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NATURAL AND SYNTHETIC POLYMERS USED IN FORMULATION OF SUSTAINED RELEASE MATRIX SYSTEMS

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ABSTRACT

The main profits of sustained release dosage form compared to a conventional dosage form, is the steady drug plasma concentration. Matrix tablets distribute as an important tool for oral controlled release dosage forms. With the increasingly interest in polymers of natural origin, the pharmaceutical world has acceptance to use most of them in their formulations. These polymers such as natural gums and mucilage are bio-compatible, cheap and easily available and preferred to synthetic and semi synthetic excipients because of their absence of toxicity, low cost, availability, soothing action, and nom irritant nature.

Keywords: Sustained release tablets, Xanthan gum, HPMC, Matrix tablets.

INTRODUCTION

Oral route is oldest and appropriate route for the administration of therapeutic agents because of low of cost of therapy and facility of administration leads to higher level of patient compliance. Normally conventional dosage form produces vast range of fluctuation in drug concentration in the blood steam and tissue with resultant undesirable toxicity and poor efficiency. Developing oral sustained release matrix tablets for drug with constant release rate has always been a provocation to pharmaceutical technologist. Sustained release drug delivery system that attains slow release of drug over an increase period of time. Sustained release matrix tablet is relatively easy to fabricate by absorbing drug molecules in slowly disintegrating.

Polymers are flattering increasingly important in the field of drug delivery. The pharmaceutical applications of polymers range from their use as binder in tablets to consistency and flow controlling agents in liquids, suspension and emulsions. Both synthetic and

natural polymers are used in pharmaceutical purpose. It can be used as film coatings to disguise the disagreeable taste of a drug, to enhance drug stability and to modify drug release characteristics.

The ideal polymer would allow the process to operate synchronously, i.e. present a balance between the principle processes of swelling, erosion, and dissolution. Controlled drug delivery system (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner.

Matrix system are widely used for the purpose of sustained release. It is the release system which prolongs the release of drug that is dispersed. The materials widely used in preparing matrix system is include both hydrophilic and hydrophobic polymers. Commonly used hydrophilic polymers include Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), xanthan gum, sodium alginate, polyethylene oxide and cross-linked homopolymers. It is usually supplied in micronized forms because small particle size is critical to the quick formation of gelatinous layer on the tablet surface.

POLYMER

The word 'polymer' is conceived from two Greek words: *poly* means many and *mer* means unit or part. polymers are the giant molecules of high molecular weight called macromolecules which are formed by joining of replicating structural units on huge scale. The replicating structural units are derived from simple and reactive molecules known as monomers and are linked to each other by covalent bonds. The process of formation of polymer from separated monomers is called polymerization.

CLASSIFICATION OF POLYMERS

- Natural polymer
- Synthetic polymer
- Semi synthetic polymer

A. Natural polymer: The polymers, which occur in nature are called natural polymers also known as biopolymers. Example of such polymers are gum karaya, gum guar, xanthan gum, starch, cellulose, chitosan, protein, polysaccharides, etc.

Chitosan: It is a linear polysaccharide. It is made by treating the chitin shells of shrimp and other crustaceans with an alkaline substance, such as sodium hydroxide. It is a fibrous substance that might block absorption of dietary fat and cholesterol. It is used to preserve the drugs and oral vaccines for sustained release into the gastrointestinal tract.

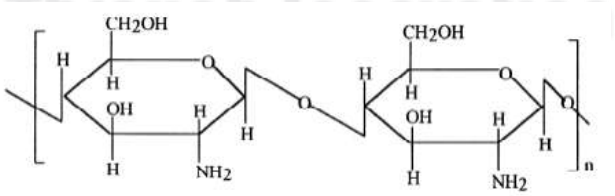


Fig 1: Chemical structure of chitosan.

Starch: starch is a polymeric carbohydrate consisting of numerous glucose units joined by glycosidic bonds called polymers. Starch is a white, tasteless and odourless powder that is insoluble in cold water or alcohol. starch derivatives like carboxymethyl starch, starch acetate and cross-linked starch have been used as a excipient's in oral tablets to steady release.

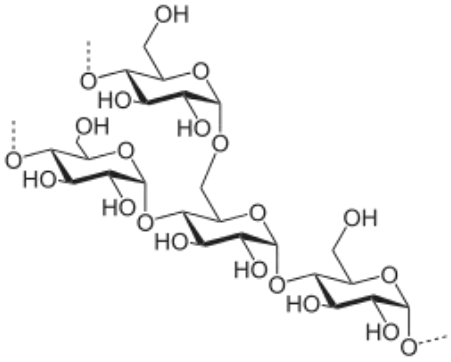


Fig 2: Chemical structure of starch.

Cellulose: It is an organic compound and a polysaccharide consist of a linear chain of several hundred to many thousands of Beta(1-4) linked D-glucose units. Cellulose is non- toxic and biodegradable. It is used to control release of drugs, as the pharmacological response of drug which is not achieved in the case of a speedy release.

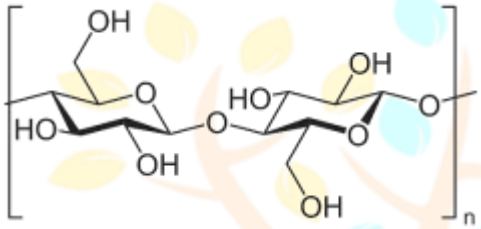


Fig 3: Chemical structure of cellulose.

Xanthan gum: It is a polysaccharide. It is used as a suspending agent for the sustain release formulations that have a swelling rate. It also an effective thickening agent and stabilizer to protect ingredients from separating. xanthan gum is used for diabetes, dry eye and many other conditions.

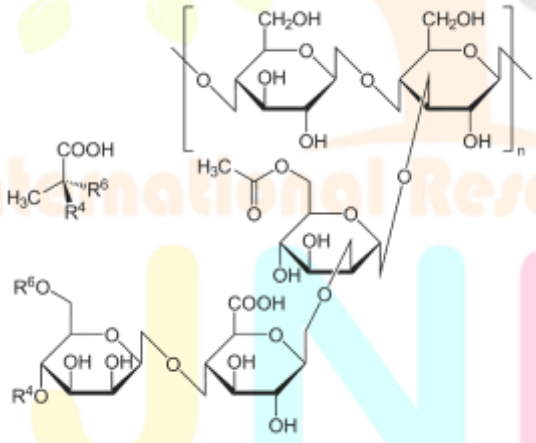


Fig.4: Structure of xanthan gum.

Gum karaya: Gum karaya, also known as Tragacanth Gum. It is sap-like material taken from a tree. It used as bulk-forming laxative to relieve constipation. karaya gum swells in the intestine, which stimulate the digestive tract to push stool through. In manufacturing, karaya gum is used as a binder and stabilizer in food.

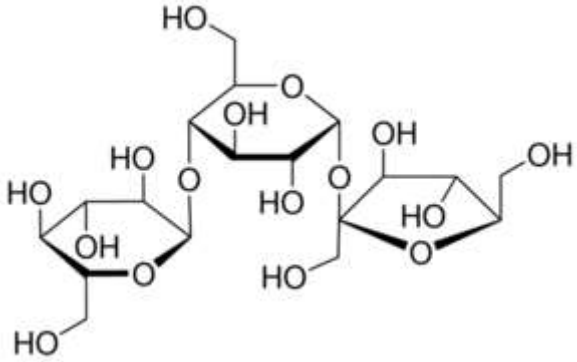


Fig.5: structure of Gum karaya.

Guar gum: It is a fibre extracted from guar plant that has stabilizing properties useful in feed. It is also used as release-modifying agent in control release tablets. Guar gum is used for diarrhoea, constipation, irritable bowl-syndrome, high cholesterol, and high blood pressure.

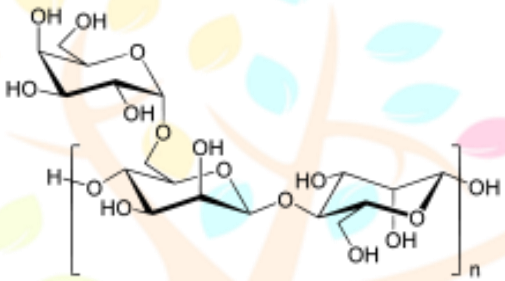


Fig.6: structure of Guar gum.

Locust bean gum: It is extracted from the seeds of the carob tree. It is also known as carob gum. It is used as a viscosity-increasing agent and as a binding agent. It helps soften stool and can reduce constipation.

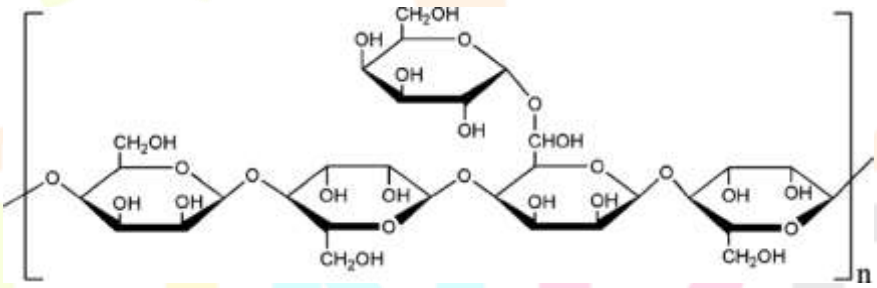


Fig.7: Chemical structure of locust bran gum.

ADVANTAGES OF NATURAL POLYMER

- ❖ Biocompatibility
- ❖ Presence of cell recognition and adhesion sites
- ❖ Similarity with native extracellular matrix
- ❖ Biodegradability
- ❖ Bioactivity
- ❖ Easily available
- ❖ Less toxic

DISADVANTAGES OF NATURAL POLYMER

- Properties depend on extraction
- Susceptibility to cross-contamination
- Difficult processing
- Low stability
- Structurally more complex
- High degree of variability in natural materials derived from animal sources

B. Synthetic polymer:

The polymer which has been synthesised in laboratory is known as synthetic polymer. These are also known as manmade polymers. Example of such polymers are polyvinyl alcohol, polyethylene, polystyrene, PVC, nylon, Teflon, epoxy etc.

Polyvinyl alcohol (PVA): It is a synthetic polymer that is soluble in water. PVA is used in a variety of medical applications because of its biocompatibility, low tendency for protein adhesion, and low toxicity. It is used as an aid in suspension polymerizations. It is also resistant to oil, grease and solvents.

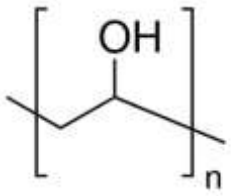


Fig 8: Chemical structure of PVA.

Polyacrylic acid: It is a biodegradable polymer that is ability to retain water and swell. It is also used as a thickening agent, suspending agent and emulsifying agent in pharmaceuticals. It is mainly used for oral applications as control release tablets.

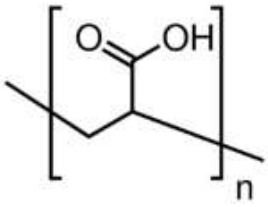


Fig.9: Chemical structure of polyacrylic acid (PAA).

Polyacrylamide: It is a synthetic polymer that is obtained from units of acrylamide. It is non-toxic polymer that is more used for sustained release delivery. various drug delivery systems are based on this polymer.

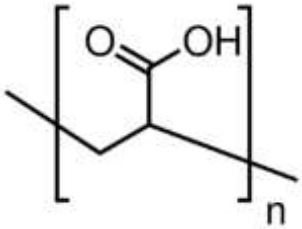


Fig.10: Chemical structure of acrylamide.

Lactide: It is biodegradable polymer which is widely used as drug delivery systems and tissue engineering.

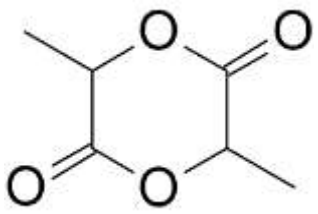
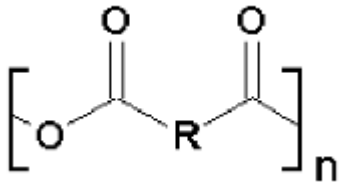


Fig.11: Chemical structure of lactide.

Polyanhydride: It is a polymer identified by anhydride bonds that join repeat units of the polymer spine chain. It is capable of releasing entrapped drug by well- defined kinetics. It is synthesised by melt solution polymerization.



Fig,12: Chemical structure of polyanhydride.

ADVANTAGES OF SYNTHETIC POLYMER

- Low immune response
- Low production cost
- Appropriate mechanical properties
- Biocompatibility

DISADVANTAGES OF SYNTHETIC POLYMER

- Toxic
- Non degradable
- Loss of mechanical strength after degradation
- Low ductility
- Uncomfortable shrinkage effects

C. Semi synthetic polymer: They are chemically modified natural polymers such as hydrogenated, cellulose nitrate, methyl cellulose, starch, HPMC, silicones, etc.

Methyl cellulose: Methyl cellulose is a chemical compound derived from cellulose. It is used as a thickener and emulsifier un various food and cosmetic products, and also as a bulk-forming laxative. It is a hydrophilic white powder in pure form and dissolves in cold water. The lubricating property of methyl cellulose is of particular benefit in the treatment of dry eyes.

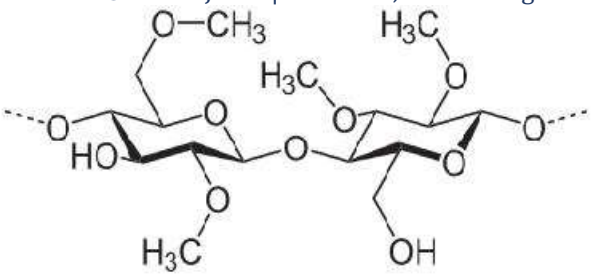


Fig 13: Chemical structure of methyl cellulose.

Hydroxypropyl methylcellulose (HPMC): It is also known as Hypromellose. It is a natural polysaccharide found in all plant parts. It is a methyl and hydroxypropyl mixed either of cellulose. It is insoluble in hot water, acetone, and chloroform. It is soluble in cold water giving a colloidal solution owing to the reversible thermal gelation property.

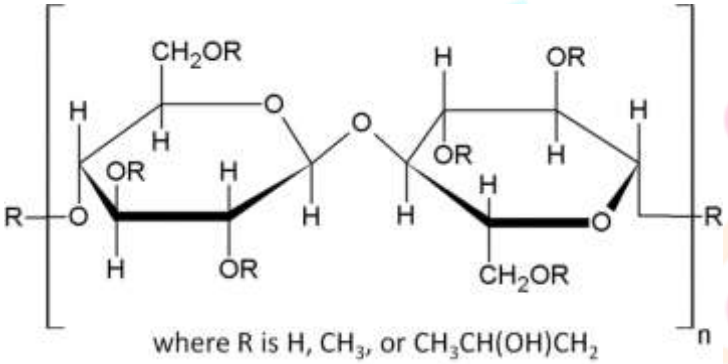


Fig 14: Chemical structure of HPMC.

Sodium carboxymethyl cellulose (Na CMC): It is cellulose gum is a cellulose derivative which have wide range of functional properties like binding, emulsifying, thickening, stabilizing agent. It is also used as a lubricant and as a disintegrant in pharmaceutical preparations. It is used to design the matrix tablets.

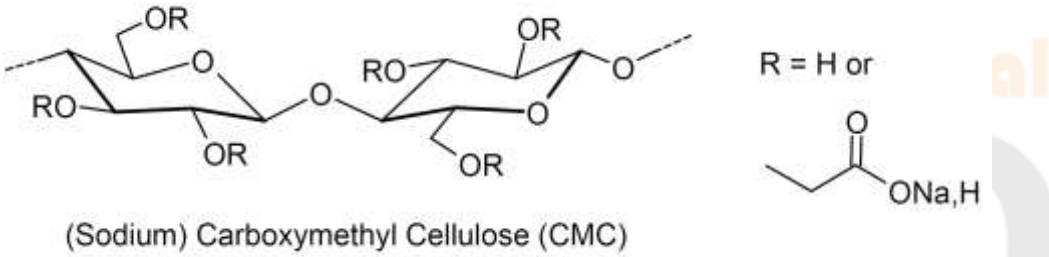


Fig.15: Chemical structure of Na CMC.

Ethyl cellulose: It is non- biodegradable and biocompatible polymer which is studied for the delay release formulations. It is mainly used as a thin- film coating material. It is also used as emulsifier in the food industry. It is insoluble in water and soluble in solvents.

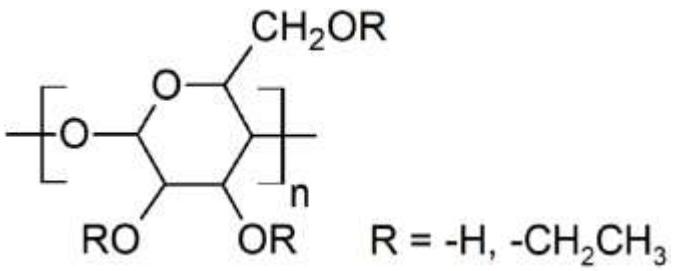


Fig.16: Chemical structure of Ethyl cellulose (EC).

CHARACTERISTICS OF IDEAL POLYMER

- Excellent surface finish can be obtained.
- Can be produced transparent or in different colours.
- Low coefficient friction.
- Low mechanical properties.
- Poor temperature resistance.

Polymers used in sustained released system:

Sr.no.	Polymer characteristics	Materials
1.	Unsolvable, immobile	Polyethylene, polyvinyl chloride, ethyl cellulose.
2.	Indissoluble	Carnauba wax, stearyl alcohol, stearic acid, polyethylene glycol, castor wax, polyethylene glycol monostearate, triglycerides.
3.	Non-ionic	Methyl cellulose, hydroxyethyl cellulose, HPMC, sodium CMC, sodium alginate.

SUSTAINED RELEASE MATRIX SYSTEM

Matrix tablets composed of drug and polymer as release delayed material that approaches in developing a sustained-release drug delivery system. Matrix tablet is Important tool for modified dosage forms. The hydrophilic polymer matrix is widely used in sustained release matrix dosage form.

PROPERTIES 0F SUSTAINED RELEASE MATRIX SYSTEM

Physicochemical properties:

1. **Aqueous solubility**

Aqueous solubility of a drug exerts its control on the absorption process in two ways-

i. By impact on the dissolution rate of a compound which confirmed the drug concentration in solution and the driving force for tissue permeation.
ii. By its effect on the ability of the drug penetrate tissues which is determined in part by its solubility in the tissue.

2. **Partition coefficient**

The important criteria evolution of the ability of a drug to probe these liquid membranes is it clear oil-water partition coefficient, write as

K=Co/Cw

where, Co= equilibrium concentration of all forms of the drug.

Cw= equilibrium concentration of all form of in an aqueous phase.

3. **Drug stability**

Drugs with low aqueous solubility have low dissolution rate and usually suffer oral bioavailability problems. Aqueous solubility of weak acids and base is governed by Pka value of pH of the medium.

4. **Molecular size**

Ability of drug to diffuse through membrane is known as diffusivity, is a function of molecule size.

5. **Protein binding**

Distribution of drug in to extra space is ruled by dissociation of drug from protein. Drug-protein complex acts as reservoir in the vascular space for sustain drug release to extra vascular tissue for drug exhibiting high degree protein binding.

BIOLOGICAL PROPERTIES

1. **Absorption**

Rate extent, uniformity of absorption are the important factors for sustained release.

2. **Distribution**

The distribution of drug in to vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics**.** Volume of distribution obeys only one compartment model

V=dose/co

where, Co-plasma drug concentration.

3. **Metabolism**

It is conversion of a drug to another chemical form and this is contemplated in the design of sustained release system for the drugs. Ability of the drug to inhibit enzyme synthesis and fluctuating drug blood level, main factors associated with metabolism.

4. **Elimination**

The rate of elimination of drug is reported quantitively by its biological half -life.

t1/2 =0.693 v/cls

where v= volume of distribution

cls=systematic clearance

cls = I.V administered dose/AUC

5. **Safety considerations and side effects**

Reduced side effects for a particular drug done by controlling its plasma concentration. To measure margin of safety of drug its therapeutic index is contemplated.

TI=TD50/ED50

Where, TD50-median toxic dose
ED50- median effective dose.

ADAVANTAGES OF SUSTAINED RELEASE MATRIX TABLETS

- Improved efficiency in treatment.
- Obtained less potential of reduction in drug activity and chronic use.
- Minimize drug accumulation.
- Avoid patient's acceptance problem due to reduced frequency of dosing.
- improved bioavailability of drugs.
- Reduced local and systemic adverse effects.
- Greater drug utilization.
- Cure more promptly.
- Reduced gastrointestinal side effects.
- Reduction in personal time to dispense.
- Reduction in fluctuation in steady-state levels.
- Reduction in health care costs through therapy.

DISADVANTAGES OF SUSTAINED RELEASE MATRIX TABLETS:

- Poor In vitro-in vivo correlation.
- Formulation cost is high.
- Difficulty to maintain stability of dosage form.
- Need high sophisticated technology for the formulation.
- Decrease potential for dosage adjustment.
- Slow in onset of action.

MECHANISM OF DRUG RELEASE FROM POLYMER

Three primary mechanism for drug release from polymer:

- Diffusion
- Degradation
- Swelling (water penetration)

Drug release from polymer by diffusion:

A. Reservoir
B. Matrix

Reservoir diffusion system:

In membrane–controlled reservoir system, the drug is contained in a core, which is adjoining by a polymer membrane, and it is released by diffusion through the rate controlling membrane. E.g. poly (N- vinyl pyrrolidone), poly (ethylene-co-vinyl acetate).

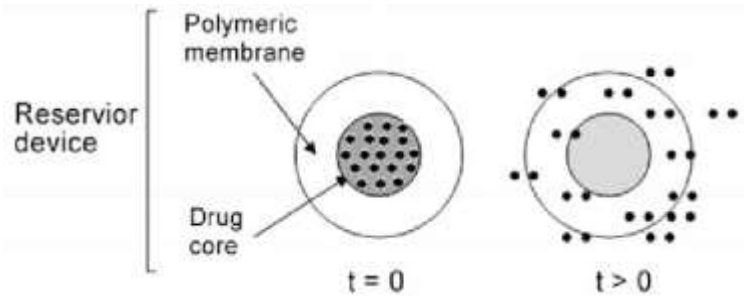


Fig 17: Reservoir diffusion mechanism.

Matrix diffusion system:

In these devices, is released again by passing through the pores or between polymer chains, and these are the processes that control the release rate. E.g. polyethylene, polyvinyl acetate.

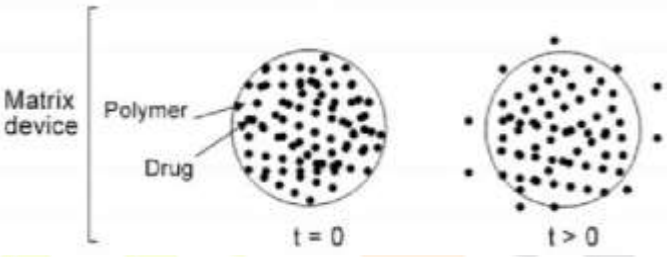


Fig 18: Matrix diffusion system mechanism.

Degradation:

The drug molecules, which are starting dispersed in the polymer, are released as the polymer starts ending or degrading.

The four most commonly used biodegradable polymers in drug delivery systems are poly (lactic acid), poly (lactic-co-glycolic acid), and polyanhydrides.

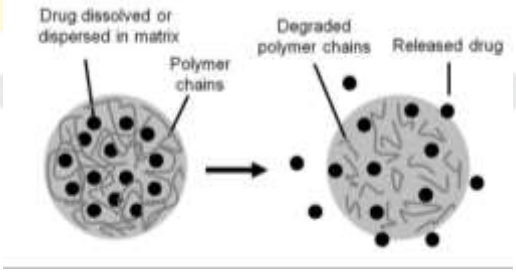


Fig 19: Degradation mechanism of drug release.

Swelling:

This type of systems are initially dry and when placed in body, absorb water or other fluid and it swells. Swelling increase aq. Solvent content within the formulation as well as the polymers tracery size, enabling the drug to spread through the swollen mesh into external environment.

e.g. (N-iso-propyl-acrylamide), ethylene-vinyl alcohol.

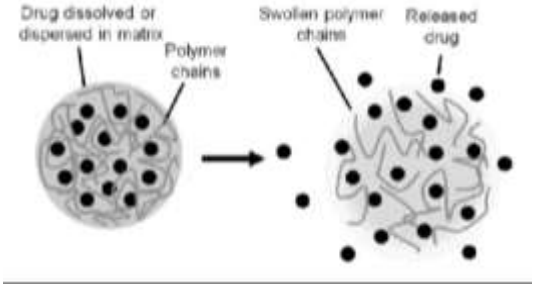


Fig 20: Swelling mechanism of drug release.

CRITERIA FOLLOWED IN POLYMER SELECTION

Polymer chosen as potential drug carrier must exhibit certain properties, as listed below:

- ❖ It should be biodegradable
- ❖ It should be compatible with the biological environment, i.e. non-toxic, non-antigenic and non-provocative.
- ❖ It must be soluble and easy to synthesis.
- ❖ It must have a finite molecular weight and narrow distribution.
- ❖ It should provide drug attachment or release sites for the possibility of incorporation of drug-polymer linkages.

Below the table show the drug to be formulated as a sustained release matrix tablet with polymer used for its preparation:

DRUG USED	DRUG CATEGORY	POLYMER USED
amlodipine	Anti- hypertensive	HPMC, Ethyl cellulose
verapamil	Calcium channel blocker	HPMC-K100M, HPMC-K4M, HPMCK15M
Tramadol	B2 blocker	HPMC-K4M, karaya gum
Theophylline	Respiratory depressant	Carbopol-934p, HPMC-K4M, HPMCK100M, Ethyl cellulose
Ranitidine HCL	H2 antagonist	Chitosan, Carbopol-940
Naproxen	Morphine antagonist	PVP, CMC, HPMC-K100M, HPMC-K15M
Miconazole	Anti- fungal	Pectin, HPMC
Losartan potassium	Anti- hypertensive	HPMC-K100M, HPMC-K4M, Eudragit- RSPO
Flutamide	Anti- androgen	HPMC-K4M, sod. CMC, Xanthan gum

Ambroxol HCL	Mucolytic, Expectorant	HPMC-K100M
Aceclofenac	Anti- inflammatory	HPMC-K4M, K15M, Guar gum
Furosemide	Anti-diuretic	Guar gum, Pectin, Xanthan gum
Metformin HCL	Anti-diabetic	HPMC-K100M, ethyl cellulose
Minocycline	Antibiotic	Ethyl cellulose, HPMC-K4M
Domperidone	Anti-emetic	HPMC-K4M, Carbopol-934
Nicorandil	Calcium channel blocker	HPMC, CMC, Ethyl cellulose
Zidovudine	Anti-viral	Carbopol-934, Ethyl cellulose
Venlafaxine	Anti-depressant	Carnauba wax, Bees wax
Alfuzosin	Alfa-adrenergic agonist	Eudragit-RSPO
Ibuprofen	Anti-inflammatory	Ethyl-cellulose
Propranolol HCL	Beta-adrenergic blocker	Locust bean gum
Acarbose	Anti-diabetic	HPMC
Aspirin	Anti- inflammatory	Ethyl- cellulose, Eudragit S100
Diclofenac sodium	Anti-inflammatory	Chitosan, HPMC
Diltiazem	Calcium channel blocker	Sodium CMC, locust bean gum
Enalapril maleate	ACE inhibitor	HPMC K4M, K100M
Itopride HCL	Prokinetic agent	Ethyl cellulose, HPMC K4M
Metoclopramide	Anti- emetic	Carboxy methyl cellulose, EC
Phenytoin sodium	Anti- epileptic	Acacia, Guar gum, Xanthan gum
Ondansetron	Anti-hypertensive	Hydroxy propyl methyl cellulose

CONCLUSION

Polymer plays an important role in the drug delivery system (DDS). but, the selection of polymers has to be taken with care regarding its toxicity, drug compatibility and degradation pattern. Biodegradable polymers have proven their potential for the development of new, advanced and efficient DDS and capable of delivering a wide range of bioactive materials.

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