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ROLE OF NATURAL POLYMER IN THE FORMULATION OF MUCOADHESIVE TABLETS

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ABSTRACT

The objective of this review is to provide the overview of the role of natural polymers in gastroretentive drug delivery system (GRDDS), its characteristics, ongoing research, trend of future developments, and applications in the field. Appropriate articles were searched from Medline database using the search term "Natural Polymer and Gastric," The approach of various natural polymers in industrial applications such as medicine and similar areas is growing rapidly in this era. It was observed biodegradable and non-toxic materials like t he natural polymers are evident by the mounting level of its use in the pharmaceutical field. Using various natural polymers has been aiding the drug delivery systems for prolongation of time as the drug transporters with the objective of improving bioavailability and therapeutic efficacy. The use of natural polymers in novel drug delivery like GRDDS to possess floating or mucoadhesive in the gastric system for the benefit of increasing gastric resident time and to improve therapeutic efficacy, particularly those drugs are having narrow therapeutic index such as carvedilol, itopride, and glipizide. The physical characteristics of natural polymers facilitates sustained, swelling, and mucoadhesive nature based on literature reviewed, therefore, natural polymers also suitable to GRDDS as like synthetic or semi-synthetic polymers. This review having lots of natural polymers like Guar gum, Tragacanth, Karaya gum, Pectin, Na Alginate, Gelatin, Xanthan gum, Gellan gum, Grewia gum, Carrageenan, Locust bean gum etc.

KEYWORDS: Oral controlled release, Gastroretentive drug delivery system, mucoadhesive polymers, Mucoadhesion, Natural polymer, Fenugreek mucilage, Simvastatin.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half- lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).[1]

These drug delivery systems suffer from mainly two adversities:

1. The short gastric retention time (GRT),
2. Unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose.[2]

To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment.[3] Also prolonged

gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.

Gastroretentive Drug Delivery System

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach,[4] low density (floating) systems that causes buoyancy in gastric fluid,[5,6,7] mucoadhesive systems that causes bioadhesion to stomach mucosa,[8] unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach,[9,10] superporous hydrogel systems,[11] magnetic systems,[12] etc. The current review deals with various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems.

Table 1: Comparison of conventional drug delivery system and GRDDS.[13]

Conventional Drug Delivery System	Gastro-retentive Drug Delivery System
High risk of toxicity.	Very low risk of toxicity.
Less patient compliance.	Improves patient compliance.
Not suitable for delivery of drugs with narrow absorption window in small intestine region.	Suitable for delivery of drugs with narrow absorption window in small intestine region.
Not much advantageous for- • Drugs having rapid absorption through GIT.	Very much advantageous for- • Drugs having rapid absorption through GIT.
• Drugs acting locally in the stomach. • Drugs which degrade in the colon.	• Drugs acting locally in the stomach. • Drugs which degrade in the colon.
No risk for dose dumping.	Possibility of dose dumping.

Mucoadhesive Tablets

Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs. The application of mucoadhesive tablets to the mucosal tissues of gastric epithelium is used for administration of drugs for localized action. Mucoadhesive tablets are widely used because they release the drug for prolong period, reduce frequency of drug administration and improve the patient compliance. Interest in controlled and sustained release drug delivery has increased considerably during the past decade and, in selected areas, it's now possible to employ fairly sophisticated system which is capable of excellent drug release control.

The self-regulating insulin delivery system by using lectin and oral osmotic tablet are illustrative examples.

The mucoadhesive drug delivery system may include the following

- Gastrointestinal delivery system.
- Sublingual delivery system.
- Vaginal delivery system.
- Nasal delivery system.
- Ocular delivery system.
- Rectal delivery system.
- Buccal delivery system.

Bioadhesive or mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach.[14] Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms.[15,16] are:

1. Wetting theory: The ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
2. Diffusion theory: Physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
3. Absorption theory: Suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4. Electron theory: Attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of

mucus in the gastrointestinal tract (GIT).

Mucoadhesive Polymer

There are two broad classes of mucoadhesive polymers: hydrophilic polymer and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties, poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxy methylcellulose (SCMC) Hydroxy propyl cellulose (HPC) and other cellulose derivative.

Hyrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

- Anionic group- Carbopol, Polyacrylates and their crosslinked modifications
- Cationic group- Chitosan and its derivatives
- Neutral group- Eudragit- NE30D etc.

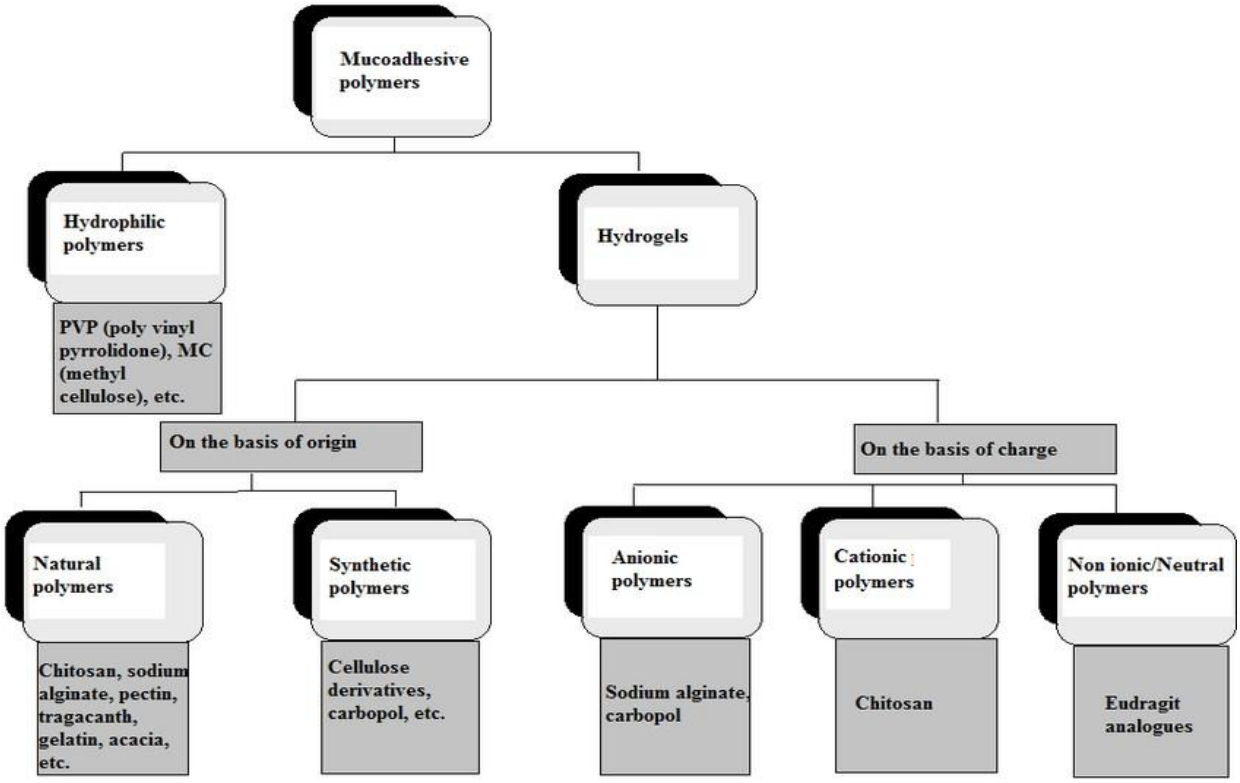

Figure I: A focus on mucoadhesive polymer.

Natural Polymers

Polymers are large chain macromolecules containing a variety of functional groups. Polymers are widely used in pharmaceutical dosage forms and food products, which include both synthetic as well as natural polymeric materials. they play an integral role in different drug delivery technologies. For example, they may be used as agents for controlled drug delivery, sustained drug delivery, targeted drug delivery and various other types of novel drug delivery systems.

The natural polymers are more superior to the synthetic polymers in respect of their highly organized macroscopic and molecular structure. This adds to their strength and biocompatibility. Moreover, their low toxicity and excellent biodegradability have also attracted researchers to pay attention towards the widespread application of natural polymers. The release rate of the drug from natural polymers depends upon several factors such as the physicochemical properties of drugs and the polymers, biodegradation rate of polymers, morphology and size of the particles, thermodynamic compatibility that exist between the polymers and the drugs, and the shape of the delivery devices.[17] The natural polymers widely used in the form of polyelectrolyte complexes in controlled drug delivery systems include three basic types:

- **Neutral polymers:** Hydroxypropylmethylcellulose (HPMC).
- **Cationic polymers:** Chitosan.
- **Anionic polymers:** κ-carrageenan, sodium alginate.

Natural gums such as acacia tragacanth and karaya are more preferred over synthetic materials for controlled drug delivery due to their cost effectiveness, easy avail ability and nontoxicity. Similarly, natural gums such as agar gum, guar gum and gellan gum have been discovered to be used as polymer for sustained drug delivery. On contact with water, these hydrophilic natural gums hydrate and swell and thus used for single unit dosage formulation. The drug release kinetics from these matrices depends on the relative magnitude of polymer hydration at the moving rubbery/glassy front within the formulation as well as the rate of polymer

erosion at the swollen polymer/dissolution medium front. In other words, drug release from hydrophilic matrices is known to be a complex interaction between swelling, diffusion and erosion mechanisms.[17]

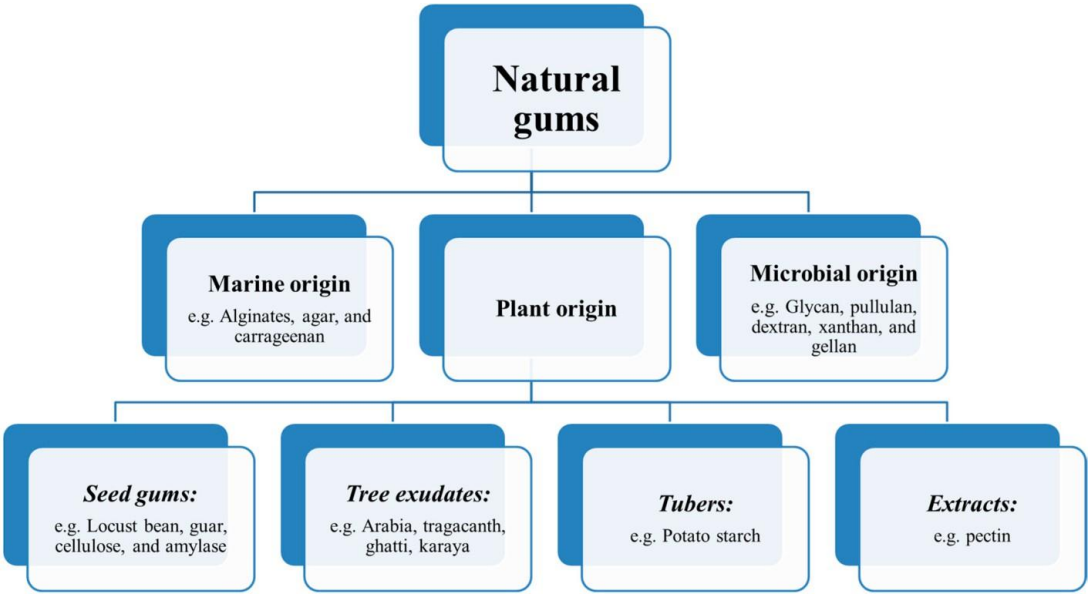

Figure II: Recent advances in natural gums.

Advantage of Natural Polymer

The various advantages of natural plant based materials include

- **Biodegradable**

Biodegradable is the naturally available and they are produced by all living organisms.

- **Biocompatible and non-toxic**

Basically, all of these plant materials are repeating sugar polysaccharides.

- **Low cost**

Cheaper to use as natural sources. The production cost is less compared with the synthetic material. In India and many other developing countries are dependent on agriculture and they are large amount of money investment on agricultures.

- **Local availability (especially in developing countries)**

In India and similar developing countries, there is promotion for the production of plants as pharmaceutical excipients being done by government and it also provide the facilities for bulk production, like gum and mucilage because of their wide applications in industries.

- **Better patient tolerance as well as public acceptance**

There is less chance of side and adverse effects with natural materials compared with synthetic one.

Disadvantages of natural gums and mucilages

- **Microbial Contamination**

The equilibrium moisture content present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.

- **Batch to batch variation**

Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gums and mucilages is dependent on environmental and seasonal factors.

- **Uncontrolled rate of hydration**

Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary.

There is a need to develop suitable monographs on available gums and mucilages.

Natural Polymer Used As Drug Delivery System[21,22]

The natural polymers are widely used in drug formulation they have various approaches for natural polymer as mucoadhesive such as biodegradable, Biocompatible and non-toxic, Low cost, Environmental-friendly processing, local availability, better patient tolerance as well as public acceptance and edible sources. Different natural polymer used in drug delivery system are listed in below.

Chitosan: Chitosan is a sugar that is obtained from the hard outer skeleton of shellfish, including crab, lobster, and shrimp. Invertebrates, insects and yeast are the main source of chitin. Chitin has antimicrobial activity, which make its wide use in packaging material. Chitosan is a

derivative of chitin. Chitosan is used for high blood pressure, high cholesterol, obesity, wound healing, and other conditions, but there is little scientific evidence to support many of its uses. Biocompatibility of chitosan allows its use in various biomedical applications. 4 investigated the safety aspects of chitosan tablets. The result of their study suggested that chitosan tablets were safe for human use. Sahasathian et al.[23] prepared sustained release tablets of amoxicillin by using chitosan as release retarding agent. The obtained results revealed that chitosan having particle size less than 75 micron showed best sustained release behavior. Chitosan was found to provide the release of drug with first order kinetics. Recently, Sogias et al.[24] studied chitosan and its half-acetylated derivative as excipient in mucoadhesive tablets. Chitosan and sodium alginate-based mucoadhesive vaginal tablets were developed by El-Kamel et al.[25] Chitosan and sodium alginate were used as matrixing agents for preparing metronidazole bioadhesive vaginal tablets. Inouye et al.[26] prepared sustained release intragastric 'floating' tablets composed of chitosan. They employed two types of chitosan (chitosan H and L). They concluded that preparation containing chitosan L showed slower drug release than preparation composed of chitosan H.

Xanthan Gum: It is hydrophilic, anionic-bacterial heteropolysaccharide, derived from fermentation of gram-negative bacteria Xanthomonas campestris. For many studies, the goal was to evaluate sustained release action of xanthan gum.[27,28] A modification in release profile of drugs is also observed on combination of polymers. Rasul et al.[29] prepared sustained release tablets of metoprolol tartrate using xanthan gum and tragacanth in different proportions. Tablets were prepared by direct compression using microcrystalline cellulose as diluents. Results showed that increase in xanthan gum amount in tablets showed increase sustained release of drug. In a study, use of xanthan gum in mucoadhesive formulations has been reported.[30] Phaechamud et al.[31] fabricated sustained-release matrix tablets containing chitosan combined with xanthan gum which prolonged the drug release more extensive as compared to that containing single polymer. By utilizing release retarding properties of xanthan gum, controlled release profile was achieved in delivery of pentoxifylline.[32]

Gellan Gum: It is an exocellular polysaccharide secreted by Pseudomonas elodea. This gum had been investigated for pharmaceutical applications such as tablet disintegrant, binder, gelling agent and controlled release polymer. Narkar et al.[33] used gellan gum in preparation of stomach- specific controlled release mucoadhesive drug delivery system. They employed amoxicillin trihydrate as model drug. The in vitro dissolution study showed that drug release upto 7 h in a controlled manner and following the Peppas model. From the results of both in vitro and in vivo mucoadhesivity study, it was revealed that gellan gum beads possess good mucoadhesivity even after 7 h.

Carrageenan: It is obtained from seaweeds of class Rhodophyceae. Red seaweeds including Iradaea aminariodes, Chondrus cripus, Euchema spinosum are the major sources. Picker et al. and Hariharan et al. suggested carrageenan use as excipient in controlled release tablets. Picker et al.[34] evaluate carrageenansn (Gelcarin GP-812 NF, Gelcarin GP- 911 NF and Gelcarin GP-379 NF) as excipients for controlled release solid dosage forms. The prepared tablets had high crushing strength. They suggested that the studied carrangeenans showed good compactibility and controlled release behavior. Picker et al.[34] and Hariharan et al.[35] suggested carrageenan use as excipient in controlled release tablets. Bonferoni et al.[36] prepared carrageenan-diltiazem complex and evaluate it as a excipient used in controlled-release formulations. In their study they found that there was the highest crushing strength and the slowest drug release, when the finest sieve fraction of complex was employed. They also suggested that drug release mechanism was surface dissolution or erosion. Bani-Jaber et al.[37] prepared interpolymeric complex of carrageenan and chitosan and evaluated its influence on drug release. It was concluded that this complex was able to sustain drug release from polymeric matrix.

Pectin: It is methoxyester of pectic acid. Plant cell walls are the major source of pectin. The different sources of pectin include sunflower, orange, lemon, carrot, mango, guava and papaya. It has more stability in acidic media.

Guar Gum: Altaf et al.[38] evaluated the use of guar gum as carrier in the formulation of sustained release systems. They formulated tablets using diltiazem as model drug. Results revealed that guar gum-based tablets could be economical alternative to diltiazem sustained release tablets. In a study performed by Al-Saidan et al.[39] results confirmed that guar gum based matrix tablet provides controlled drug delivery.

Karaya Gum: It is naturally occurring hydrophilic gum obtained from Sterculia urens. Foster et al.[40] prepared gastric retentive gel composed of sodium alginate and karaya gum. They suggested that sodium alginate karaya gum gels can be utilized for designing gastric retentive dosage forms.

Locust bean Gum: Malik et al.[41] evaluated locust bean gum as super disintegrants they fabricated orodispersible tablets of nimesulide, by using locust bean gum. Results of their study concluded that tablet formulation containing 10% locust bean gum showed 13 seconds disintegration time. Vijayaraghavan et al.[42] evaluated combination of locust bean gum with chitosan as a mucoadhesive excipient for buccal tablets. Thus it was suggested that the excipient give sufficient mucoadhesive applications. Tragacanth Gum: Iqbal et al.[43] evaluated combination of polyvinylpyrrolidone

K90 with gum tragacanth for sustained release by using diclofenac sodium as model drug. They carried out in vitro and in vivo release study. Both these studies showed that gum tragacanth could be used for sustain release of drug.

Simvastatin as Mucoadhesive Tablet

Simvastatin is HMG Co-A (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors widely used in the treatment of hyper cholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides, and raises high- density lipoprotein levels. Simvastatin undergoes extensive first pass metabolism in liver due to which the oral bioavailability is less dose size i.e., in few mg. Hence, it is suitable candidate for mucoadhesive drug delivery.[18]

Methods of Simvastatin tablet using natural polymer: Fenugreek Mucilage

Trigonella foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family. Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids. Ability of the husk to form mucilage, its binding properties in solid dosage forms were studied. Mucilage derived from the seeds of fenugreek evaluated as a matrix formulation containing pro pranolol hydrochloride.

Fenugreek seeds (250g) were soaked in double distilled water at room temperature and then boiled with sufficient amount of double distilled water under stirring condition in a water bath until slurry was prepared. Then the slurry was cooled and kept in refrigerator overnight to settle out undissolved materials. The upper clear solution was decanted off and centrifuged at 1000 rpm for 30 minutes. The supernatant was separated and concentrated at 50-55º C on a water bath to a third of its original volume. Solution was cooled down to room temperature and was poured into thrice volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried.[19]

Mantry et al., (2013) formulated the sustained release matrix tablet of Simvastatin and studied the effect of matrix former Xantham Gum and Guar Gum separately. Simvastatin is an anti-hyperlipidemic drug and short half-life (t1/2) and usually oral dose regimen (5 to 40 mg) taken to 4 times a day. To reduce the frequency of administration and to improve the patient compliance, sustained release formulation of simvastatin is desirable. The maximum drug release was found to be 90% over a period of 12 hours in guar gum-based tablets (F4). Similarly, maximum drug release was found to be 90% over a period of 12 hours in Xanthan gum-based tablets (F1). This indicates that the minimum quantity of guar gum and Xanthan gum that is drug to gum ratio of 1:1 is required to prepare the sustained release matrix tablets of Simvastatin.

CONCLUSION

Review of the literature indicates that gastroretentive drug delivery systems can be used to increase the gastric resistance time of dosage form, which led to increased bioavailability of various drugs. mucoadhesive gastroretentive tablet is developed using naturally occurring plant based polymers showed desirable high-drug content, mucoadhesive strength, swelling index and adequate release characteristics. The use of natural gum in pharmaceutical dosage forms is of increasing interest due of their low production cost, lesser toxic effects and regulatory acceptance. The gastroretentive mucoadhesive tablets of Simvastatin may be formulated as mucoadhesive tablets using Fenugreek seeds mucilage by direct compression method.

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