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STUDY OF WIDELY DIVERGENT DEVELOPMENT OF NON BIODEGRADABLE AND ITS APPLIANCES

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Abstract

Polymers, also known as macromolecules, are very large molecules consisting of many repeating units and are formed by a process called polymerization, which links together small molecules known as monomers and these linked together gives chains of polymers. The polymeric carrier molecule provides both controlled, sustained, release pattern and a means of protecting the drug from the physiological environment until it needed. Controlled drug delivery of chemotherapeutic agents by biodegradable polymers is a new strategy that has been added to the therapeutic arsenal available for treatment of malignant neoplasm. The use of polymer for local drug delivery minimizes systemic toxicity. A number of substances both biodegradable as well as non biodegradable have been investigated for the preparations and also act as building blocks. These materials include the polymers of synthetic or natural origin and also modify natural substances examples like methyl methacrylate, acrolein, gelatin, starch etc. The non biodegradable polymers are not degraded in human body but they are excreted from body as in original form. These polymers are now used widely in number of preparation such as sustain release, enteric coating, film coating, blackening layer which lay down the standards to widen its role in novel drug delivery system.

Keywords: Non biodegradable polymer, Blackning layer, Carrier

Introduction

Polymers, also known as macromolecules, are very large molecules consisting of many repeating units and are formed by a process called polymerization, which links together small molecules known as monomers. The monomer's can be linked together in various ways to give rise to linear polymer, Branched polymers or cross linked polymers [(1)].

Classification of polymer:

The most common way of classifying polymers is to separate them into three groups.

A) Thermoplastics:

i) Crystaline.

ii) Amorphus.

B) Thermosets.

C) Elastomers.

Thermoplastics:

Molecules in a thermoplastic are held together by relatively weak intermolecular forces so that the material softens when exposed to heat and then returns to its original condition when cooled. Most linear and slightly branched polymers are thermoplastic. All the major thermoplastics are produced by chain polymerization. Thermoplastics have a wide range of applications because they can be formed and reformed in so many shapes. Some examples are food packaging, insulation, automobile bumpers, and credit cards [(2)].

Thermosets:

A thermosetting plastic, or thermoset, solidifies are irreversibly when heated. Thermosets cannot be reshaped by heating. Thermosets usually are three-dimensional networked polymers in which there is a high degree of cross-linking between polymer chains. The cross-linking restricts the motion of the chains and leads to a rigid material [(2,3)]. Thermosets are strong and durable. They primarily are used in automobiles and construction. They also are used to make toys, varnishes, boat hulls, and glues.

Elastomers:

Elastomers are rubbery polymers that can be stretched easily to several times their unstretched length and which rapidly return to their original dimensions when the applied stress is released. Elastomers are cross-linked, but have a low cross-link density. The polymer chains still have some freedom to move, but are prevented from permanently moving relative to each other by the cross-links.

Polymerization Method:

Polymerization method can be broadly classified into two groups:

a) Polymerization method for chain polymerizations.

b) Polymerization method for step-growth polymerizations.

a) Polymerization method for chain polymerizations.

- Bulk polymerization
- Solution polymerization
- Suspension polymerization
- Emulsion polymerization

Bulk Polymerization:

This process involves the polymerization of neat monomer and two situation can arise. In one the polymer is not soluble in the monomer, so solid polymer precipitate as the polymerization process takes place. In the other the polymer is soluble in the monomer, so the viscosity of the polymer mass increase with time until it is completely converted to solid polymer.

Solution Polymerization:

In this procedure the monomers are dissolved in a suitable solvent and than polymerized. The chosen solvent should be a solvent for both polymer and monomer. Because end product is a solution of polymer in a solvent, stirring throughout the process is possible; thus heat evolved is controlled by means of external cooling. The concentration of monomer in solvent should be adjusted to avoid a excessive viscous final solution[1,4]. The polymer is isolated by either solvent evaporation or precipitation of the polymer solution into a large excess of nonsolvent. Residual solvent is removed from the polymer by heating in a vacuum oven.

Suspension Polymerization:

In this procedure the monomer is dispersed in a dispersing medium, and polymerization occurs in the monomer droplets suspended in a dispersing medium. Although nonaqueous media can be used, water is used almost as a dispersing medium. Suspension polymerizations are used with free radical polymerization where the initiator is dissolved in the monomer, which is than dispersed in water using an emulsifying agent. Polymerization is initiated in the monomer droplets dispersed in the aqueous media. Polymer obtain by this polymerization method are spheres, typically between 0.01-0.5cm in diameter.

Emulsion Polymerization: Experimentally, this polymerization procedure is identical to suspension polymerization. But differ in that the initiator is insoluble in the monomer and soluble in water. Because of this difference, the kinetics of the polymerization process is distinctly different. Polymer particle produced by this method are typically 0.1µm in diameter.

b) Polymerization method for step- growth polymerization:

Bulk Polymerization: This method is not exothermic, so heat dissipation is not a problem and this method is excellent method.

Solution Polymerization: This is also an excellent polymerization method.

Interfacial Polycondensation:

This is a specialized method using two mutually immiscible solvent, each containing one monomer and where the polycondensation reaction occurs at the interface between two solvents [(1)].

POLYMER PROPERTIES:

Molecular weight and Molecular weight distribution:

Because polymerization is a random process, molecule within a given polymer mass will have different molecular weight, and for this reason molecular weight of polymer are described in terms of average molecular weight. The most common molecular weight are the number average molecular weight, M_n. the weight average molecular weight, M_w. and viscosity average molecular weight, M_v. the ratio of M_w/M_n is also known as Polydispersity index. For $M_w / M_n = 1$ the polymer is monodispersed. i.e all polymer molecules within polymer mass have the same molecular weight. Polydispersity depend on the preparative method used to synthesis the polymer.

Table 1 Polydispersity index of different polymerization method.

Method of polymerization	**Polydispersity index**
Anionic polymerization	1
Chain polymerization	20
Step growth polymerization	2

As the molecular weight rises, the magnitude of mechanical property also increases.

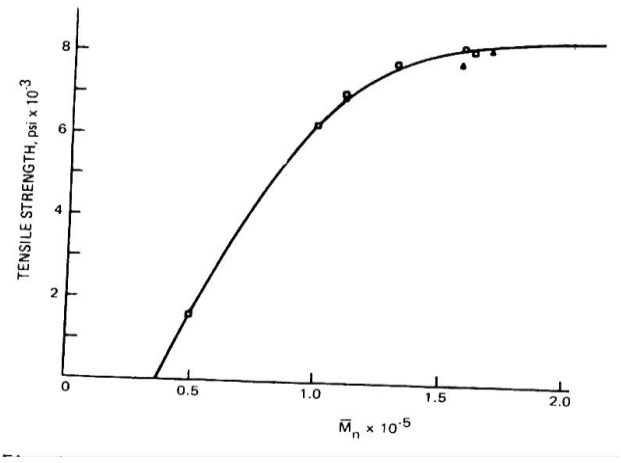


Fig.1 Molecular wt. versus Tensile strength

In fig.1. Increase in tensile strength of polystyrene with increase in number average molecular weight. Thus polymer with M_n=40,000 has no tensile strength, but as the molecular weight increase the tensile strength increase ultimately level off at M_n=150,000[1,3]. However, molecular entanglement is also important and appreciable tensile strength cannot be achieved until the molecular weight is high enough for a significant entanglement network to form.

Polymer hydrophobicity:

According to nature of polymer-water interaction polymer can be classified as:

- **Hydrophobic polymer:**

These polymers are essentially water impermeable and when placed in an aqueous environment, will absorb very little water. The amount of absorb water should be less than 5 wt %. Structural parameters that contribute to polymer hydrophobicity, chain stiffness and high degree of Crystallinity [1,3].

- **Hydrophilic polymer:**

These are polymers that absorb more than 5 wt % water. structural parameter that contribute to polymer hydrophilicity are chain flexibility, absence of crystallinity, and presence of certain groups such as amino, carboxyland hydroxyl etc.

- **Water soluble polymer:**

Some polymers are freely soluble in water, even though they are of high molecular weight. Ex. Polyvinyl alcohol, polyacrylic acid, polyacrylamide, polyethylene oxide.

- **Hydrogel:**

These are highly hydrophilic or water soluble polymers that have been cross linked by means of covalent bond.

Glass transition temperature:

At low enough temperature, all amorphous polymers exist in a glassy state. In the glassy state, polymers are characterized by their hardness, stiffness and brittleness. As the temperature is raised, polymer undergoes transition, known as glass transition temperature, $T_{g,,}$ where they changes from a glass to a rubbery elastomer or flexible plastic. This transition takes place over a narrow temperature range [1,3]. As a consequence of this transition, the polymer undergoes abrupt change in properties. Among these are coefficient of expansion, permeability, heat content, refractive index, and hardness. The glass transition temperature, also known as second order transition, its value is closely related to intermolecular forces and chain stiffness. Above the T_g segmental motion of polymer chain take

place, it follows that very flexible polymer, where rotation about bonds along the polymer chain is possible. Polymer with strong intermolecular interactions will tend to have high T_g values.

Crystallanity:

Polymers that have a regular structure are able to achieve a regular packing of polymer chain and crystallize. The driving force for crystallization is a closer packing of polymer chains with consequent enhancement of intermolecular attraction. Due to crystallinity the polymers become stiffness, tough and reduce swelling in solvent. Crystalline region are impermeable to diffusing molecule and water; increase in crystallinity decrease in polymer permeability and also reduce the rate of hydrolysis.

Polymer Characterization

Molecular weight:

Osmomerty:

This method is used to determine the number average molecular weight, M_n. although in the measurement of any colligative property of a solution (such as freezing point depression, elevation of boiling point or osmotic pressure) can be used to determine the molecular weight of dissolved solute, only osmotic pressure is sensitive. If this membrane separates two compartments, one filled with pure solvent and the other with polymer solution, the activity of the solvent in the two compartments is different because polymer molecules cannot pass through the membrane; as a result, an osmotic pressure driving solvent into the polymer solution compartment will develop[3,5].

Light scattering:

Scattering of light by liquids can be related to local fluctuation in density due to thermal motion of molecules. From measurement of light scattering of dilute polymer solution, it is possible to derive the weight average molecular weight, M_w [6].

Viscometry:

They allow molecular weight determination of unknown polymers; viscometry is a relative method and required calibration with sample of polymer of known molecular weight. Determination of polymer molecular weight by measurement of the viscosity of polymer solution is based on the fact that, as polymer molecular weight increases, so does the viscosity of its solution. The viscosity is measured by timing flow of the solution between two marks in various viscometers.

Gel permeation chromatography:

Gel permeation chromatography is procedure whereby polymer molecules are separated according to their size. This method also a relative method, is capable of measuring not only molecular weight, but molecular weight distribution [1,5]. In this procedure a dilute polymer solution is pumped through a series of columns containing porous beads with different pore sizes. Typical detectors are a differential refractometers, UV or IR detectors. Molecular weight can be determined only if the method is first calibrated with known polymer molecular weight and plot the graph of molecular weight versus retention time.

Thermal analysis:

Thermo gravimetric analysis:

This method uses a thermo balance that is capable of continuously and very accurately the weight of the sample contained in a pan. The pan is placed in a furnace and the temperature of the furnace slowly raised, usually at 5°C to 10°C/min. The technique is used to determine thermal stability of polymers.

Differential Scanning Calorimetry(DSC)

This an extremely useful techniques for measuring glass transition temperature, crystalline melting point, heat of fusion and heat of crystallization.

Principle of DSC the reference and sample placed are placed in two small metal containers and heated by individual heaters. The temperature of both samples, monitored by thermocouples, is then gradually raised in such a manner that the temperature of sample and reference remains same. Then, if the sample suddenly absorbs heat, its heater will supply additional heating to maintain its temperature equal to the reference and if the sample suddenly evolves heat the heater will supply less heat. This way, transition temperature can be very accurately measured by monitoring the electric current going to the heater [1,5].

Thermo mechanical analysis: (TMA)

This techniques measures deformation of a substance under non-oscillatory load as a function of the temperature of the sample, which is placed on a platform and contacted with a probe.

c) Mechanical properties:

Mechanical properties of polymer are most conveniently determined by measuring their stress-strain relationship. Stress is stretching force applied to the sample, and strain is elongation of the sample under given stress. Because stress-strain relationship in polymer is time dependent.

SYNTHESIS OF ADDITION POLYMERS:

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. A pi-bond in the monomer is converted to a sigma-bond in the chain growth polymer; the polymerization reaction is usually exothermic by 8 to 20 kcal/mol.[7] It is useful to distinguish four polymerization procedures fitting this general description.

- Radical Polymerization
- Cationic Polymerization
- Anionic Polymerization
- Co-ordination Catalytic Polymerization
- Radical Chain-Growth Polymerization

The formulas of some common initiators and equations showing the formation of radical species from these initiators are as below.

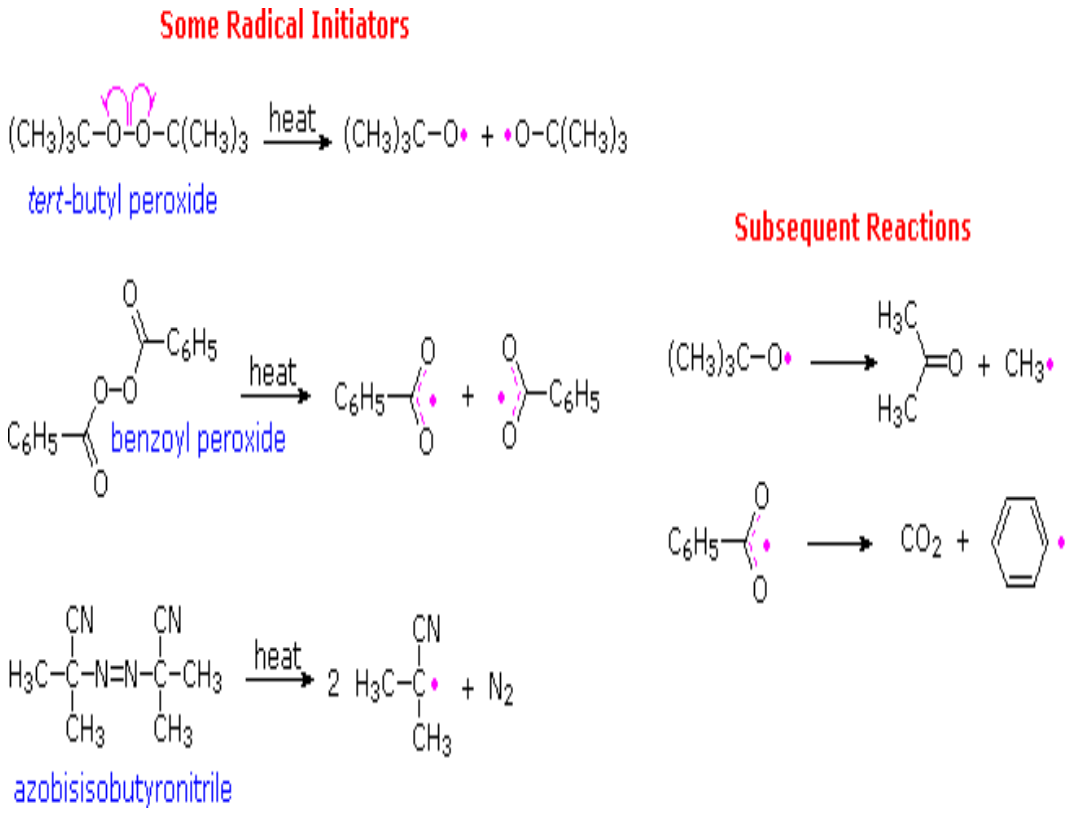


Fig.2: Radical initiator

By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical[1,7].

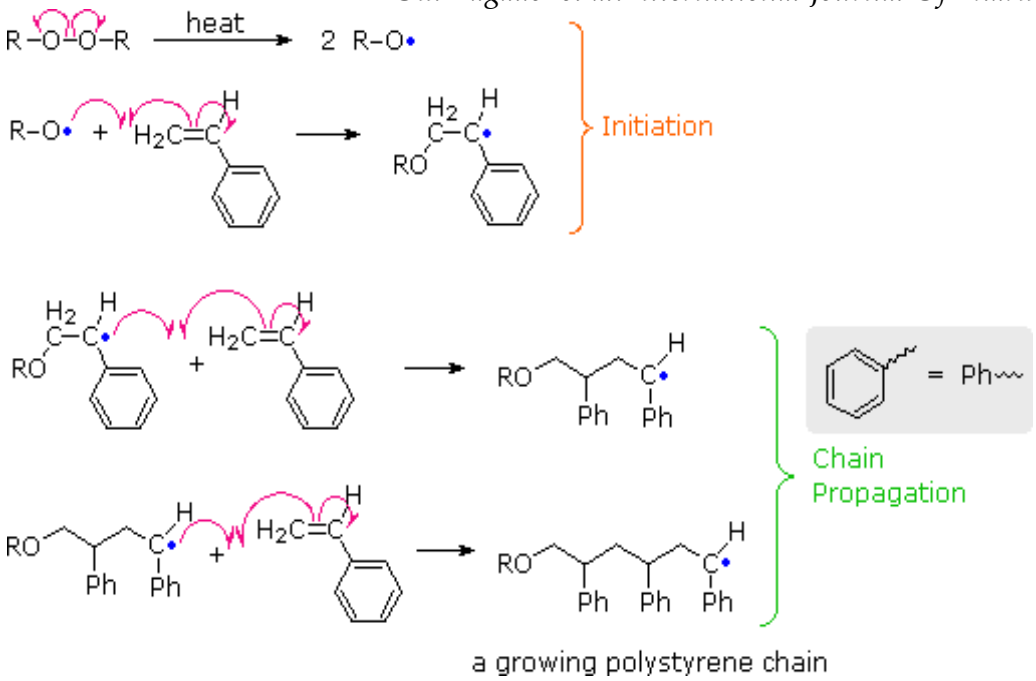


Fig.3: Chain propagation

Once started a radical polymerization might continue unchecked, producing a few extremely long chain polymers. Larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations

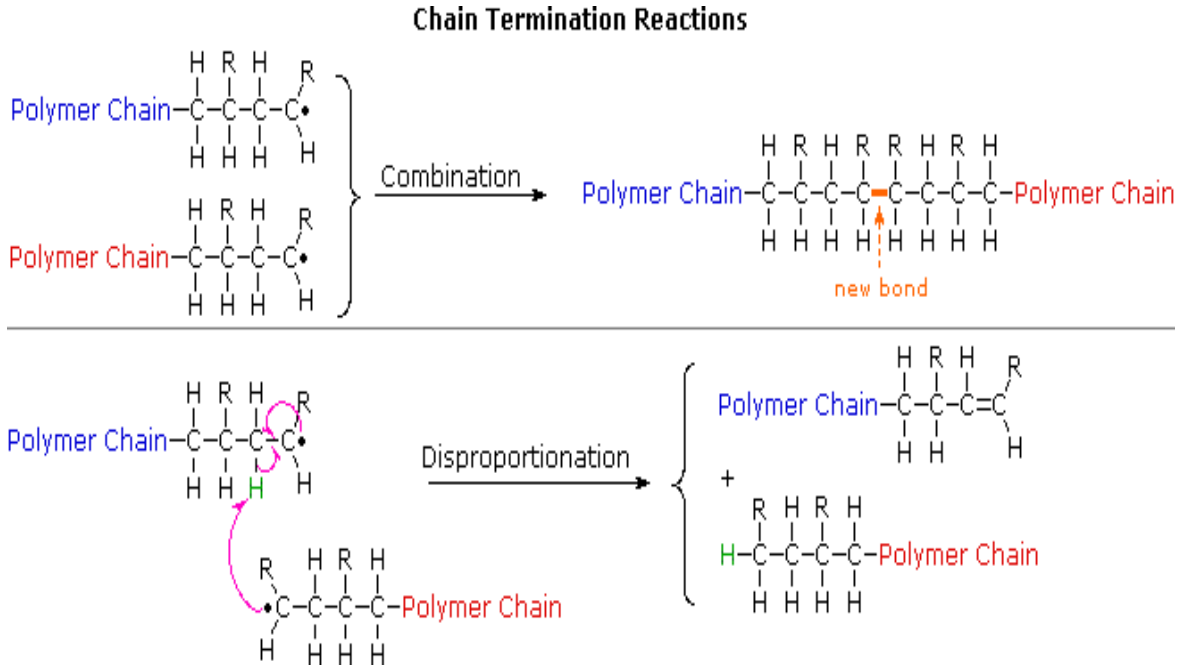


Fig.4: Chain termination

Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equation[7].

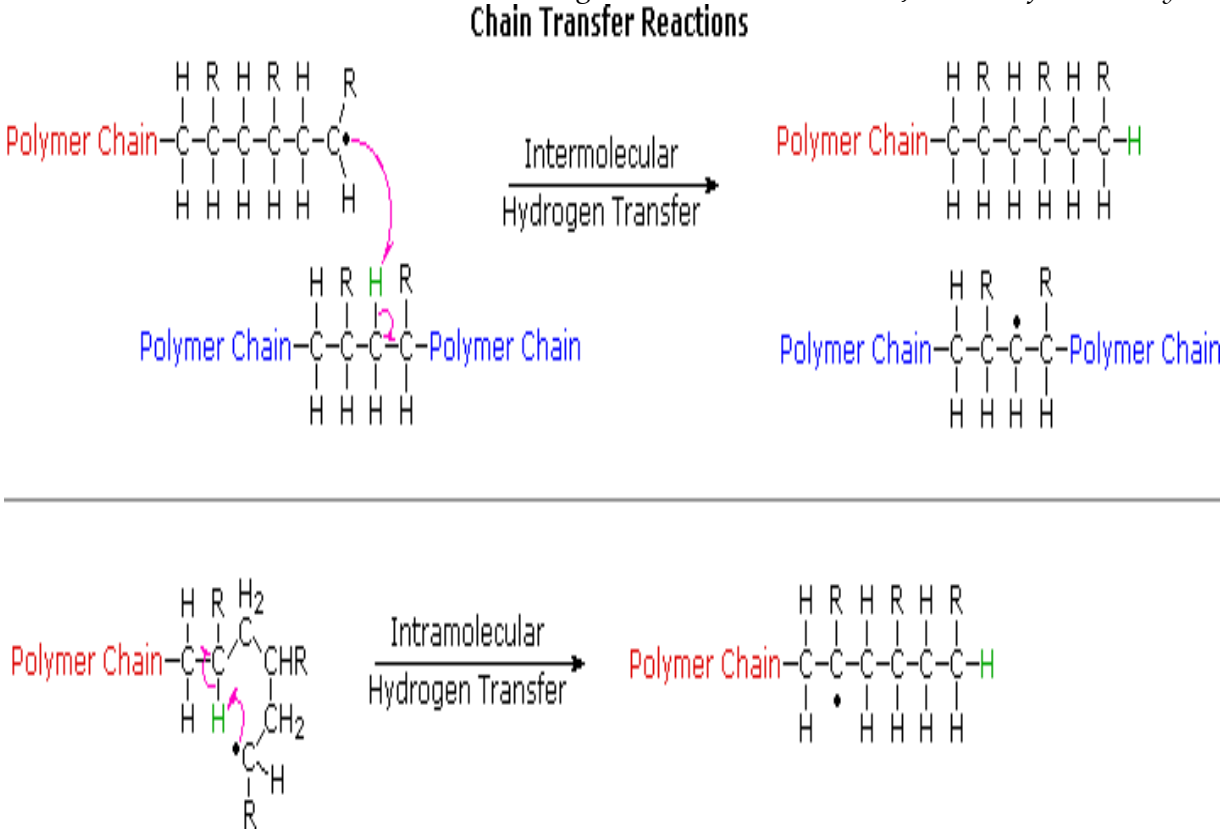


Fig.5: Chain transfer reaction.

Cationic Chain-Growth Polymerization:

The initiator is an acid, and the propagating site of reactivity is a carbocation. Only monomer that contains an electron donating substituents on the double bond that is capable of stabilizing a cation will undergo cationic polymerization. This process is similar to radical polymerization, as demonstrated by the following equations. Chain growth ceases when the terminal carbocation combines with a nucleophile or loses a proton, giving a terminal alkene.

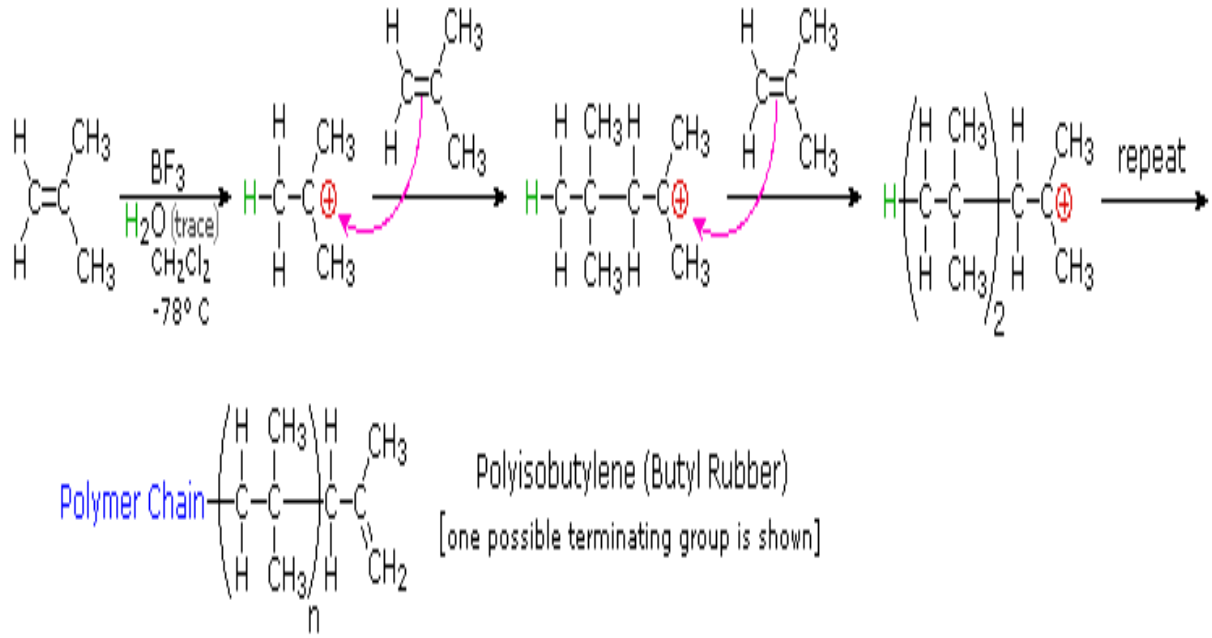


Fig.6: Cationic Chain-Growth Polymerization:

Monomers bearing cation stabilizing groups, such as alkyl, phenyl or vinyl can be polymerized by cationic processes. These are normally initiated at low temperature in methylene chloride solution. Strong acids, such as $HClO_4$, or Lewis acids containing traces of water (as shown above) serve as initiating reagents. At low temperatures, chain transfer reactions are rare in such polymerizations, so the resulting polymers are cleanly linear (unbranched) [3,7].

Anionic Chain-Growth Polymerization:

The initiator is a nucleophile, and the propagating site of reactivity is a carbanion. Only monomers having anion stabilizing substituents, such as phenyl, cyano or carbonyl are good substrates for this polymerization technique. Chain growth may be terminated by water or carbon dioxide, and chain transfer seldom occurs. Many of the resulting polymers are largely isotactic in configuration, and have high degrees of crystallinity.

Example: treatment of a cold THF solution of styrene with 0.001 equivalents of n-butyllithium causes an immediate polymerization.

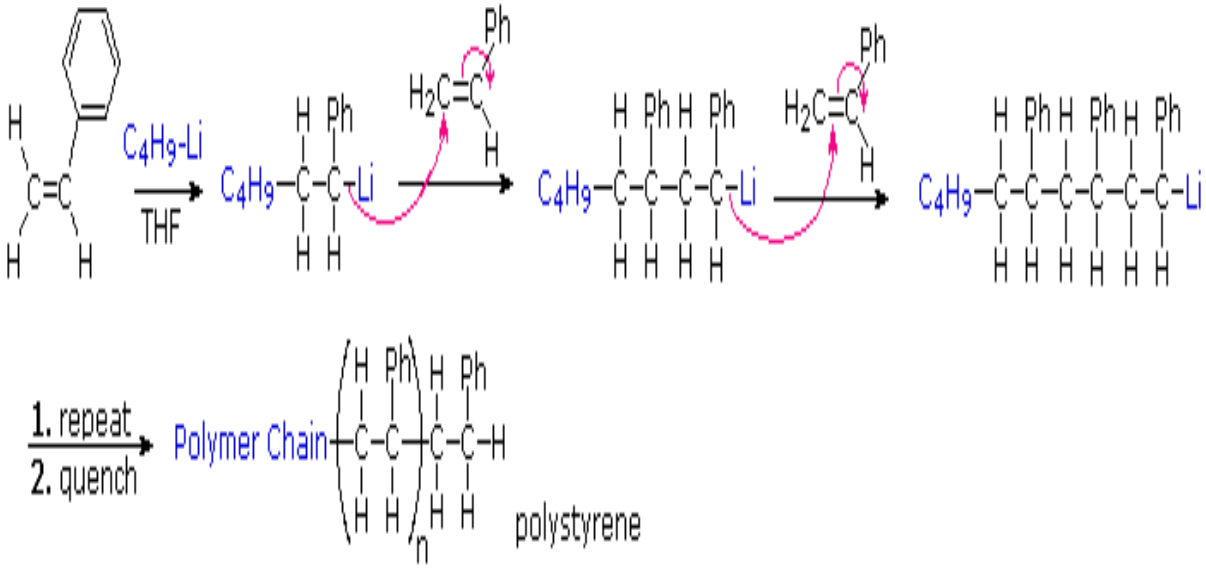


Fig.7: Anionic Chain-Growth Polymerization

Species that have been used to initiate anionic polymerization include alkali metals, alkali amides, alkyl lithiums and various electron sources. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place[3,7].

Ziegler-Natta Catalytic Polymerization:

An efficient and stereospecific catalytic polymerization procedure was developed by Karl Ziegler (Germany) and Giulio Natta (Italy) in the 1950's. For the first time, the synthesis of unbranched, high molecular weight polyethylene (HDPE) was done.

Ziegler-Natta catalysts are prepared by reacting certain transition metal halides with organometallic reagents such as alkyl aluminum, lithium and zinc reagents. Others have been suggested, with changes to accomodate the heterogeneity or homogeneity of the catalyst. Polymerization of propylene through action of the titanium catalyst gives an isotactic product; whereas, a vanadium based catalyst gives a syndiotactic product.

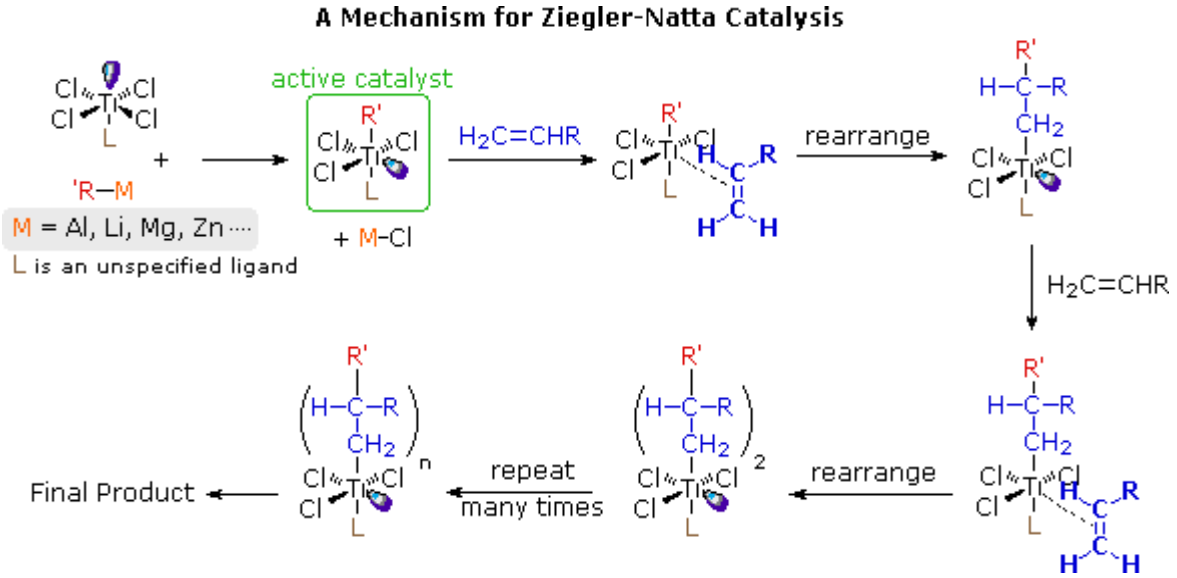


Fig.8: Ziegler-Natta Catalytic Polymerization.

Synthesis of Copolymers

The synthesis of macromolecules composed of more than one monomeric repeating unit has been explored as a means of controlling the properties of the resulting material. The following examples refer to a two component system, in which one monomer is designated A and the other B.

Statistical Copolymers Also called random copolymers. Here the monomeric units are distributed randomly, and sometimes unevenly, in the polymer chain: ~ABBAAABAABBBABAABA~.

Alternating Copolymers Here the monomeric units are distributed in a regular alternating fashion, with nearly equimolar amounts of each in the chain: ~ABABABABABABAB~.

Block Copolymers Instead of a mixed distribution of monomeric units, a long sequence or block of one monomer is joined to a block of the second monomer: ~AAAAABBBBBBB~AAAAAAA~BBB~.

Graft Copolymers As the name suggests, side chains of a given monomer are attached to the main chain of the second monomer: ~AAAAAAA(BBBBBBB~)AAAAAAA(BBBB~)AAA~.

Addition Copolymerization:

Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers, or if one monomer is much more reactive a nearly homopolymer of that monomer. In cases where the relative reactivities are different, the copolymer composition can sometimes be controlled by continuous introduction of a biased mixture of monomers into the reaction[3,7]. Formation of alternating copolymers is favored when the monomers have different polar substituents (e.g. one electron withdrawing and the other electron donating), and both have similar reactivities toward radicals.

Block Copolymerization:

Several different techniques for preparing block copolymers have been developed, many of which use condensation reactions. The unquenched polymer has been termed a living polymer, and if additional styrene or a different suitable monomer is added a block polymer will form. This is illustrated for methyl methacrylate in the following diagram.

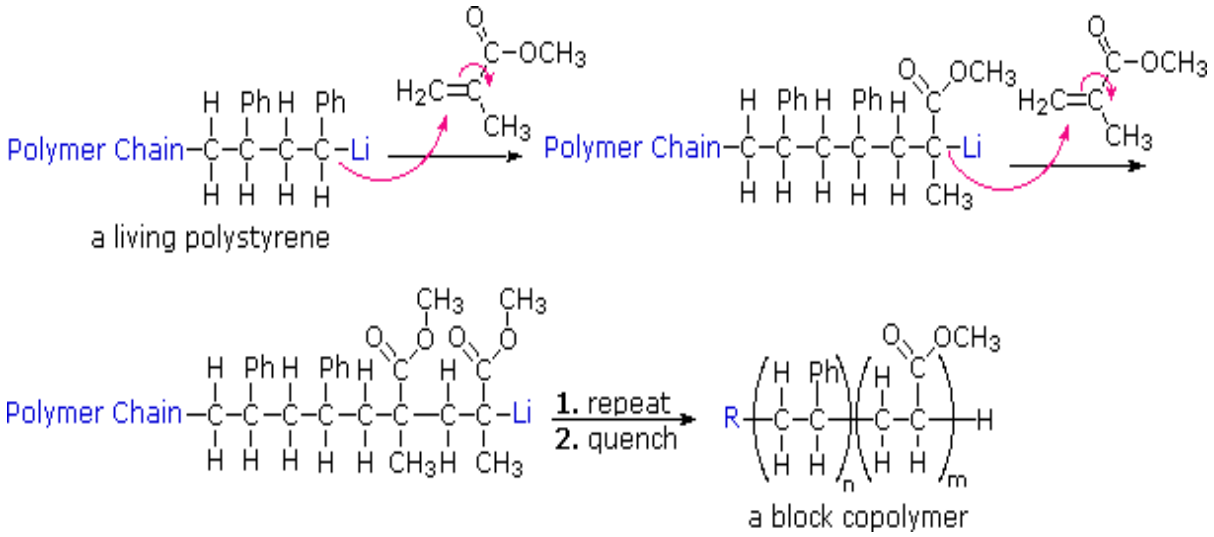


Fig.9: Block Copolymerization.

Step Growth Polymerization

Unlike chain polymerization step growth polymerization do not have discrete initiation, propagation, and termination step. Condensation polymerization can be carried out by a condensation of two monomer, each monomer bearing two identical functional groups on the same molecule or by the self condensation of one monomer bearing two appropriate functional group[1].

Non Bio-Degradable Polymers

Introduction: These polymers are not degraded in human body but they are excreated from body as in original form. These polymers are now used widely in number of preparation such as sustain release, enteric coating, film coating, blackening layer.

Classification:

Classification is based on the origin of polymer [3].

1) Natural polymers **:** e.g. Cellulose

2) Synthetic polymers **:** e.g Poly isobuthylcyanoacrylate

Poly isohexylcyanoacrylate

Poly (methyl mehacrylate)

3) Semisynthetic polymers: e.g. Ethyl cellulose, Hydroxylpropyl methylcellulose

Mechanism of drug release through non bio-degradable polymers

Drug release through non bio-degradable polymers by three mechanism [8,9].

1) Reservoir type: In which the drug is surrounded by a rate controlling polymer membrane. (Which can be nonporous, or micro porous)

2) Matrix type: In which the drug is distributed through polymeric matrix.

In both cases, drug release is governed by diffusion, i.e the drug moiety must diffuse through polymeric membrane. Selection of reservoir type or matrix type system depends on number of factor;

- ✓ The drugs physiochemical properties
- ✓ The desired drug release rate
- ✓ Desired delivery duration
- ✓ availability of manufacturing facility

It is generally easier to fabricate a matrix type system then reservoir system, so this may determine the selection of matrix system. But a reservoir system may be chosen in preference to matrix system. This is because reservoir system can provide zero ordered controlled release, where as drug release generally decrease with time if matrix system is used.

3) Matrix and reservoir type system: Combination of both system in one system to achieve beneficial effects.

1) Reservoir type system: Reservoir type system follows two mechanisms.

- **Solution diffusion :**

For solution diffusion drug reservoir is bounded by a polymeric membrane which has compact, nonporous structure and function as a rate controlling barrier. Even through the space between the polymer chain may be smaller than

size of the drug molecule, drug can still diffuse through the polymeric chains due to the continuous movement of polymer chains by Brownian motion.

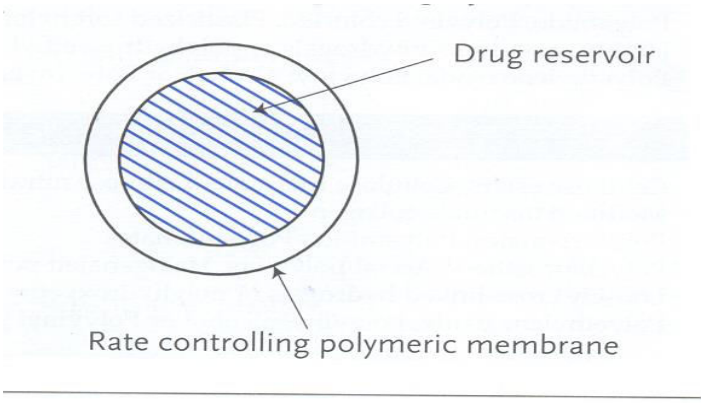


Fig.10: Reservoir type non bio-degradable polymer

For transport through the membrane, there are three barriers to be circumvented.

The reservoir- membrane interface (Donor), The rate controlling membrane (Barrier), The action site interface (Receptor).

The drug molecule in reservoir compartment initially partition into the membrane, than diffuse through it, and finally partition into the action site. The rate of drug diffusion follows Ficks Law.

$$\mathbf{dm/dt = (dk/h).\ A.\ \Delta C}$$

Where

dm/dt = the rate of drug diffusion

D = the diffusion coefficient of the drug in the membrane

K = the partition coefficient of the drug into the membrane

H = the membrane thickness

A = the available surface area

ΔC = the conc. Gradient

$$\mathbf{\Delta C \approx C_r}$$

$$\mathbf{(dk/h).\ A = K_1}$$

$$\mathbf{dm/dt = K_1 C_r}$$

Where K_1 is a pseudo rate constant and is depend on the factor D, A, k & h. this is the familiar form of the first order rate equation and indicate that the rate of diffusion is proportional to drug concentration.

So that the concentration of drug (C_r) in the system always remains constant so that eq. simplifies to;

$$dm/dt=K_2$$

Where K_2 is constant and is depend on C_r.

Above equation is familiar form of a zero order rate equation and indicate that drug release rate does not vary with time. Thus the release rate of a drug from this type of system device is constant during the entire time that remains in body [(8)].

Table-2: Polymer providing solution diffusion mechanism.

Polymers	**Uses**
Polydimethyl siloxane	Antifoaming agent, Viscosity increasing agent
Poly(ethylene vinyl acetate)	Coating agent, Lubricants
Polyethylene	Viscosity increasing agent
Polyisopropene	Viscosity increasing agent
Polyisobutylene	Viscosity increasing agent
Polybutadiene	Viscosity increasing agent

Pore diffusion:

In some cases, the rate controlling polymeric membrane is not compact but porous. Microporous membrane can be prepared by making hydrophobic polymer membrane in the presence of water soluble material such as poly(ethylene glycol), which can be subsequently removed from the polymer matrix by dissolving in aqueous solution.The transport of drug molecule across such porous membrane is termed pore diffusion. The selection of solvent importance, sinces it affect drug permeability and solubility [(8)]. As for the non porous reservoir device, in the microporous system, both; the surface area of the membrane and the drug concentration in reservoir compartment remain unchanged, thus 'M α t' kinetics is again demonstrated and zero orded controlled release is attained.

Table 3 Polymers providing pore diffusion mechanism.

Polmers	**Uses**
Cellulose ester	Enteric coating, tablet binder
Cellulose triacetate	Suspending agent, film former
Polyhydroxyethyl methacrylate	Film former, tablet binder
Polyethylene oxide	Tablet binder, thickening agent
Polyvinyl alcohol	Coating agent, stabilising agent
Povidon	Disintegrant, Suspending agent

2) Matrix-type system :

In a matrix type system the drug is distributed throughout polymeric matrix. Matrix type systems are fabricated by physically mixing the drug with a polymer powder. Matrix system follows following mechanism.

Dissolved: The drug is soluble in the polymer matrix (known as monolithic solution).

Dispersed: The drug is present above the saturation level, additional drug exist as dispersed particles in polymer matrix (known as monolithic dispersion)

Porous: With further increase in total drug payload, the undissolved drug particles keep in contact with one another. This increased the diffusion time results in a decrease in the release rate from the device with time.

$$\mathbf{M \alpha t^{1/2}}$$

This $M \alpha t^{1/2}$ release kinetics is observed for the release of up to 50% – 60% of the total drug content. Thereafter, the release rate usually decline expontially [8,10,11].

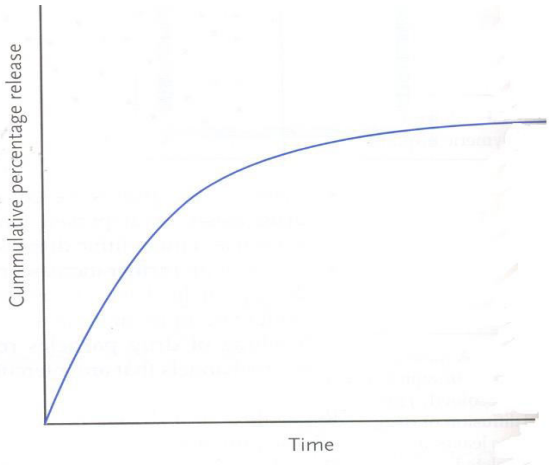


Fig.11: Cumulative percentage release

2) Reservoir and Matrix hybrid type system:

Reservoir and matrix hybrid type non degradable polymeric system are also available such system are design in an attempt to improve the $M \alpha t^{1/2}$ the release kinetics of a matrix system, so that release approximates the zero order release rate of reservoir system.

Examples of non-biodegradable polymers

Ethyl cellulose:

Nonproprietary name: BP **:** Ethyl cellulose

PhEur **:** Ethyl cellulosum

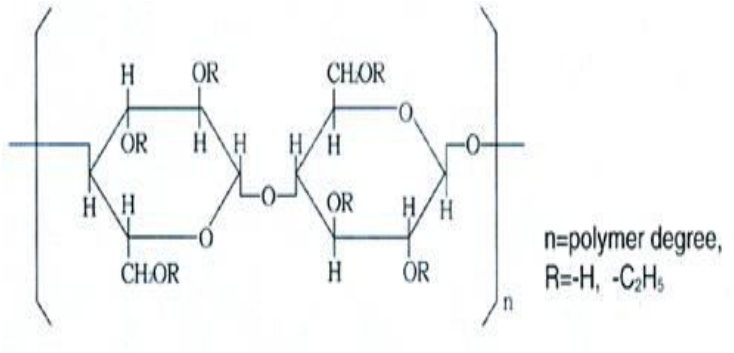
USPNF **:** Ethyl cellulose

Synonyms : AquacoatECD, Aqualon, Ethocel

Chemical name : Cellulose ethyl ether

Empirical formula : $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_NC_{12}H_{23}O$

Structural formula :



Functional category: Coating agent, Flavouring fixative, Tablet binder, Table filler,Viscosity increasing agent.

Description : Ethyl cellulose is tasteless, free flowing, white to light tancolou powder.

Typical properties:

Bulk density : 0.4 g/cm^3

Glass transition temperature: 129-133^o C

Moisture content : Ethyl cellulose absorbs very little water from humid air and that small amount evaporates readily.

Solubility: Practically insoluble in glycerin, water and propylene glycol. Freely soluble in ethanol and chloroform.

Specific gravity: 1.12-1.15g/cm^3

Viscosity: The viscosity of EC measure typically at 25 ^{0}C using 25% w/v Ethyl cellulose dissolved in a solvent blend to 80% toluene; 20% Ethanol w/w

Table 4 Viscosities of Ethyl cellulose grade.

Ethyl cellulose grade	Viscosity (m.pas)	Mean particle size (µm)
Ethocel std 4 premium	3-3.3	-
N-7	5.6-8	-
Ethocel std 7FP premium	6-8	5-15
Ethocel std 7 premium	6-8	310
T-10	8-11	-
N-10	8-11	-

Ethocel std10FP premium	9-11	3-15
Ethocel std10P premium	9-11	375
N-14	12-16	-

Incompatibilities: incompatible with paraffin wax and microcrystalline cellulose.

Method of manufacturing: Ethyl cellulose is prepared by treating pure cellulose with an alkaline solution, followed by ethylation of alkaline cellulose with chloroethane.

Application in pharmaceutical formulation:

- In oral formulation as a hydrophobic agent for tablet and granules.
- To improve the stability of formulation e.g. ethyl cellulose inhibit the oxidation.
- EC dissolved in organic solvents to produce water insoluble film.
- Drug release through Ethyl cellulose coating by diffusion mechanism.
- Ethyl cellulose coated beads have tendency to absorb the pressure and hence Protect the film from fracture during compression.
- Ethyl cellulose being coated as a dry or wet granulated with solvent (95% Ethanol) as binder.
- Ethyl cellulose produce hard tablet with low friability and poor dissolution.
- In topical formulation Ethyl cellulose is used as a thickening agent in cream, Lotion and gels.
- Additionally used in cosmetics and food products [(12)].

Table 5 Uses of Ethyl cellulose.

Uses	**Concentration (%)**
Microencapsulation	10-20
Sustain release tablet coating	3-20
Film coating	1-3
Tablet granulation as binder	1-3

Hydroxy propyl methyl cellulose:

Nonproprietary name: BP –Hpromellose

JP- HPMC

PhEur- Hypromellosum

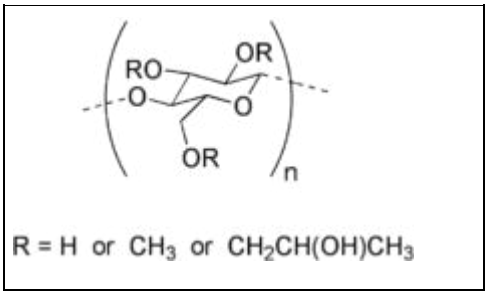
USP- Hypromellose

Synonyms **:** Benecel MHPC, E464, HPMC, Metolose, Tylopur.

Chemical name **:** Cellulose hydroxylpropyl methyl ether

Molecular weight **:** Approximately 10,000-1500,000

Structural formula



Functional category: Coating agent, film former, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Description: HPMC is an odorless, tasteless, and white to creamy white fibrous or granular power.

Typical properties:

Acidity/ alkalinity : PH 5.5-8

Autoignition temperature : 360^{o} C

Bulk density : 0.341 g/cm^{3}

Tapped density : 0.557 g/cm^{3}

True density : 1.326 g/cm^{3}

Solubility: Soluble in cold water and forming a viscous colloidal solution; practically insoluble in chloroform, ethanol and ether.

Specific gravity : 1.26

Viscosity:

Table 6 Typical viscosity values for 2% w/v aq. Solution of HPMC at 20^{o} C.

Methocel products	**Nominal viscosity (m.pas)**
Methocel K100 premium LVEP	100
Methocel K4M premium	4000
Methocel K15M premium	15000

Methocel K100M premium	100,000
Methocel E4M premium	4000
Methocel F50 premium	50

Incompatibilities: HPMC is incompatible with some oxidizing agent.

Method of manufacturing: Purified form of cellulose obtained from cotton linters is reacted with sodium hydroxide solution to produce swollen alkali cellulose that is chemically more reactive then untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ether of cellulose.

Application in pharmaceutical formulation:

- Widely used in ophthalmic and topical formulation.
- In oral products, used as tablet binder, film coating, and matrix for extended release tablet.
- Low viscosity grade are used in aqueous film coating solution, while high viscosity grade are used with organic solvents.
- As suspending and thickening agent in topical formulation.
- Compared to methyl cellulose HPMC produce clear and undispersed fiber solution therefore preferred in ophthalmic formulation.
- As an emulsifier, suspending agent and stabilizing agent in topical gel and ointment.
- Additionally in mfg of capsule, adhesive in plastic bandages, wetting agent for hard contact lenses.
- Also in cosmetics and food products [(12)].

Case study:

Devlopment and invitro evaluation of buccoadhesive tablet of Metoprolol tartrate by using Ethyl cellulose and HPMC as polymer[(13-14)].Buccoadhesive tablet of metoprolol tartrate was delvloped to prolong its release and improve bioavailability. Carbopol 934P was used as a bioadhesive polymer, Methocel K $_4$M was added as a matrix former, ethyl cellulose added for backening layer.

Table-7: Concentration of polymers.

Formula	**Carbopol**	**Methocel**
F_1	1	1
F_2	1	2
F_3	2	1

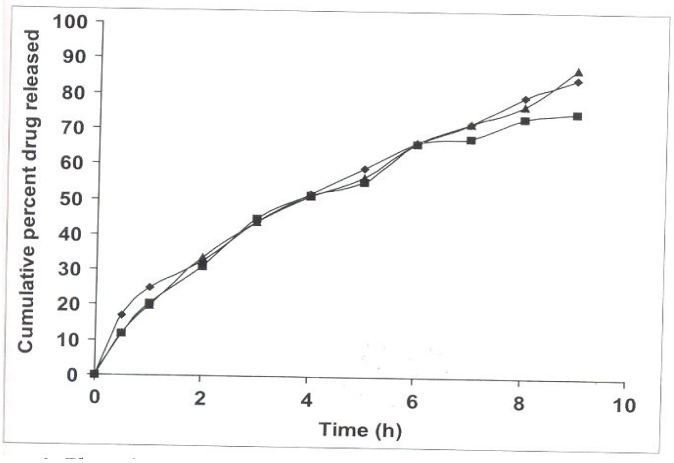


Fig.12: Plot of cumulative Percentage Drug Release in vitro versus time.

Drug Release from formulation F1, F2, F3.

Polyvinyl alcohol:

Nonproprietary name: poly (vinylis acetas)

Synonyms : alcotex, eluanol, geluatol.

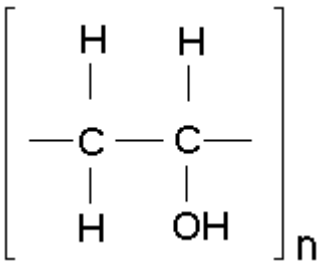
Empirical formula :$(C_2H_4O)n$

Molecular weight:

Table 8 commercially available grades of Poly vinyl alcohol.

Grades	Molecular weight
High viscosity	≈ 200000
Medium viscosity	≈ 130000
Low viscosity	≈ 20000

Structural formula:



Functional category: coating agent, Lubricant, Stabilising agent, Viscosity increasing agent.

Description: PVA occurs as odourless, white to cream colored granular power.

Typical properties:

Table-9: Commercially available grades of Poly vinyl alcohol.

Grades	Dynamic viscosity of 4 %w/v aqueous solution at 25°C

High viscosity	40-65
Medium viscosity	21-33
Low viscosity	4-7

Refractive index: 1.49-1.23

Solubility: soluble in water; slightly soluble in ethanol ;insoluble in organic solvent.

Method of manufacturing: PVA is produced through the hydrolysis of polyvinyl acetate. The hydrolysis proceeds rapidly in methanol, ethanol or mixture using alkalies or mineral acid as catalyst.

Incompatibities: PVA under goes reaction typical of compound with sec.hydroxy group such as esterification incompatible with inorganic salts especially sulphates, phosphates, it decomposes in strong acid.

Application in pharmaceutical formulation: PVA used in

- Topical pharmaceutical and ophthalmic formulation as sustain releasing agent.
- As stabilizing agent in emulsion (0.25-0.3%).
- Artificial tears and contact lens solution for lubrication purpose.
- Sustain release formulation for oral administration.
- In transdermal patches as sustain release agent.
- May be made into microspheres when mixed with glutaraldehyde solution[12,11].

(Table 10)

Povidone:

Nonproprietary name: Povidonum

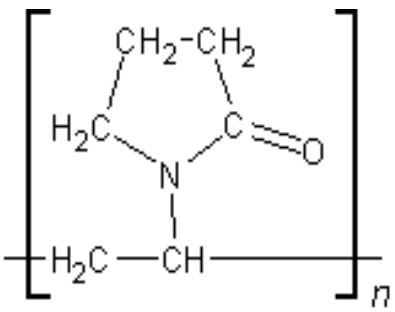
Synonyms **:** Polyvidone, Polyvinyl Pyrrolidone, PVP

Chemical name **:** 1 Ethenyl 2 Pyrrolidone, Homopolymer.

Empirical Formula **:** $(C_6H_9NO)_n$

Molecular Weight **:** 2500-3000000

Structural Formula:



Functional Category: Disintigrant, Dissolution Aid, Suspending Agent , Tablet binder.

Method of manufacturing:

Povidone is manufactured by Reppe process. Acetylene and formaldehyde are reacted in the presence of highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butindiol and than cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia; this is followed by Ninylation reaction in which pyrrolidone and acetylene are reacted under pressure the monomer vinylpyrrolidone than polymerized to give povidone.

Application in Pharmaceutical Formulation: Povidon used as

- Binder in wet granulation process.
- Solubilizer in Oral & Parenteral formulation.
- Enhance Dissolution of poorly soluble drugs.
- Suspending Agent, Stabilizing agent & Viscosity enhancer in topical & oral suspension & solution.[12]

(Table 11)

Case Study:

The rate of dissolution of danazol was improved by co grinding them with HPMC and PVP result in more sustain release of drug.

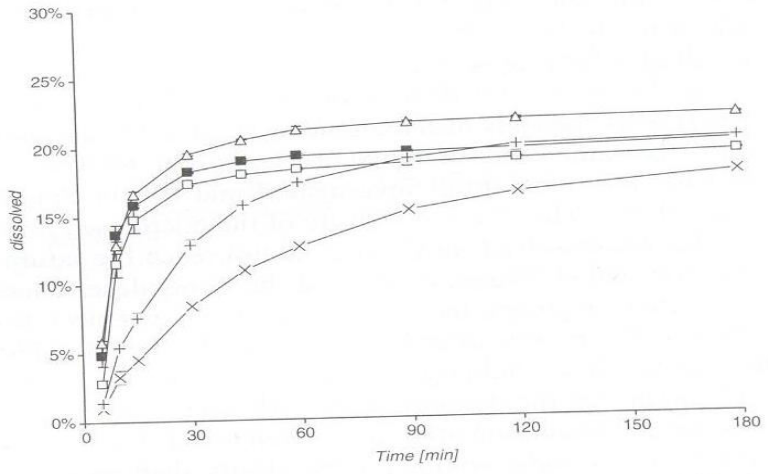


Fig.13: Dissolution profile

Polymethacrylates:

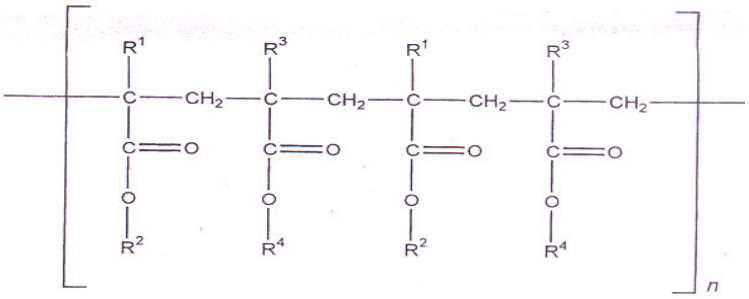
Nonproprietary Names: BP: Methacrylic acid—ethyl acrylate copolymer (1 : 1)

PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum 1: 1

USPNF: Ammonio methacrylate copolymer Methacrylic acid copolymer

Synonyms **:** Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates Structural Formula

Structural Formula



Functional Category: Film former; tablet binder; tablet diluent.

Description:

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios.

- Eudragit E 'is cationic polymer based on dimethylamino ethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH 5). Eudragit E is available as a 12.5% ready-to-use solution in propanol—acetone (60:40). It is Light yellow in color with the characteristic odor of the solvents.

- Eudragit L and S, also referred to as methacrylic acid copolymers in the USPNF 23 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester approximately 1: 1 in Eudragit L (Type A) and approximately 1:2 in Eudragit S (Type B). Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6—7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. Eudragit L-1 00 and Eudragit s-1oo are white free-flowing powders with at least 95% of dry polymers. Eudragit PS 30D is the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate, and methacrylic acid. The ratio of free carboxyl groups to ester groups is approximately 1 : 10. It has been designed for the use in enteric-coated solid-dosage forms and dissolves in aqueous systems at pH >7.

- Eudragit RL and Eudragit RS, also referred to as ammonio methacrylate copolymers in the USPNF 23 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with Eudragit RL (Type A)

having 10% of functional quaternary ammonium groups and Eudragit RS (Type B) having 5% of functional quaternary ammonium groups.

- Eudragit RD100 is in the powder form, which can be redispersed in water and used as rapid disintegrating films. The composition for Eudragit RD100 is Eudragit RL100 and carboxymethylcellulose sodium (90: 10).
- Eudragit NE 30 D and Eudragit NE 40 D are aqueous dispersions of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low Viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give PH-independent drug release.[9]
- Eudragit L 30 D-5S, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 23 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1: 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.
- Eastacryl 30D, Kollicoat MAE 30 D, and Kollicoat MAE 30 DP are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USPNF 23 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media, but soluble in the small intestine.
- Eudragit L 100-55 (prepared by spray-drying Eudragit L 30 D-55) is a white, free-flowing powder that is redispersible in water to form a latex that has properties similar to those of Eudragit L 30 D-SS.
- Acryl-EZE and Acryl-EZE MP are also commercially available as redispersible powder forms, which are designed for enteric coating of tablets and beads, respectively (Table 12)

Applications in Pharmaceutical Formulation:

1. Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced;
2. Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast.
3. Eudragit LS and PS types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g. Eudragit L is soluble at pH > 6; Eudragit S and PS are soluble at pH> 7.

4. Eudragit RL, RS, RD 100, NE 30 D and NE 40 D are used to form water-insoluble film coats for sustained-release products. Eudragit RL films are more permeable than those of Eudragit KS, and films of varying permeability can be obtained by mixing the two types together.
5. Eudragit L 30 D-SS is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.
6. Eudragit L 100-55 is an alternative to Eudragit L 30 D-55. It is commercially available as a redispersible powder. Acryl-EZE and Acryl-EZE MP are also commercially available as redispersible powder forms, which are designed for enteric coating of tablets and beads, respectively.
7. Eastacryl 30 D, Kollicoat MAE 30 D, and Kollicoat MAE 30 DP, are aqueous dispersions of methacrylic acid—ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.
8. Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5—20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10—50%.
9. Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.

Case study:

Formulation and invitro evaluation of gastric oral floating tablet of glipizide by using HPMC and PVP as polymer in different concentration [15-17].

(Table 13)

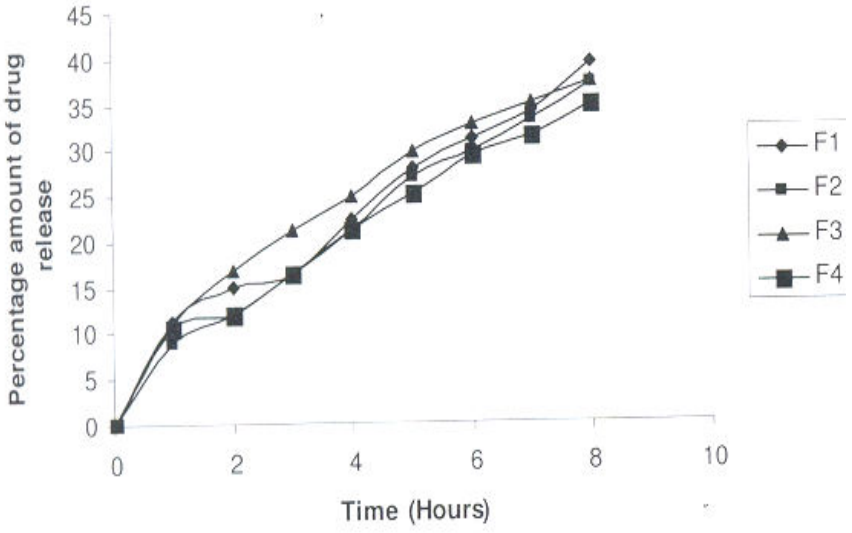


Fig.14: Cumparative Drug Release Profile of F1 to F8.

Dimethicone:

Nonproprietary name: Dimethicone, Dimethiconum

Synonyms :Dimethylpolysiloxane; Imethylsilicone fluid; methypolysiloxane

Empirical formula : $[-(CH_3)_2SiO-]n$

Functional Category : Antifoaming agent, Emollient

Description :Dimethicone are clear liquid available in various viscosities

(Table 14)

Solubility: Miscible with ethyl acetate, Mineral oil, Toluene; soluble in isopropyl myristate; insoluble in glycerin, water.

Method of manufacturing:

Dimethicone is poly(dimethyl siloxane) obtained by hydrolysis and polycondensation of dichlorodimethyl silane and clorotrimethyl silane. The hydrolysis product contain active silanol group through which condensation polymerization proceed. by varying the proportion of chlorotrimethyl silane which act as chain terminator silicones of varying molecular weight may be prepared.

Application in pharmaceutical formulation:

- Dimethicone of various viscosities are widely used in cosmetics and pharmaceutical prepration .
- In topical o/w emulsion dimethicone is added to the oil phase as an antifoaming agent.
- Dimethicone is hydrophobic and is widely used in topical barrier prepration[(12)].

Table-10: Uses of Poly vinyl alcohol in different concentration.

Uses	**Conc. in %**
Emulsifying agent	0.5
Ophthalmic formulation	0.25-3.00
Topical lotion as stabilizing agent	2.5

Table-11: Uses of Povidon.

Uses	Concentration (%)
Carrier for drug	10-20
Dispersing Agent	Up to 5
Eye drops as sustain releasing agent	2-10
Suspending Agents	Up to 5
Tablet Binder/Diluents & Coating Agent	0.5-5

Table-12: Typical Properties

Acid value:	300—330 for Eudragit L 12.5, L 12.5 P, L 100, L 30 D-SS, L
	100-55, Eastacryl 30D, Kollicoat MAE 30 D, and Kollicoat
	DP180—200for MAE 30
Alkali value:	162—198 for Eudragit E 12.5 and E 100;
	23.9—32.3 for Eudragit RL 12.5, RL 100, and RL P0;
	27.5—31.7 for Eudragit RL 30D;
	12.1—18.3 for Eudragit RS 12.5, RS 100, and RS P0;
	16.5—22.3 for Eudragit RS 30D.

Density:

Density (bulk):	0.390g1cm^3
Density (tapped):	0.424 g/cm^3
Density (true):	0.811—0.821 g/crn^3 for Eudragit E;
	0.83—0.85 g/cm^3 for Eudragit L, S 12.5 and 12.5
	1.058—1.068g1cm^3 for Eudragit FS 30D;
	0.831—0.852g1cm^3 for Eudragit L, S 100;
	1.062—1.072g/crn^3 for Eudragit L 30 D-55;
	0.821—0.841 g/cm^3 for Eudragit L 100-55;
	0.816—0.836g1cm^3 for Eudragit RL and RS 12.5;
	0.816—0.836g1cm^3 for Eudragit RL and RS P0;
	1.047—1.057g/cm^3 for Eudragit RL and RS 30 D;
	1.037—1.047g1cm^3 for Eudragit NE 30D

Table-13: Concentration of polymers.

Polymer	**F1**	**F2**	**F3**	**F4**
HPMC (mg)	30	40	20	30
PVP (mg)	10	10	10	10
Eudragit Rs 100	-	-	10	10

Table -14: Typical properties.

Sr.No.	Properties	Units
1	Acid value	<0.01

2	Density	0.94-0.98g/cm^3 at 25^o C
3	Refractive index	1.401-1.405
4	Kinematic viscosity	20-1300mm2/s
5	Viscosity	20-30000mm^2/s

Conclusion

A number of substances both biodegradable as well as non biodegradable have been investigated for the preparations and also act as building blocks. These materials include the polymers of synthetic or natural origin and also modify natural substances examples like methyl methacrylate, acrolein, gelatin, starch etc. The non biodegradable polymers are not degraded in human body but they are excreted from body as in original form. These polymers are now used widely in number of preparation such as sustain release, enteric coating, film coating, blackening layer which lay down the standards to widen its role in novel drug delivery system.

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