. Amorphous or glassy polymers do not generally have a sharp melting point; instead, they soften or melt over a wide range of temperature. Crystallinity increases the strength and stiffness of Polymer; as a result of increased intermolecular interactions. An increase in crystallinity shifts the optical properties of a polymer .For e.g. from transparent (amorphous) to opaque (semicrystalline). This is due to the differences in the refractive indices of the amorphous and crystalline domains, leading different levels of light scattering. From a pharmaceutical point of view, good barrier properties are required when polymers are used as a packaging or as a coating material. Crystallinity enhances the barrier properties of the polymer. Small molecules like drugs or solvents; usually cannot penetrate or diffuse (impermeable) through crystalline domains. Therefore, crystalline polymers show better barrier properties and durability in the presence of attacking molecules. Diffusion and solubility are two important phenomena that are related to the level of crystallinity in a polymer. On

the other hand, for the release of a intended drug or an active material, less crystalline or an amorphous polymer is preferred. In a given polymer, Crystallinity depends on its topology and isomerism (linear versus branched; isotactic versus atactic), polymer molecular weight, intermolecular forces, pendant groups (bulky versus small groups), rate of cooling, and stretching mode (uniaxial versus biaxial). Anisotropy is another unique property of a crystalline polymer or polymer-containing crystalline domains. Crystal cell exhibit different properties along longitudinal and transverse directions, this causes the polymer to behave like an anisotropic material.

Thermal Transitions

Thermal transitions in polymers may occur in different orders. In other words, the volume of a polymer can alter with temperature as a first- or second-order transition. When a crystal melts, the polymer volume increases significantly because solid turns into a liquid. The melting temperatureTM shows first-order thermal transition in polymers.

On the other hand, the volume of an amorphous polymer gradually changes over a large temperature range (so-called glass transition temperature). This behaviour indicates a second-order thermal transition in polymers. T_m and T_g of a given polymer can be respectively detected by differential scanning calorimetry (DSC) as an endothermic peak and a baseline shift. These

two thermal transitions signify the structural movement of the crystalline and amorphous regions of a polymer chain.

Glass Transition Temperature

T_g is an expression of molecular motion and is dependent on many factors. Therefore, the T_g is not an absolute property of a material and has influenced by the factors affecting the movement of polymer chains. Amorphous polymers are hard, stiff, and glassy at temperatures well below the T_g, although they may not brittle necessarily. On the other hand, at temperatures well above the T_g, polymers are rubbery and liquid (might flow). For linear organic polymers the T_g values ranges from -100°C to above 300°C. Even though some organic polymers have T_g values above 300°C, they decomposes at temperature below their transition temperatures. From a pharmaceutical standpoint, T_g is an crucial factor for solid dosage forms.

For example, a chewable dosage form has to be soft and flexible at mouth temperature at about 37°C. This means the polymer used as a chewable matrix in the dosage form should be softened at this temperature. Pharmaceutically acceptable polymers with their T_g values close to the service temperature of 37°C serve as the best candidates.

In smoking cessation; Nicotine gum (Nicorette) gum is used as an aid. It provides low levels of nicotine, which lessens the

physical signs of withdrawal symptoms. The nicotine is released into the mouth upon chewing the gum by the patient. After placing a piece of the Nicorette gum into the mouth, the patient should chew it slowly for several times. The patient should stop chewing it once he or she feels a tingling sensation or a pungent taste in the mouth. At this point the nicotine is being released and the patient should keep the gum in the buccal area (in other words, between the cheek and the gum) and leave it there until the taste or tingling sensation is almost gone. The patient can start chewing it for a few more times and then stop once the taste comes back. The patient should repeat this for a period of about 30 min or until the peppery taste or tingling sensation does not return. The reason behind it is that the patient “parks” the gum is because the release of nicotine should be slow and constant. Chewing will release the nicotine too quickly resulting in nausea, hiccups or stomach problems. At this time the patient should also avoid drinking or eating. Segmental motion in polymers is facilitated by the empty space (free volume) in between the polymer chain ends. As the free volume increases, polymer segments achieve more freedom to move and this affects the temperature at which the movement occurs. For example: low and high density polyethylenes are diverse in terms of the size of the free volume inside their structures. A low density polymer occupies more volume

as compared with its high-density counterpart at a given weight. This implies that the polymer chain in general and the chain segments in particular can move more easily resulting in a lower Tg value.

Tg and the length of the polymer chain

Long polymer chains offer smaller free volume as compared to their shorter counterparts. Since lower Tg values are because of more free volume, polymers having short chains or having low molecular weight possess lower Tg values.

Tg and polymer chain side group

A side group may be bulky or polar in nature. Because of its steric hindrance, higher temperature is required to induce segmental motion in polymers having bulky groups. For example, polystyrene and polypropylene are different just in terms of their side groups, phenyl versus methyl, respectively. Larger the size of the phenyl group, much higher is the Tg value of polystyrene, 100°C as opposed to -20°C for polypropylene. On the other hand, stronger intermolecular interactions are due to polar side groups that appreciably affect the segmental motion of the polymer chains. Poly(vinyl chloride) is similar to polyethylene except hydrogen atom; it is substituted by one chlorine atom. Chlorine is having more polarity than hydrogen, the PVC (polyvinylchloride) polymer displays a much higher Tg value of 100°C as compared to -120°C for polyethylene.

Tg and polymer chain flexibility

Flexible polymer chains exhibit higher entropy (degree of randomness; desire to move) than rigid chains. Flexible and rigid chain corresponds to liquid and solid respectively. Groups such as phenyl, amide, sulfone and carbonyl either find inside of the backbone or present as a side group hanging on the backbone affecting the overall flexibility of polymers. For example, poly (ethylene adipate) and poly (ethylene terephthalate) are structurally very similar except for the phenylene residue in phthalate and the butylene residue in adipate respectively. This results in almost a 100⁰C temperature difference in Tg values of the two polymers (−70⁰C versus 69⁰C respectively).

Tg and polymer chain branching

Linear polymer chains are having smaller free volume as opposed to their branched counterparts, therefore; higher Tg values are supposed to have for linear polymers. On the other hand, hindrance or restriction to segmental motion is imposed by branches in branched polymers for which higher Tg values are expected. Therefore branching has no noticeable effect on the Tg unless the whole structure of the polymer is known.

Tg and polymer chain cross-linking

Linear chains had higher entropy and the desire to move; compared to cross linked chains hence, they display low Tg values. Upon addition of cross-links to linear polymer chains, there is slowing down of chain

movement which results in less entropy at a given temperature and hence leads to higher Tg value. Tg values are expected to be very high For very densely cross-linked polymers to the extent that the polymer starts to decompose before it shows any segmental motion.^{2, 37-39}

CHARACTERISTICS OF POLYMERS

In order to adhere to mucosal surface or epithelial cell for polymers they must ideally possess certain characteristics:

- **Flexibility**

The flexibility of bioadhesive polymers is important because it regulates the extent of interpenetration between the polymers and mucosal/epithelial surfaces.

- **Hydrophilicity**

Polymers that are hydrophilic in nature are able to form strong adhesive bonds with mucosal membranes because the mucus layer contains large amount of water.

- **Hydrogen bonding**

Hydrogen bonding between the entangled polymer chains form strong adhesive bonds, therefore the presence of hydrogen bond forming groups such as -OH and -COOH groups are vital in large quantities.

- **High molecular weight**

Polymers with a high molecular weight are desirable because they provide more available bonding sites (active sites).

- **Surface tensions**

Surface tension is essential to spread the bioadhesive polymer into the mucosal layer epithelial surface.^{2, 38}

CLASSIFICATION OF POLYMERS

- **On The Basis Of Source Of Origin**

1. Natural polymers

Natural polymers or Biopolymers are polymers obtained by living organism. Natural polymers used in the industry since the early 1940 in the form of water soluble binder, thickening agent and film forming agents. Natural polymers are very useful and its demand is increasing day by day. Biopolymers are made up of proteins which linked together by an amide linkage (-NH₂-NH₂-) between amino acids. Examples: Cellulose, Dextrose, Lactose, Starch, Shellac, Gelatin, Acacia, Tragacanth.

CELLULOSE

It is derived from a natural polymer; it is having variable chain length and hence variable molecular weight. Powdered cellulose occurs as a white or almost white, odourless and tasteless powder of different particle sizes. Particle size is ranging from a free flowing, fine or granular dense powder to a coarse, fluffy, nonflowing material. The use of powdered cellulose is as a tablet diluent and filler in two-piece hard capsules; in both contexts it acts as a bulking agent to increase the physical size or mass of the dosage form for formulations containing a small amount of active substance (API). Powdered cellulose is

excellent in compression properties, although the flow properties of most brands are poor. However, low-crystallinity powdered cellulose exhibits properties that are different from standard powdered cellulose and has display potential as a direct-compressible excipient. Powdered cellulose has been investigated as an substitute to microcrystalline cellulose as an agent to assist the manufacturing of pellets by extrusion/spheronization process. However, powdered cellulose alone needs too much water and due to movement of water during extrusion, it is unable to used as an extrusion/spheronization aid on its own. Powdered cellulose is also used extensively as an adsorbent and thickening agent in cosmetics and food industries. In soft gelatin capsules, powdered cellulose can be used to reduce the sedimentation rate of oily suspension fills. It is also having use in the powder base material of powder dosage forms, and as a suspending agent in aqueous suspensions for peroral delivery. It may also be used to decrease sedimentation during the manufacturing of suppositories.

DEXTROSE

Dextrose is available as odourless, sweet in taste, colourless crystals or as a white crystalline or granular powder. The JP XV describes dextrose as dextrose anhydrous; the PhEur 6.3 specifies dextrose as either dextrose anhydrous or dextrose monohydrate

and the USP 32 specifies dextrose as dextrose monohydrate. Dextrose is very commonly used in solutions to adjust tonicity (tonicity adjusting) and as a sweetening agent. Dextrose is also used in wet granulation technique, as diluent and binder, and as direct-compression tablet diluents and binder, 222. Dextrose is primarily use in chewable tablets. Although dextrose is comparable as a tablet diluent to lactose, tablets produced with dextrose monohydrate require more lubrication, are less friable, and have a tendency to harden (1–3). During tableting, to improve the stability of active materials that are sensitive to oxidation the mildly reducing properties of dextrose may be used. Dextrose is used therapeutically and is the preferred source of carbohydrate in parenteral nutrition regimens.

LACTOSE

Lactose is naturally occurring sugar or simple carbohydrate, found only in the milk of mammals (milk sugar). All commercial lactose is obtained from the milk of cows as a by-product of the dairy industry. Chemically lactose is the disaccharide; consist of two simple sugars D-galactose and D-glucose. In other words, the lactose molecule comprises one molecule of D-galactose chemically linked to one molecule of D-glucose. Lactose has two isomeric forms, known as alpha and beta (designated a-lactose and b-lactose). In direct compression tableting applications;

anhydrous lactose is widely used. Due to its low moisture content it can be used with moisture-sensitive drugs. It may also be have use in intravenous injections. Lactose is often used as tablet or capsule filler or diluents and to a more limited extent in lyophilized products, infant feed formulas and in dry-powder inhalations.

STARCH

Starch consists of two polysaccharides; linear amylose and branched amylopectin, based on (D)-glucose. Both polymers are arranged in a semicrystalline structure and in the starch granule, amylopectin forms the crystalline portion. The exact structure of starch is not fully understood yet. So in starch grain, there is no specific distribution pattern of amylose and amylopectin molecules. According to the most recent scientifically recognized models, both molecules are organized in similar structures; probably as clusters. The different configurations of these molecules resulting in different behaviour in cold aqueous solutions. Amylose (only linear 1, 4 linkage) shows a high tendency for crystallization (retrogradation) producing an insoluble adduct, whereas amylopectin (branched polymer) after few days shows mild jellification, resulting opaque and highly viscous preparations.

The molecular weight depends on the origin and the nature of the starch. It has range between 50 and 500 million Da. Amylopectin

is having a higher molecular weight than amylose.

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent and disintegrant (according to its limit). As a diluent, starch is having applications in the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations.

Starch is also used in dry-filled capsule formulations; for volume adjustment of the fill matrix and to improve powder flow, especially when using dried starches. Starch quantities of 3–10% w/w can act as an antiadherent and lubricant in tableting and capsule filling. In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. The required binder ratio should be calculated by optimization or evaluation studies, using parameters such as tablet friability and hardness, disintegration time and drug dissolution rate and time.

One of the most common use of starch as tablet disintegrant at concentrations of 3–25% w/w; a typical concentration is 15%. When starch is used, a prior granulation step is required in most cases to avoid problems with insufficient flow and segregation. A starch–lactose compound has been introduced enabling the use of granular starch in direct

compression, improving the tableting process and the disintegration time of the tablets. However, starch that is not pregelatinized does not have the tendency to compress well and leads to increased tablet friability and capping, if used in high concentrations. Upon balancing the elastic properties of starch with adapted excipients has been shown to improve the compaction properties in tableting.

SHELLAC

Shellac is the excretory product of the "lac" bug, a tropical insect. It is a complex organic polymeric molecule(s) that contains carboxylic acid as functional groups. Shellac is used in enteric coating; to coat enteric pills so that they do not dissolve in the stomach, instead in the lower intestine, which alleviates upset stomachs. It is also used as a coating on pills to "time release" medication. Shellac is a natural resin that may be obtained in a variety of colours ranging from light yellow to dark red in the form of hard, brittle flakes with or without wax, depending on the refining process. The different types of shellac are bleached shellac, bleached dewaxed shellac, dewaxed and decolorized shellac, dewaxed flake shellac, dewaxed orange shellac, dewaxed shellac, orange shellac, purified shellac, refined bleached shellac, regular bleached shellac, regular waxy shellac, wax-containing shellac and white shellac. The flakes may be crushed or milled to convert

into coarse or fine powder. Bleached shellac is supplied as a coarse off-white powder. Shellac is tasteless and having a faint odour. The typical odour of shellac is because of a complex fragrance system.⁷

GELATIN

Gelatin product is obtained by partial hydrolysis of collagen; acquired from the skin, white connective tissue, and bones of animals. Gelatin is a protein which is soluble in warm (or hot) water but insoluble in cold water. Gelatin is extensively used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system, although it is most frequently used in the manufacturing of either hard or soft gelatin capsules. Gelatin capsules are available as unit-dosage forms designed mainly for oral administration. In the market, Soft gelatin capsules also include those for rectal and vaginal administration. Hard capsules can be filled with solid (powders, granules, pellets, tablets and mixtures thereof), semisolid and liquid fillings, whereas soft capsules are mainly filled with semisolid or liquid fillings. In hard capsules, the active drug is always incorporated into the filling, while in soft capsules the drug substance can also be incorporated into the thick soft capsule shell. Gelatin is soluble in warm water ($>30^{\circ}\text{C}$). First gelatin capsule swells initially and

finally dissolve in gastric fluid to release its contents rapidly.

Hard capsules are manufactured in two pieces; one cap and another is body, by dipping lubricated stainless steel mold pins into a $45\text{--}55^{\circ}\text{C}$ gelatin solution of specified viscosity which depends on the size of the capsules and whether cap or body are to be formed. The gelatin is taken up by the pins as a result of gelation process and the resulting film thickness is controlled by the viscosity of the solution. The capsule shells are passed through a stream of cool air to aid setting of the gelatine and thereafter they are slowly dried with large volumes of humidity controlled air heated to a few degrees above ambient temperature and blown directly over the pins. The capsule halves are isolated from their pins trimmed and fitted together. Gelatin that is used to produce hard capsules may also contain various colouring agents and antimicrobial preservatives. The gelatin used to form the soft shells has a lower gel strength compared to that used for hard capsules and the viscosity of the solutions is also lower, which results in more flexible shells. Additives to soft shell formulations are plasticizers such as polyalcohols (glycerin, propylene glycol, polyethylene glycol). Sorbitol can be added as moisturizing agent, whereby the larger amount of water will act as plasticizer. Colouring and opacifying agents are also employed. The filling can

have interaction with both the gelatin and the plasticizer chemically.²⁴

ACACIA

Acacia is a complex loose aggregate of sugars and hemicelluloses with a molecular weight of approximately 240,000–580,000 Da. The aggregate consists essentially of an arabic acid nucleus connected with calcium, magnesium, and potassium along with the sugars arabinose, galactose and rhamnose. Family- Leguminosae. Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often combining ratio with tragacanth. It is also used in the manufacturing of pastilles and lozenges and as a tablet binder, upon using incautiously; it can produce tablets with a prolonged disintegration time. Acacia has also been used as a bioadhesive and has a role in novel tablet formulations and modified release tablets. It is also used in cosmetics, confectionery, food products and spray-dried flavours.

XANTHUM GUM

Xanthum gum is also known as Corn sugar gum. This gum is produced through a pure culture by fermentation of a carbohydrate with *Xanthomonas campestris* and then purified. It is basically sodium, potassium or calcium salt of the high molecular weight polysaccharide which is containing D-glucose, D-mannose, D-glucuronic acid and

not less than 1.5% of pyruvic acid. It is used as a stabilizer, thickener and emulsifier extensively in pharmaceutical, cosmetic industries and in food industries for dairy products. The pseudo plastic property of this gum enables toothpastes and ointments in the both cases provide to hold their shape and also to spread readily.

AGAR

Agar (or) Agar-Agar is known as Japanese Isinglass, Chinese-Isinglass or Vegetable Gelatin. The dried Agar-Agar generally occurs in bundles comprising thin, membranous agglutinated strips, in cut, flaked or granulated forms. It is used as emulsifying, suspending, stabilizing, thickening or gelling agent and as bulk laxative. It is also used in the manufacturing of jellies, confectionery products, tissue culture studies and in microbiology.

CARRAGEENAN

Carrageenan is the hydrocolloid obtained from the red seaweed through extraction with water or aqueous alkali. It recovered either by the alcoholic precipitation or drum drying or freezing. It is hugely used as dissolution rate retarding polymer in case of sustained release dosage forms in many pharmaceutical industries. Carrageenan is also used in pharmacy and food industries as a suspending and gelling agent. Tooth paste,

creams, lotions and other cosmetic products are also manufactured by using carrageenan.

STERCULIA GUM

Sterculia gum is the dried gummy exudate obtained from the *Sterculia urens* Roxb. Karaya gum contained of an acetylated and branched heteropolysaccharide with a huge component of D-galacturonic acid and D-glucuronic acid as residues. Its granular grades are used as a bulk laxative and the powdered gum is also used in lozenges, pastes and dental fixative powders. It had been proved particularly useful as an adhesive for stoma appliances.

CHITOSAN

A natural polymer Chitosan is obtained by deacetylation of chitin and it is found in shell fish. It is a novel drug carrier material and it increases the dissolution rate of controlled release matrix tablets. The additional properties of chitosan are as gel former, coating agent, and also showing induction of desirable properties such as mucoadhesion and permeation enhancement that is improving the oral bioavailability of a drug. For the first time microcapsules were prepared from Gum Karaya and Chitosan using the principle of complex coacervation with a continuous oil-phase.

ISPAGHULA

Ispaghula husk consisting of dried seeds of

the plant *Plantago ovata* Forsk. It contained basically mucilage, which is found in the epidermis of seeds. In the granulation of materials mucilage is used as binding agent for preparation of compressed tablets. It is also used as a suspending and thickening agent because of its high swelling factor and ability to provide a uniform viscous solution. It is selected in pharmaceutical industries as enteric coated material, tablet disintegrator and also used in sustained release drug formulations.

POLYETHYLENE GLYCOL (PEG)

The various Polyethylene glycol polymers were suggested for use as Suppository bases. Long chain polymers exist as liquids when their average molecular weight ranges from 200 to 600, and as a wax like solids when their molecular weights are above 1000. Their water solubility, hygroscopicity, and vapor pressure decreased with increased in molecular weights. They did not hydrolyze or degraded. Several bases had different physical characteristics. Polyethylene glycols having a molecular weight of 1000 or above are freely soluble in water and they are also soluble in many organic solvents, including aliphatic ketones and alcohols, chloroform, glycol ethers, esters.¹²⁻¹⁴

2. Semi-Natural/ Semi-Synthetic polymers

These are the naturally occurring polymers and derived through chemical modifications.

For example: Cellulose, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Methyl Cellulose (HMC), Microcrystalline Cellulose, Cellulose Acetate Pthalate (CAP), etc. Semi synthetic polymers are good in properties and expensive in comparison to natural polymers. They are used as Disintegrating agent, Binder, Diluent and Coating material in solid dosage forms like tablets and capsules. They are also the part of many dosage forms like microspheres, solid dispersion, emulsion, and many controlled release dosage forms.

MICRO CRYSTALLINE CELLULOSE (MCC)

Microcrystalline cellulose is the purified and partially depolymerized cellulose that have the properties as a white, odorless, tasteless, crystalline powder which is composed of porous particles. At present it is available in different particle sizes and moisture grades. It is widely used in pharmaceuticals as primarily as a binder and diluent in the oral tablets and capsules formulation where it is basically used in wet granulation and direct compression processes. It is also having some lubricant and disintegrant properties that made it useful in tableting. Microcrystalline cellulose is used in cosmetics and food products. It is not absorbed systemically by following oral administration and thus had little toxic potential. Consumption of large quantities of cellulose may lead a laxative effect and also showing a problem when

cellulose is used as an excipient in pharmaceutical formulations.

SODIUM CARBOXY

METHYLCELLULOSE

Carboxymethylcellulose sodium is used for producing thixotropic gels as suspending vehicles in cosmetic and pharmaceutical formulations. It basically aids dispersion and serve as a protective colloid. Less than 1% solid Concentrations produced fluid dispersions, while concentrations of more than 1.2% solids produced thixotropic gels. It imparts emulsion stability and suspension, when it is properly dispersed by which it provides variety of products, and is used in nasal sprays, topical sprays and lotions, oral suspensions, emulsions, creams and gels. Carboxymethylcellulose sodium is used in a huge range of pharmaceutical formulations and had low oral, dermal and inhalation toxicity. It had nonirritating property to the eyes and skin, and also nonsensitizing to the skin.¹⁷⁻²⁰

HYDROXY PROPYL METHYL CELLULOSE (HPMC)

HPMC is water soluble cellulose ether and it could be used as a hydrophilic polymer for the preparation of controlled release solid dosage forms like tablets, capsules etc. Water penetrated in the matrix and hydrating the polymer chains which is lastly disentangle from the matrix. It generally helps in the

recognition about the drug release from matrices and it follows two mechanisms: drug diffusion through the swelling gel layer and release by matrix erosion of the swollen layer. Therefore, it quantified the percent contribution of diffusion and erosion to the overall drug release. The diffusional release rates of HPMC of different molecular weight were independent of average molecular weight of the polymers. The erosion process indicated that polymer diffusion of the HPMC polymer chains through the aqueous diffusion layers were the rate limiting step and generally polymer erosion was found to be inversely related to the average molecular weight of polymer.²⁰

CELLULOSE ACETATE PHTHALATE

A partial acetate ester of cellulose is known as Cellulose acetate phthalate. It is one of the materials that had been selected for harmonization. Whenever solutions are being prepared then cellulose acetate should always be added to the solvent, not the reverse is considered.

At present various grades of cellulose acetate are available with having different physical properties. Different combination of properties made it useful in enteric coated tablets and capsules because it is resistant to the acid condition of stomach but it is soluble in the alkaline environment more, of the intestinal tract.

3. Synthetic polymers

Man made polymers are known as synthetic polymers.¹⁷

- **Homo polymers**

Polymers composed of the same monomeric units are known as Homo polymers. For example: polyvinylpyrrolidone (PVP).

POLYVINYLPIRROLIDONE

It is insoluble and soluble matrix former (Kollidon SR):

- Polyvinyl acetate 80%
- Povidone (PVP) 19%
- Na-lauryl sulphate
- Silicon dioxide 1%

Povidone dissolves and form a porous structure by which the drug will slowly released (diffusion). Dissolution of matrix is independent on pH and on ion content of the GI fluids.²⁰

ZEIN

Zein is the prolamine gained through hydro-alcoholic extraction from corn and produced as a byproduct during its manufacturing. Prolamines are the alcohol soluble proteins in cereal grains which have a major characteristic of being insoluble in aqueous media. It was first isolated in the year 1821 and was immediately subjected to the extensive investigation due to its film-forming property and for solubility behavior. In the food industry zein was mainly used as a coating polymer for fruits, nuts and for

candies. It prevents deterioration or desiccation over storage. This application was favorable due to the ability for forming clear, tough, glossy and grease-proof coating with an excellent resistance against microbial attack. There are other application areas that are the coating of paper, where the large quantities were consumed for improving grease and scuff resistance. A lot of efforts were undertaken for developing coatings that have increased water resistance for the application. Films having higher water resistant nature that were achieved by mixing zein with hydrophobic substances like e.g.; oils and waxes. The increased moisture resistance of zein in the combination with fatty acid and oil coatings attracted the attention to its use as a biodegradable packaging material. At present the main use of zein in the pharmaceutical area is that as protective coating to improve the appearance of immediate release tablets and it is appreciated also as a binder for granulation processes. New interest came up recently for the zein as a coating material for taste masking process. Combinations with oil and wax were used as effectively suppress the release of active substance from the encapsulated particles and then masking the unpleasant taste of the drug.

- **Co-polymers**

A heteropolymer or copolymer is a polymer that derived from the two (or more) monomeric species. For example: ABS

plastic, carbopol, styrene acrylonitrile, Nitrile rubber, styrene isoprene styrene (SIS) and ethylene vinyl acetate. These are the very expensive species and used in pharmaceutical industry. For example: polyaspartamides, 2-hydroxypropyl-methacrylate polymers (HPMA), polyglycolic acid, polyamidoamines, polylactic acid, polydioxanone, polycaprolactone etc. It is mainly used in cancer therapies, biotechnology and in drug targeting etc.

POLYETHYLENEIMINES

The polymerization of the ethyleneimine produced a highly cationic polymer of low molecular

weight which is especially used as a drainage aid in papermaking.

POLYAMIDE-AMINES

The condensation process of adipic acid with diethylenetriamine and epichlorhydrin produces a low molecular weight copolymer into which all the amine groups are quaternized through the epichlorhydrin. The manufacturing process takes place in the two steps:

- Condensation of diethylenetriamine with adipic acid.
- Followed by condensation with the epichlorhydrin in order to produce tertiary amine groups and also cause branching and crosslinking.

The solubility of the system is maintained by controlling the degree of branching between the epoxy groups on the one polymer chain and the secondary amine on another chain. The polyamide-amines are basically used in papermaking as a dry strength additive.

POLYAMINE-BASED POLYMERS

These are basically condensates of halogenated compounds (dichloroethane, epichlorhydrin, etc.) with polyamines. They covered an entire family of polymers and some of which have been observed in flocculation applications.²⁰

POLYETHYLENE OXIDES (PEO)

These had a very high molecular weight (2 to 8 millions) and they do not have an electric charge, they are non-ionic in nature because of a free electron pair on the oxygen atom. These products are specifically showing to the flocculation of silica. They are also used in the flotation of ores and the reduction of head losses. They are also used in paper as a retention agent in newsprint production and as a forming agent for “tissue” paper.

SULPHONATED COMPOUNDS

- The sodium polystyrene sulphonate or sodium polyvinylsulphonate type are the compounds which are highly anionic polymers of low molecular weight.
- Copolymers of acrylic acid with a particular, 2-acrylamido-2

methylpropanesulphonic acid (AMPSA).^{2, 18, 37}

POLYACRYLATE-TYPE DISPERSANTS

The dispersants are basically sodium polyacrylates of low molecular Weight.^{18, 36}

• Based on Reaction Modes

1. Condensation polymers

Polymers formed by a condensation reaction and releasing small molecules as by-products such as water or methanol. Example: Polyesters.

2. Addition polymers

An addition polymer is a polymer which is formed through an addition reaction. By which many monomers bond together through rearrangement of bonds without having the loss of any atom or molecule. Example: Polyethylene glycol, Nylon 6, Nylon 6, 6.

• Based On Physical Property

1. Thermoplastics

It is also known as a thermosoftening plastic and is a polymer that turns into a liquid when heated and frozen to a very glassy state when cooled significantly. Most of the thermoplastics are high in molecular weight, they are the polymer whose chains are associated through weak Vander Waals forces like polyethylene, stronger dipole-dipole interactions and hydrogen bonding like nylon, also having stacking of aromatic rings and polypropylene. A thermoplastic is a plastic made from the polymer resins that becomes a homogenized liquid when heated

and also hard when cooled. When frozen becomes glass-like and subject to fracture. These characteristics which are lend the material as reversible. Then it represents that it can be reheated, reshaped, and frozen repeatedly. These qualities also make thermoplastics recyclable. There are dozens of kinds of thermoplastics which are having varying crystalline organization and density. Some types that are commonly producing at present are polyurethane, polypropylene, polycarbonate, and acrylic. Celluloid, which is considered as the first thermoplastic.¹¹

2. Thermosetting

A cured thermosetting plastic is also known as a thermoset which is a polymer material that irreversibly cures. The cure may be done by either heat (generally above 200 °C or 392 °F), or a chemical reaction (two-part epoxy, for example), or irradiation like as electron beam processing. Thermoset materials are generally liquid or malleable prior for curing and for designed to be molded into their final form, or used as adhesives. Others are solid like molding the compound which is used as in semiconductors and integrated circuits (IC). Once it will hardened as a thermoset resin, then it will cannot be reheated and melted back to a liquid form. According to IUPAC recommendation, A thermosetting polymer is a pre-polymer in a soft solid or viscous form that changes irreversibly into an infusible, insoluble polymer network through

curing. Curing could be induced by the action of heat or suitable radiation, or both.^{2, 18-24}

POLYMERS FOR DRUG DELIVERY (Shown in Fig. 1)

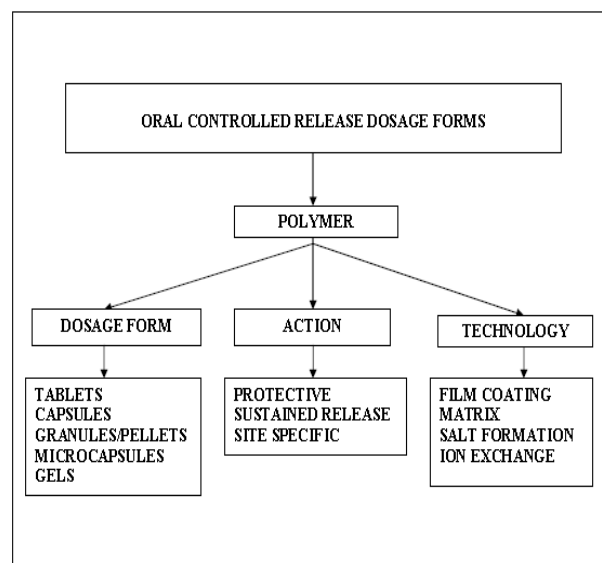
In recent years, polymers have been used in the development of devices for controlling drug delivery or for replacing failing natural organs. In oral delivery of drugs, polymers act as coatings, binders, taste maskers, protective agents, drug carriers and release controlling agents.

Targeted delivery to the lower part of the gastrointestinal tract (e.g. in the colon) was made possible by using polymers that protect drugs during their passage through the acidic environment of the stomach. Transdermal patches use polymers as backings, adhesives or drug carriers in matrix or membrane products. Biodegradable polymers have been made possible the controlled delivery of proteins and peptides. Biocompatibility is the key difference between early polymers and pharmaceutical polymers.

Once a polymer had been identified it is must to understand the polymer nature in-vitro and in-vivo. Biomaterials, Biodegradation, Biocompatible, Bioerosion, etc are terms which were used interchangeably to describe the polymers used for microencapsulation. Biodegradation of polymers is basically of two kinds: homogenous and heterogenous. Heterogenous biodegradation starts at the surface of the microparticle and proceeds to the layers beneath by which the drug being

released as the polymer degrades and in the case of Homogenous degradation; it involved a random cleavage the bulk of the polymer matrix.

- One of the ahead distinct polymer systems for Controlled Release (CR) involved using of hydroxypropyl methylcellulose (now officially called as Hypromellose) for diffusional matrices system. Initially CR dosage forms were made by using natural substances like shellac, waxes, or vegetable gums etc. It concludes technically polymeric nature, but were not well defined or well characterized earlier. This accounted for challenges for reproducibility of release, and the major fact that in old era, the standards for reproducibility were much less stringent than they are at present. Hypromellose is accessible in a huge range of molecular weights (MWs) that could be used to alter the rate of release. Hypromellose is scientifically water soluble, but its rate of dissolving is vastly dependent on MW.^{33, 34}
- Acrylic-based polymers could achieve both Delayed Release (DR) and Sustained Release (SR), such as cellulose acetate phthalate. These can be acquired in powder form, but were commercially available as aqueous dispersions, which



[Fig. 1: Polymers For Drug Delivery.]

reduces the demand for extensive preparation steps. They may need the addition of some plasticizers and detackifying agents for rendering the polymers flexible and for preventing agglomeration during processing. Various grades of enteric polymers had been designed to dissolve at different pH ranges, usually from 5.5 to 7.5. Stomach fluids range from pH 1.5 to 4.5, which is depending on the amount of food substances present. Acrylic-based or reverse enteric polymers are non-ionic and slightly hydrophobic and also do not dissolve at neutral pH (for example in the mouth). Thus, these polymers are consequently used to mask the taste of bitter or foul-tasting Active Pharmaceutical Ingredients (APIs).^{12-17, 25-27, 36}

- Biodegradable polymers are the alternatives to those drug delivery systems which can be administered through a normal 22-23 gauge needle and which

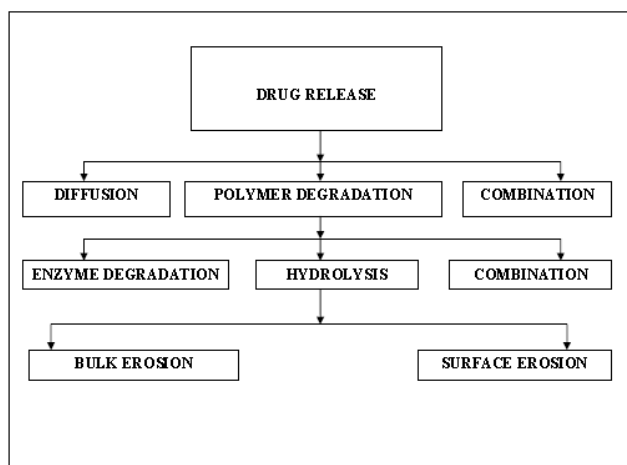
have no need of surgical recovery after complete drug had been released.

DRUG RELEASE MECHANISMS FOR POLYMERIC DRUG DELIVERY

The two broad categories of polymer systems had been analysed:

- Reservoir Device
- Matrix Device

The Reservoir device involved the encapsulation of a drug within the polymer shell, and Matrix device explains about a system in which a drug had physically entrapped within a polymer network. Then, the drug would either released by diffusion out of the polymer matrix or by erosion (due to degradation) of the polymer or by a combination of these two mechanisms (Shown in Fig. 2).²⁵⁻³⁵



[Fig.-2 Drugs release mechanisms]

The drug release profiles were governed by different properties; both of the polymer, the drug and the carrier system. Polymer dependent factors include the molecular weight and its distribution, the comonomer

ratio and the distribution of monomer, and the percentage of low molecular weight species, the crystallinity, whether the polymer is an end-capped or non-end-capped polymer. The drug dependent parameters include the molecular weight, the solubility in the dissolution medium and drug-polymer interactions. The carrier system involved the morphology, the drug loading, porosity, particle size and the distribution, etc

Conclusion:

Polymers are widely used in the formulation of tablets and capsules. These are intended with the purpose of either tablet coating or capsule shell formulation. Now a days, polymers are used as a suspension aid, soluble lubricants, tablet binders and diluents, superdisintegrants in controlled release coatings, non animal soft capsules, innovative solutions etc. Polymers are of natural, semi synthetic and synthetic in origin. Actually in drug formulation, the concept of using polymers is widely used in case of solid dosage forms. These have application in microencapsulation techniques, biodegradable polymers and co-polymers. Combinations of polymers are also in use. The chemistry of polymers is very important and they are used according to their structural properties. These polymers are available in various grades and used accordingly. HPMCP (Hydroxypropyl methylcellulose phthalate) is generally used in oral pharmaceutical formulations as an enteric

coating material for tablets or granules. Different natural, semi synthetic and synthetic polymers are employed for their binding and drug release properties. In Capsules, polymers are used in the formation of its outer covering or shell. Some polymers act by dispersion, some by dissolution and some by encapsulation of the drug or active material within it. Pharmaceutical grade Polymers are used in formulating tablet and capsules and contains all the desired properties suitable in the formulation of solid dosage forms. Polymers are now be used in the manufacturing of block copolymer and in the development of biodegradable polymers.

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