ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

A DETAILED DESCRIPTION OF SYNTHETIC AND NATURAL POLYMERS WHICH ARE USED IN THE FORMULATION OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW

RAJESWARI KOLA*, BADA PRAGATHI KUMAR
Department of Pharmaceutics
Nimra College of Pharmacy, Vijayawada
***Corresponding author: E.Mail:rajeswarikola@gmail.com**

ABSTRACT

To control the drug release rate from the formulation, polymers are being used as the main tool. They are used as rate controlling agents, taste masking agents, protective and stabilizing agents in the oral drug delivery system. Their application in drug delivery system has been identified because of their unique properties. Advances in polymer science led to the development of novel drug delivery systems which can be modified by chemical or carrier based or drug entrapment or within pumps placed in the desired bodily compartments. To reduce the frequency of dosing and to increase the effectiveness of the drug by localisation at the site of action, to provide uniform drug delivery certain polymers are used. These polymers are classified as natural polymers, semi synthetic and synthetic polymers. By using these particular polymers the drug release can be sustained for a certain period of time and drug release can be maintained at a uniform rate. Today polymeric materials still provide most important avenues of research. This review focuses on the polymers which are used in sustained release formulations.

KEY WORDS: sustained release, polymers, controlling agents, Eudragit, HPMC.

1. INTRODUCTION

Polymers are compounds with high molecular masses formed by monomers. The word poly means ‘many’ in Greek meros mean ‘units or parts’. They consist of different functional groups. Because of their unique properties polymers are extensively used in pharmaceuticals. The new technology in polymer based drug release system offer possibilities in administration of drugs. Pharmaceutically these polymers are used as a binder in tablets, flow controlling agents in liquids, suspension and emulsions, as film coating agents to mask unpleasant taste of drug, to enhance drug stability, to modify the release characteristics of the drug. The rate of the drug release from a matrix product depends on the initial drug concentration and relaxation of the polymer chains, which overall displays a sustained release characteristic (Kathryn E. Uhrich, 1999).

The goal in designing sustained release drug delivery system is to reduce frequency of dosing, to increase the effectiveness of the drug at the required site thereby minimising or eliminating side effects, providing uniform drug delivery. Sustained release has received most of the attention because of the fact that there is more feasibility in dosage form.

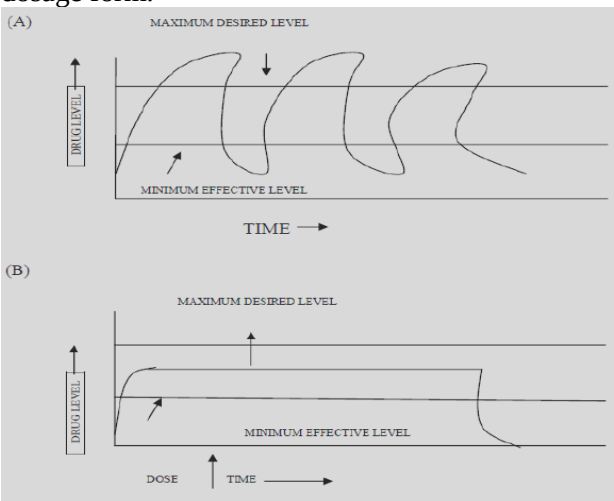


Figure.1.Showing the difference between conventional drug delivery system and sustained release drug delivery system.
(A) Graph representing conventional drug delivery system
(B) The graph represents the therapeutic window between the minimal therapeutic concentration and the maximum therapeutic concentration

In conventional drug therapy, the administration of drug by oral, intramuscularly, intravenously, rectal routes drug cannot be maintained for a longer period of time at therapeutic range (Reja M, Quadir MA, 2003). Plasma drug concentration in therapeutic concentrations can be maintained for a longer period of time by using novel drug delivery systems, which are further classified in to

1. Delayed release

2. Sustained release
3. Site –specific release
4. Receptor targeting

1.1. Sustained release drug delivery system: In modern therapeutics controlled release or sustained release dosage forms have become extremely popular. The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems modifying the physiological parameters. Sustained release drug delivery system not only prolongs the duration of action but also implies the predictability and reproducibility of drug release kinetics.

Advantages:

1. Improved therapeutic efficacy.
2. Decreased local and systemic side effects.
3. Reduced gastrointestinal irritation.
4. Reduction in fluctuation in drug level.
5. Improved patient compliance
6. Less dosing frequency, reduce night time dosing.

Disadvantages:

1. Increased first pass metabolism.
2. Increased instability, insufficient residence time.
3. Poor *in-vitro/in-vivo* correlation.
4. Retrieval of drug is difficult in case of toxicity.
5. Reduced potential for dose adjustment of drugs.

Parameters for selection of drug for sustained release drug delivery system:

Parameter	Preferred value
Molecular Weight:	< 1000
Solubility:	> 0.1µg/ml for pH 1 to 7.8
Pka:	non ionised moiety > 0.1 % at pH 1to 7.8
Apparent Volume of distribution:	larger Vd and MEC, larger dose size is required
Absorption mechanism:	Diffusion
Release:	Should not influence by pH and enzymes
Elimination half life:	Between 0.5 and 8 hours
Total clearance:	Should not be dose dependent
Absolute bioavailability:	Should be 75% or more

2. VARIOUS POLYMERS USED IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM

2.1. Hydroxy Propyl Methyl Cellulose (HPMC) (pharmaceutical excipients 5th edition)

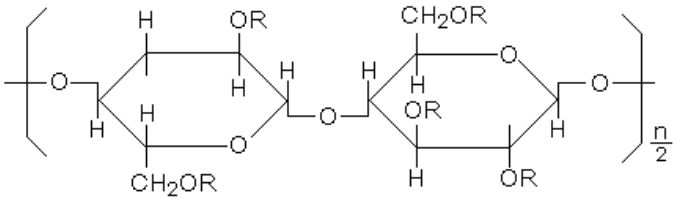


Figure.2.Molecular structure of HPMC

In the formula, 'n' stands for agglutination degree, 'R' stands for -H,-CH_3 or -$CH_2CHOHCH_3$.

Properties: White to off-white fibrous powder or granules swells in water to produce a viscous colloidal solution non-ionic. HPMC is multifunctional water soluble polymer

Solubility: Dissolves slowly in cold water, insoluble in hot water, soluble in most polar solvents, insoluble in anhydrous alcohol, ether and chloroform.

Density: 1.39 gm/c.c

Surface activity: Aqueous solutions are surface active, form films upon drying and undergo reversible transformation from sol to gel upon heating and cooling metabolic inertness - Used as food and drug additives.

Enzyme resistance: Enzyme-resistant HPMC products provide excellent viscosity stability during long-term storage.

pH stability: HPMC (cellulose ethers) are stable over a pH range of 3 to Thickening - Thicken both aqueous and non-aqueous systems. The viscosity is related to the molecular weight, chemical type, and concentration of the specific HPMC product.

Functional category: Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; Tablet binder; viscosity-increasing agent

Applications:

- Used in controlled-release formulations.
- Typical products used in controlled release include METHOCEL K100 Premium LV, K4M Premium, K15M Premium, K100M Premium , E4M Premium, and E10M Premium CR.
- METHOCEL E and METHOCEL K are the most widely used for controlled-release drug formulations.

Types of Methocel:

- Methocel K100 Premium LVEP 2208 100
- Methocel K4M Premium 2208 4000
- Methocel K15M Premium 2208 15 000
- Methocel K100M Premium 2208 100 000
- Methocel E4M Premium 2910 4000
- Methocel F50 Premium 2906 50
- Methocel E10M Premium CR 2906 10 000
- Methocel E3 Premium LV 2906 3
- Methocel E5 Premium LV 2906 5
- Methocel E6 Premium LV 2906 6
- Methocel E15 Premium LV 2906 15
- Methocel E50 Premium LV 2906 50

Major factors responsible for the choice of HPMC as sustained release polymer: Drug solubility is one of the most influential factors for designing a drug release pattern. Highly water- soluble drugs require higher amounts of HPMC The higher viscosity of HPMC or amount of HPMC in the tablet can decrease the drug release rate. Generally an optimum content of HPMC in the tablet is at least 20%. If the content is below 20 %, there is a risk for initial erosion or excess dissolution in the first stage.

Preparation method also affects the dissolution profile due to the difference of HPMC particle distribution in the tablet. In the case of wet granulation, most of the water can be taken up by HPMC, resulting in the separation of METOLOSE and the other components. (i.e.large particles with high METOLOSE content and ungranulated drug in the fine particle fraction.) Direct compression methods can avoid such processing factors. HPMC is exclusively designed for a hydrophilic matrix agent having tighter specifications, which is especially suitable for direct compression application. The matrix system has several advantages as follows:

1. It is very simple and easy to establish a formulation.
2. The tablet is completely dissolved and thus achieves good bioavailability.
3. It is easy to control the dissolution profile by selecting a specific grade.
4. The matrix system is an economical method for obtaining controlled release products.

2.2. Hypromellose: It is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

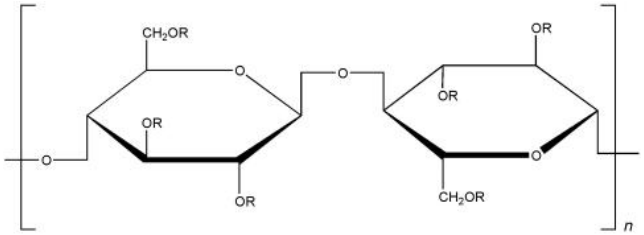


Figure.3.Molecular structure of Hypromellose

Properties:

Molecular weight: approximately 10 000–1 500 000

Acidity/alkalinity: ph = 5.5–8.0 for a 1% w/w aqueous solution.

Density (bulk): 0.341 g/cm3
Density (tapped): 0.557 g/cm3
Density (true): 1.326 gm/c.c
Melting point: browns at 190–200°c; chars at 225–230°c. Glass transition temperature is 170–180°c.
Moisture content: hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether.
Stability and storage conditions: hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at ph 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°c, depending upon the grade and concentration of material.
Applications:

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
- In oral products, hypromellose is primarily used as a tablet binder and in film-coating
- As a matrix former in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80 % w/w in tablets and capsules.
- Depending upon the viscosity grade, concentrations of 2–20 % w/w are used for film-forming solutions to film-coat tablets.
- Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.
- Hypromellose is also used as a suspending and thickening agent in topical formulations.
- Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

2.3. Hypromellose acetate Succinate
Chemical name: (2-hydroxypropyl methyl ether, acetate succinate)
Molecular weight: Approximately 55,000–93,000
Applications: Hypromellose acetate succinate is commonly used in oral pharmaceutical formulations as a film coating, as well as enteric coating material for tablets or granules

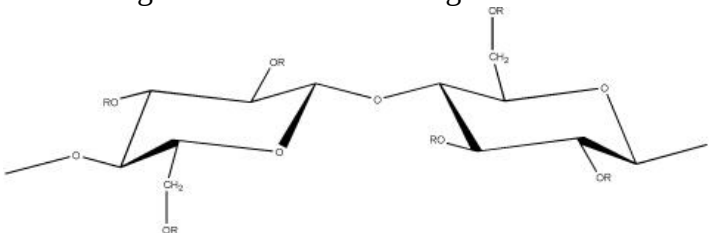


Figure.4.Molecular structure of Hypromellose acetate succinate

2.4. Polyvinyl alcohol (PVA) (Wade and Weller, 1994 and Martindale, 1999)
Molecular formula: (C2H4O) n

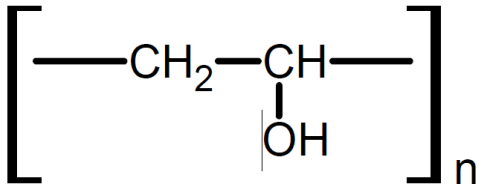
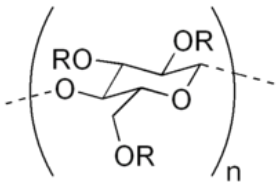


Figure.5.Molecular Structure of Poly Vinyl Alcohol (The value of 'n' lies between 500 to 5000)
Properties:
Melting range: 220 to 240 ^{o}C
Description: White to cream colored, odorless granules.

Solubility: It is soluble in water at room temperature. Solution may be affected more rapidly at somewhat higher temperatures, insoluble in organic solvents.
Viscosity: 35-50 cp (4% of solution at 20 ^{o}C).
Infrared spectrum: Principle peaks at wave number (cm-1) 3308, 2940, 1456, 1339, 1144, 1097, 921, 850, 590
Packaging and storage: Store in a well-closed container
Pharmaceutical uses:

- PVA is used in concentrations of 1% to stabilize emulsions.
- It is used to increase viscosity of ophthalmic preparations thus prolonging contact of the active ingredients with the eye and are present in some ocular lubricants and contact lens,
- Wetting agent in preparation of jellies, which dry rapidly when applied to skin to form soluble plastic films.
- It is commercially used in the preparation of transdermal patches
- **e.g.** Nitro-Dur. It is widely used in many ophthalmic and topical preparations. It is nontoxic,non-irritant and has been cleared for food contact.

2.5. Ethyl cellulose (Wade and Weller, 1994**):**



R = H or CH_2CH_3

Figure.6.Molecular structure of Ethyl Cellulose

Synonyms: Aquacoat, Ethocel, Surelease.
Chemical name: Cellulose ethyl ether
Functional category: Coating agent, tablet binder, viscosity–increasing agent.
Description: Ethylcellulose is a tasteless, free–flowing, white to light tan colored powder.
Stability and storage: Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than cellulose esters. Ethylcellulose is subjected to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of an antioxidant and a compound with light absorption properties between 230 to340 nm. The bulk material should be stored in a dry place, in a well-closed container at a temperature between 7–32°C.
Applications

- Ethylcellulose is widely used in oral and topical pharmaceutical formulations.
- The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.
- Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasanttaste, or to improve the stability of a formulation, e.g. ethylcellulose dissolved in propan–2–ol is used to coat ascorbic acid granules to prevent oxidation.
- Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.
- Ethylcellulose dissolved in an organic solvent, or solvent mixture, can be used on its own to produce water–insoluble films. Higher viscosity ethylcellulose grades tend to produce stronger and tougher films.
- Ethylcellulose films may be modified to alter their solubility, by the addition of hydroxypropylmethylcellulose, polyethyleneglycol or a plasticizer.
- An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacom (FMC Corporation) may also be used to produce ethylcellulose films without the need of organic solvents.
- Ethylcellulose is also widely used in microencapsulation
- In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95 %). Ethylcellulose produces hard tablets, with low friability; they may however demonstrate poor dissolution.
- In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions or gels, provided an appropriate solvent is used. Ethylcellulose is additionally used in cosmetics and food products.

Incompatibilities: Incompatible with paraffin wax and microcrystalline wax.

2.6. Eudragit (Wade A and Weller P. J, 1994**):**

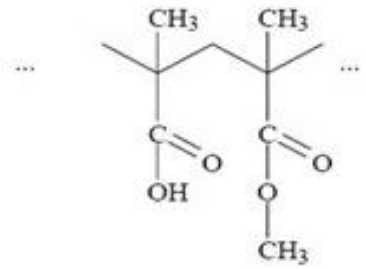


Figure.7.Molecular Structure of Eudragit

Synonyms: Eudragit; polymeric methacrylates.

Functional category: Film–former, tablet binder, tablet diluent.

Description: Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, an aqueous dispersion, or as an organic solution. A (60:40) mixture of acetone and propan–2–ol is most commonly used as the organic solvent.

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to approximately pH 5).

Eudragit E is available as a 12.5% ready–to–use solution in propan–2–ol/acetone (60:40). It is light yellow in colour with the characteristic odour of the solvents. Solvent–free granules contain > 98% dried weight content of Eudragit E.

Eudragit L and S are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L and approximately 1:2 in Eudragit S. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats, which are resistant to gastric media, but soluble in intestinal fluid. They are available as a 12.5% solution in propan–2–ol without plasticizer (Eudragit L 12.5 and S 12.5); and as a 12.5% ready–to–use solution in propan–2–ol with 1.25% dibutyl phthalate as plasticizer (Eudragit L 12.5 P and S 12.5 P).

Stability and storage conditions: Dry powder polymer forms are stable at temperatures less than 30 °C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least two years, if stored in a tightly closed container at less than 30 °C. Dispersions are sensitive to extreme temperatures and phase separation occurs below 0 °C. Dispersions should therefore be stored at temperatures between 5–25 °C and are stable for at least one year after shipping from the manufacturer's warehouse provided filled in a tightly closed container at the above conditions.

Applications:

- 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.
- Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, Eudragit L and S types are used as enteric coating agents, since they are resistant to gastric fluid. Different types are available which are soluble at different pH values, e.g. Eudragit L 100 is soluble at > pH 6, Eudragit S 100 is soluble at > pH 7.
- Eudragit RL, RS and NE 30 D are used to form water insoluble film coats for sustained release products. Eudragit RL films are more permeable than those of Eudragit RS, and by mixing the two types together, films of varying permeability can be obtained.
- Eudragit L 100–55 is a redispersible powder and is an alternative to Eudragit L 30 D–55 for aqueous enteric coating.
- 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%. 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.

2.7. Eudragit L-100:

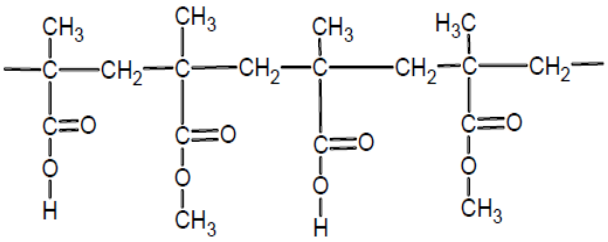


Figure.8.Molecular structure of Eudragit L-100

Synonyms*:* Polymethacrylate, Polymeric methacrylate

Chemical name: Poly (methacrylic acid methyl methacrylate)

Description: Eudragit L-100 is a white, free flowing powder with at least 95% of dry polymers. It is an anionic co-polymerization product of methacrylic acid and methyl methacrylate. It is soluble at > pH 6. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L-100. It is readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus affording film coats which are resistant to gastric media, but soluble in intestinal fluid.

Solubility: It is freely soluble in acetone, alcohol and sodium hydroxide. It is insoluble in dichloromethane, ethyl acetate, petroleum ether and water.

Stability and storage conditions: Dry powder polymer forms are stable at temperature less than 30 ^{o}C for at least two years, if stored in a tightly closed container.

Applications: Widely used as enteric coating material in oral pharmaceutical formulations.

2.8. Eudragit RSPO:

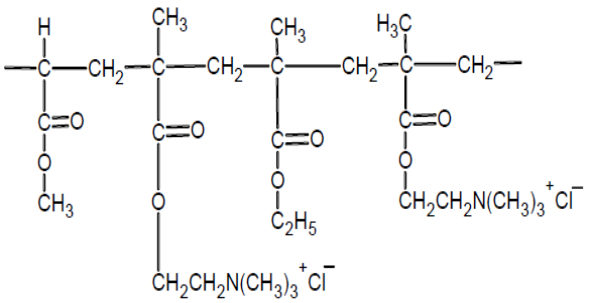


Figure.9.Molecular Strucure of Eudragit RSPO

synonym: Ammonio methacrylate copolymer

chemical name: Poly (ethylacrylate, methyl methacrylate, trimethyl ammonioethylmethacrylate chloride) 1:2:0.1.

Description: Eudragit RS PO is characteristically the same polymer as Eudragit RS. It is a fine white powder with slight amine like odor and contains 97% dry powder. It is synthesized from acrylic acid and methacrylic acid esters with 5% functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH independent permeability of the polymers. It is a water insoluble polymer and films prepared are only slightly permeable to water.

Solubility: It is freely soluble in acetone, alcohols, dichloromethane, solvent ethyl acetate and insoluble in petroleum ether and water.

Applications: It is used for the preparation of sustained release products.

2.9. Xanthan gum:

Synonyms: Corn sugar gum, Keltrol, Merezan, Polysaccharide B-1459, Rhodigel

Empirical formula: Xanthan gum is a polysaccharide with -D-glucose backbone like cellulose, but every second glucose unit is attached to a trisaccharide consisting of mannose, glucuronic acid, and mannose. The mannose closest to the backbone has an acetic acid ester on carbon 6, and the mannose at the end of the trisaccharideis linked through carbons 6 and 4 to the second carbon of pyruvic acid.

Source: Xanthan Gum is produced by the bacterium Xanthomonascampestris, which is found on cruciferous vegetables such as cabbage and cauliflower. The negatively charged carboxyl groups on the side chains because the molecules to form very viscous fluids when mixed with water.

Description: Xanthan gum occurs as a cream or white-colored, odorless, free flowing, fine powder.

Functional category: Stabilizing agent, suspending agent, viscosity increasing agent

Solubility: Practically insoluble in ethanol and ether, Soluble in cold or warm water

Stability and storage conditions: Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12) and temperature between 10-60°C. Solutions are also stable in the presence of enzymes, salts, acids and bases. The bulk material should be stored in a well-closed container in a cool, dry place

Safety: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and it is generally regarded as nontoxic and non-irritant at the levels employed as pharmaceutical excipients.

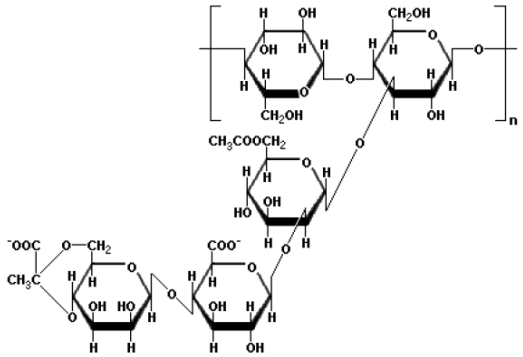


Figure.10.Molecular structure of Xanthum gum

Applications: Xanthan gum is widely used in oral and topical formulations, cosmetics, and foods as a suspending and stabilizing agent. It has also been used to prepare sustained release matrix tablets.

2.10. Guar gum

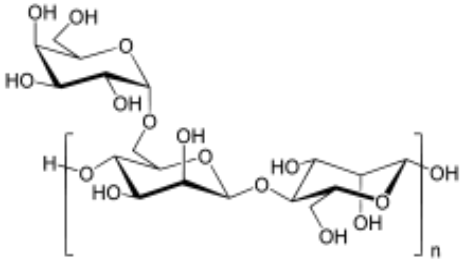


Figure.11.Molecular structure of guar gum

Molecular weight: 25,000 Daltons

Melting point: ~90°C

Source: Guar gum is obtained from endospermic seeds of Cyamopsis tetragonolobus belonging to family Leguminosae.

Properties: Guar gum occurs as nearly odorless, white to yellowish-white powder with a bland taste. Chemically guar gum is polysaccharides composed of galactose and mannose. It is made up of a linear chain of β-D-mannopyranose joined by β-(1–4) linkage with α-D-galactopyranosyl units attached by 1, 6- links. Synthetic derivatives of guar gum such as guar acetate, guar phthalate, guar acetate phthalate, oxidized guar gum and sodium carboxymethyl guar have also been investigated for their pharmaceutical applications. Oral administered guar gum-based colon-targeted 5- Fluorouracil tablets are successfully prepared which shows the better results.

3. CONCLUSION

Sustained release drug delivery system can be considered as the progenitor of the concept of 'magic bullet'. Polymeric drug delivery is the most exciting technique now-a day because of its possibility of delivering drug to a targeted site with maximum therapeutic effect at a required rate. Although there are potential uses in nanotechnology, medical imaging and catalysis, the most promising role for these micelles is drug delivery, but it is crucial that they disassemble in the right place to ensure that the drug is released where it is needed. Successfully developing these novel formulations will obviously require assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials.

Much of the development of novel materials in sustained drug delivery is focusing on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features.

REFERENCES

Beneke CE, Viljoen AM, Hamman JH, Polymeric Plant-derived Excipients in Drug Delivery, Molecules, 14, 2009, 2602-2620.

Evans WC, Trease & Evans' Pharmacognosy, 14th edition, Harcourt Brace & co, Asia PTE Ltd, Singapore, 1996, 191-217

Hydroxy Propyl Methyl Cellulose sustained release technology, Drug. Dev. Ind. Pharm., 15, 1989, 975–999.

Jani GK, Shahb DP, Prajapati VD, Jain VC, Gums and mucilage's: versatile excipients for pharmaceutical formulations, Asian Journal of Pharmaceutical Sciences, 4 (5), 2009, 308-322

Kathryn E, Uhrich, Scott M, Cannizzaro, Robert S, Langer, Polymeric Systems for Controlled Drug Release, Chem. Rev, 99, 1999, 3181-3198.

Kokate C, Purohit A, Gokhle S, Pharmacognosy, 42 edition, Nirali Prakashan, Pune, 2008, 7.1-7.43

Malviya R, Srivastava P, Kulkarni G, Applications of Mucilage's in Drug Delivery- A Review, Advances in Biological Research ,5 (1), 2011,01-07

Martindale: The Complete Drug Reference, 32nd Edn, Partiff K. (Ed), The Pharmaceutical Press, 1999, 1472.

Martindale: The Complete Drug Reference, 32nd Edn. Partiff K. (Ed), The Pharmaceutical Press, 1999, 1474.

Pawan P, Porwal M, Saxena A, Role of natural polymers in sustained drug delivery system: Applications &recent, Int. Research Journal of Pharmacy, 2(9), 2011, 6-11.

Reja M, Quadir MA, Haider SS, Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled- release drug delivery, J Pharm Sci, 69, 2003, 274-291.

Wade A and Weller P J, Hand Book of Pharmaceutical Excipients, 2nd Edn, The Pharmaceutical Press, London, 1994, 186-190, 383, 384, 362-366.

Wallis TE, Textbook of Pharmacognosy, 5th edition, CBS Publishers and Distributors, 287-475