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Review Article

A Novel Approach of Gastroretentive Drug Delivery : In Situ Gel

Swapnali R.Shinde*[1], Preeti Sable[1], Babita B. Lodhi[1], Sarfraz khan[2]

[1]Department of Quality Assurance, Shri Bhagwan College of Pharmacy, N-6, Cidco, Aurangabad. 431001.
[2]Department of Quality Assurance, Dr. Y.S. Khedkar College of Pharmacy, N-6, Cidco, Aurangabad. 431001.

Abstract

Over the past few decades, advances in in situ gel technologies have spurred development in many medical and biomedical applications including controlled drug delivery. Many novel in situ gel-based delivery matrices have been designed and fabricated to fulfill the ever-increasing needs of the pharmaceutical and medical fields. In situ gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner. Many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-coglycolide) and poly-caprolactone etc. are used in the preparation of in situ gelling system. Mainly in situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. In situ gelling system becomes very popular nowadays because of their several advantages over conventional drug delivery systems like sustained and prolonged release of drug, reduced frequency of administration, improved patient compliance and comfort.

Key words: Gastro retention, Floating In situ gel, Stomach specific drug delivery, sustained release, biodegradable polymers, floating drug delivery

***Corresponding Author: Swapnali R.Shinde**, Department of Quality Assurance, Shri Bhagwan College of Pharmacy, N-6, Cidco, Aurangabad. 431001. Mobile No. 9665549714 Email: 7swapnalishinde@gmail.com

1. Introduction

The development of in situ gel systems has received considerable attention over the past few years. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively

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constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, in situ forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort.[1,2,3] In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very strong gels, they can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of in situ gels. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic cross- linking[4,5,6]. So, in situ gels are administered by oral[7], ocular[8], rectal[9], vaginal[10], injectable[11] and intra-peritoneal route[12] Recent advances in in situ gels have made it possible to exploit the changes in physiological uniqueness in different regions of the GI tract for the improved drug absorption as well as patient's convenience and compliance.

Advantages of floating drug delivery system[5-8]

Floating drug delivery systems have numerous advantages listed below:

1) The principle of HBS can be used for any particular medicament or class of medicament.

2) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

3) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

4) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.

5) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

6) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

7) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

8) Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric

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retention will extend the time within which drug absorption can occur in the small intestine.

9) Certain types of drugs can benefit from using gastro retentive devices. These include:

•Drugs acting locally in the stomach;
•Drugs those are primarily absorbed in the stomach;
•Drugs those are poorly soluble at an alkaline pH;
•Drugs with a narrow window of absorption;
•Drugs absorbed rapidly from the GI tract; and
•Drugs those degrade in the colon.

Advantages of *in situ* forming polymeric delivery[6]

- Ease of administration
- To increase local bioavailability
- Reduced dose frequency
- Improved patient compliance
- Its production is less complex and so lowers the investment

Disadvantages of floating drug delivery systems[5-7]

1) There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.

2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.

3) Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

NEED OF FLOATING DRUG DELIVERY SYSTEM

Oral dosage forms pose low bioavailability problems due to their rapid gastric transition from stomach, especially in case of drugs which are less soluble at alkaline pH of intestine. Similarly, drugs which produce their local action in stomach get rapidly emptied and do not get enough residence time in stomach. So, frequency of dose administration in such cases is increased. To avoid this problem floating drug delivery system has been developed.



Figure No.1: In-situ formation of floating gel

APPROACHES GASTRO RETENTIVE 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 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 of drugs[13]

Several gastro retentive drug delivery approaches being designed and developed.

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A. Floating drug delivery systems (FDDS)

Floating FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. Floating systems can be classified as effervescent and noneffervescent system.

I) Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acidor matrices containing chambers of liquid that gasify at body temperature. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed.

II) Noneffervescent systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms.
Excipients used most commonly in these systems include hydroxyl propyl methyl cellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide
and polycarbonates[14]

B. Raft forming systems

On contact with Gastric fluid A gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles. This forms raft layer on top of gastric fluid which releases drug slowly in stomach. Such formulation typically contains antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. They are often used for gastro esophageal reflux treatment as with liquid Gaviscon[15].

C. Bioadhesive drug delivery systems

Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach, by increasing the duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GIT. Mucus secrated continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Bioadhesion is an interfacial phenomenon in which is biological, are held together by means of interfacial forces. The attachment could between an artificial material and biological substrate, such as adhesion

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between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the GIT, the ear, nose and eye. These represent potential sites for attachment of bioadhesive system and hence.

D. Swelling and expanding systems

These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time. These systems, since they exhibit the tendency to remain longed at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network. These crosslinks prevent the dissolution of the polymer and hence maintain the physical integrity of the dosage form.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period. On the other hand, a low degree of cross-linking results in the extensive swelling of the system, succeeded by the rapid dissolution of the polymer.

E. High density systems

These dosage forms have a density(3g/ml) far exceeding that of normal stomach contents(1g/ml) and thus retained in rugae of the stomach and are capable of withstanding its peristaltic movements. The density of these systems should atleast be 1.004 g/ml. This is accomplished by coating the drug with heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc[16].

E. Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimension. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive systems or included as a separate component.

Several methods were suggested to provide for the self-unfolding effect.

1. The use of hydrogels swelling in contact with the gastric juice.
2. Osmotic systems, comprising an osmotic medium in a semipermeable membrane.
3. Systems based on low-boiling liquids converting into a gas at the body temperature[17].

Factors affecting the floating drug delivery system[12,13]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system:

Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density;

Size – dosage form units with a diameter of more than 7.5 mm are reported to have

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an increased GRT compared with those with a diameter of 9.9 mm;
Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes;
Single or multiple unit formulation – multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow coadministration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms;
Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer;
Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release;
Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins
and fats;
Frequency of feed – the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC;
Gender – mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface);
Age – elderly people, especially those over 70, have a significantly longer GRT;
Posture – GRT can vary between supine and upright ambulatory states of the patient;
Concomitant drug administration – anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
Biological factors – diabetes and Crohn's disease, etc.

Approaches to Produce *In situ* Gel

Different approaches and mechanisms utilized or involved in producing the *in situ* gel formation are as follows[18]

- Based on producing physical changes
- Based on producing chemical changes
- Based on physiological stimuli
- Dilution-sensitive.
- Electrical signal-sensitive.
- Light-sensitive.
- Glucose-sensitive

In situ Gel Formation by Physical Changes[19]

This approach involves either swelling or diffusion phenomenon. In swelling, polymer in the system absorbs water from the surrounding environment and swells to form a viscous gel (e.g. glycerol mono-oleate). In diffusion, solvent in which the drug and polymer is dissolved or dispersed, diffuse into the surrounding tissues causing the precipitation of the polymer to form gel (e.g. N-methyl pyrrolidone).
***In situ* Gel Formation Based on Chemical Changes or Stimuli:** Change in the chemical environment of system may

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lead to gel formation by producing polymeric cross linking.

Ionic cross linking[31,32,33]

In presence of the various ions present in the body fluids, e.g. Na+, K+, Ca2+, Fe3+ etc., ion sensitive polysaccharides, e.g. carragenan, gellan gum, pectin etc., undergotransition in phase due to development of the polymer cross linking, e.g. Sodium alginate undergoes gel formation in presence of calcium chloride.

Enzymatic cross-linking[27]

Enzymes present inthe body fluids may also cause cross linking to form a polymer network and is considered, as most convenient mode of gel formation.

***In situ* Gel Formation by Physiological Stimuli:**

Physiological stimuli that can induce gel formation include change in temperature and change in pH of the system.

In situ gel formation depending on change in temperature[19,21]

In this approach, temperature dependent phase transition from less viscous solution to comparatively high viscosity gel is seen. Change in temperature causes abrupt change in the solubility of polymer within system and polymerpolymer interaction occurs to form a solvated macromolecule of hydrophobic nature. Temperature sensitive polymers are the most studied class for producing the *in situ* gel characteristics, e.g. Polyacrylic acid, polyacrylamide etc

In situ gel formation due to change in pH of system[22] Polymers, such as polyacrylic acid and its derivative (carbopol), polymethacrylate etc., undergo gel formation because of change in the pH, due to presence of various ionizable groups in the chemical structure of the polymer. Polymer with anionic groups leads to increase in swelling with increase in the pH, while polymer with cationic groups shows a decrease in the swelling.

Dilution-Sensitive

This type of hydrogel contains polymer that undergoes phase transition in presence of higher amount of water. By having a system undergoing phase transition as a consequence of dilution with water a higher amount of polymer can be used. E.g:-Lutrol F68

Electrical Signal-Sensitive

Hydrogels sensitive to electric current are usually made of polyelectrolytes such as the pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field. Chitosan gels as matrices can be used for electrically modulated drug delivery.

Light-Sensitive

Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscle or as the *in situ* forming gels for cartilage tissue engineering. Polymerizable function groups and their initiator like ethyl eosin and camphor Quinone can be injected in to tissue and applied electromagnetic radiation usedto form a gel by enzymatic processes. For that long ultraviolet wavelengths are used.

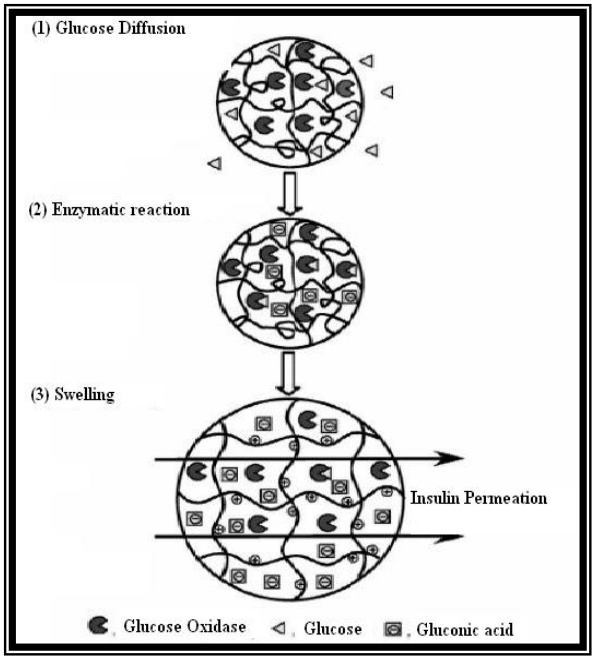
Glucose-Sensitive

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Another approach is based on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A, where insulin is displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system. An

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alternative route through phenylborate-poly(vinyl alcohol) polymers is also possible.

Figure No.2. Glucose Sensitive Mechanism



MECHANISM OF *IN- SITU* GELATION-[5-8]

These are aqueous liquid solutions before administration, but gel under physiological conditions. Several possible mechanisms lead to in-situ gel formation are:-Ionic cross-linkage, pH change & temperature modulation. Polymer solutions of gellan, pectin & Na-alginate etc contains divalent-ions complexed with Na-citrate that are breakdown in acidic environment of stomach to release free divalent ions (ca+2).causes the in situ gelation of orally administered solution. It involves formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations& hydrogen bonding with water.

MECHANISM F FOR FLOATING IN SITU GEL

While the system is floating on the stomach the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F is on the higher positive side (Fig. 3). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations[56]

F = F buoyancy - F gravity = (Df - Ds) g v

Where,

F= total vertical force,

Df = fluid density,

Ds = object density,

v = volume

g = acceleration due to gravity

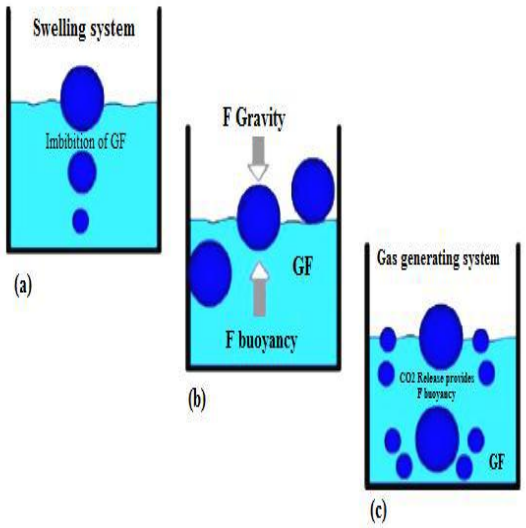


Figure3. Mechanism of Floating System, GF = Gastric fluid

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Suitable drug candidates for gastro retention:

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolong in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effect and provide their therapeutic effects without the need for repeated dosage with a low dosage frequency. Sustain release in the stomach is also useful for therapeutic agents that the stomach does not readily absorbed, since sustain release prolongs contact time of the agent in the stomach or in the upper part of small intestine, which is where absorption occur and contact time is limited under normal or average condition, Example. material passes through the small intestine in as little as 1-3 hrs[14]

In general, appropriated candidate are molecules that have poor colonic absorption but are characterizes by better absorption, properties at the upper part of GIT:

- Narrow absorption window in GIT, E.g. Riboflavin and Levodopa.
- Primarily absorbed from stomach and upper part of GIT, Example: Calcium supplements, Chlordizepoxide and Cinnarazine.
- Drugs that are locally in the stomach, Example. Antacids and Misoprostol.
- Drugs that degrade in the colon, Example. Ranitidine HCl and Metronidazole.
- Drugs that disturbs normal colonic bacteria, Example. Amoxicilline trihydrate.

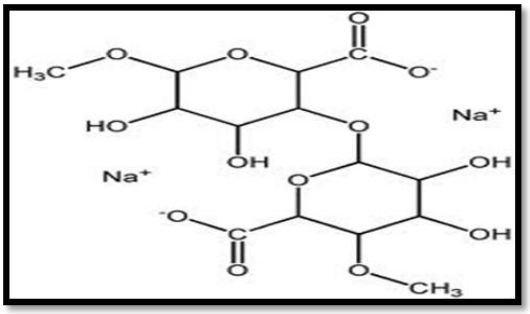
Table 1: Good candidates for gastroretentive drug delivery system[20]

The need for gastro retentive dosage form (GRDFs) has led to extensive efforts in both academic and industry towards the development of such delivery systems. These efforts resulted in GRDFs that were designated, in large part, based on following approaches.

Polymers Frequently Used for *In situ* Gelling for Gastro Retentive Reasons

Sodium alginate[23,24,25]

Sodium alginate is a widely used polymer of natural origin.Chemically, it is alginic acid salt, consisting of –Lglucuronic acid and -D-mannuronic acid residues connected by 1,4-glycosidic linkages. Solution of alginates in water form firm gels in presence of di-or trivalent ions (e.g. calcium and magnesium ions). Alginate salts, specifically, sodium alginate is mostly used for preparation of gel forming solution, for delivery of the drugs and proteins. Alginate salts are considered most favourable because of biodegradable and non toxic nature, with additional bio-adhesive property .Sodium alginate is a salt of Alginic acid - a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions. The results indicated that the alginates form compact structures when the ionic radical of the cation are lower. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.



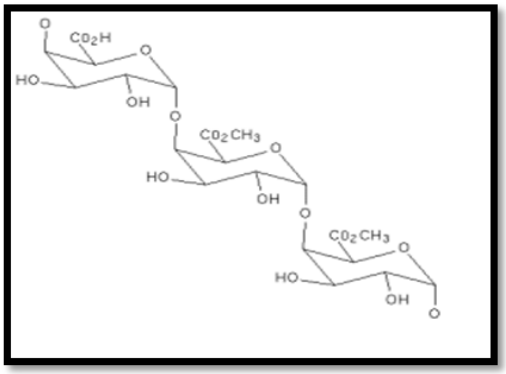
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Table No. 1 : Good candidates for gastroretentive drug delivery system

Sr.No.	Drug	Category	Bioavailability
1	Verapamil	Calcium channel blocker	20-35%
2	Nifedipine	Calcium channel blocker	45-65%
3	Omeprazole	Proton pump inhibitor	35-60%
4	Atenolol	Antihypertensive	40-50%
5	Propranolol	Antihypertensive	4-26%
6	Verapamil	Antihypertensive	18-35%
7	Diltiazem	Calcium channel blocker	40%
8	Lidocaine	Local Anaesthetic	35%
9	Clarithromycin	Antibiotic	50%
10	Ramipril	ACE Inhibitor	28%

Pectin

These are plant origin anionic polysaccharides isolated from the cell wall of most plants and basically consist of -(1-4)-D-galacturonic acid residues. Pectin undergoes gel formation in presence of medium, a stiff gel is produced. The gelling capacity divalent ions (e.g. Ca) which causes cross linking of the is determined on the 2+ basis of stiffness and time galacturonic acid units (ionic cross linking) and also in the period for which gel remains, as such.presence of the H+ ions (pH dependent gelling). Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an a-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in thenatural product. The hydroxyl groups may also be acetylated. Pectin gelation characteristics can be divided into two

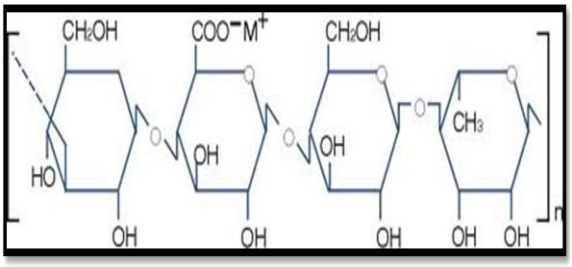


types: high-methoxy and low-methoxy gelation. Gelation of highmethoxypectin usually occurs at pH < 3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content.[19]

Gellan gum

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Gellan gum (FDA approved) secreted by the *Sphingomonas elodea (Pseudomonaselodea)* and chemically is



anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of -D-glucuronic acid (1 unit), -L-rhamnose (1 unit) and -D-glucuronic acid (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to presence of cations (e.g. Na+,K+,Ca2+). Gellan gum is an anionic deacetylatedexocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It is a water soluble polysaccharide. It forms a gel via formation of double helices, followed by their ionic cross-linking. [24,25,26]

Xyloglucan

It is a plant based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4)- -D-glucan having (1-6)- -D xylose units as branches which have partial (1-2)- -D-galactoxylose substitution. Xyloglucan, itself, does not undergo gel formation but dilute solutions partly degraded by galactosidase exhibit gelling properties on heating (temperature dependent gelformation). Besides the use in oral drug delivery, it is alsobeing used for ocular and rectal drug delivery. Xyloglucan has shown a very low gelation time of up to few minutes. Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. Xyloglucan is composed of heptasaccharide, octasaccharide and nonasaccharideoligamers, which differ in the number of galactose side chains. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol–gel transition on heating.[19]

Pluronic F-127

Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide.[31] Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEOPPO- PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω- hydroxypoly (oxyethylene) a poly (oxypropylene) b poly (oxyethylene) a block copolymer. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelation by temperature change.

Xanthum gum

Xanthan gum is a high molecular weight extra cellular polysaccharide

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produced by the fermentation of the gramnegative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvicacid groups in the side chain.[25]

Chitosan

Chitosan is a biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2[26]. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosanaqueous solution**.[27]**

Carbopol

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution,while reducing the acidity of the solution. Various water triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo changes in solubility with change in environment temperature. Pluronic ™ F 127. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week.[28]

APPLICABILITY OF IN SITU POLYMERIC DRUG DELIVERY SYSTEM

Oral drug delivery system

The pH-sensitive hydrogels have a potential use in site specific delivery of drugs to specific regions of the GI tract. Hydrogels made of varying proportions of PAA derivatives and crosslinked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property.[29] Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and insulin were investigated in order to develop a potential colon-specific drug delivery system. W. Kubo et al. developed the formulations of gellan and sodium alginate both containing complexed calcium ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was studied. For the oral in situ gel delivery system pectin, xyloglucan& gellan gum natural polymers are used. Pectin formulation for sustained delivery of paracetamol has been reported.[31] Advantages of pectin is water soluble so, no need to add organic solvent.

Ocular drug delivery system

In ocular delivery system natural polymers like gallan gum, alginic acid & xyloglucan are most commonly used. For local ophthalmic delivery system various

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compounds like antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response because high tear fluid turn over & dynamics which cause rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel was developed.[32] To improve the bioavailability viscosity enhancers such as Hydroxy Propyl Methyl Cellulose, Carboxy Methyl Cellulose, Carbomers, Poly Vinyl alcohol used to increase the viscosity of formulation in order to prolong the precorneal residence time & improve the bioavailability, ease to manufacture. Penetration enhancer such as preservatives, chelating agent, surfactants are used to enhance corneal drug penetration.[33]

Nasal drug delivery system

In nasal in-situ gel system gallan gum & xanthan gum are used as in-situ gel forming polymers Momethasone furoatewas evaluated for it‘s efficacy for the treatment of allergic rhinitis.[34] Animal study were conducted using allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%).

Rectal drug delivery system

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments,creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum,sometimes they can migrate up-wards to the colon that makes them possible for drug to undergo the first-passeffect. Choi et al. developed novel in situ gelling liquid suppositories with gelation temperature at 30–36°C. Poloxamer 407 and/ or poloxamer 188 were used to confer the temperature-sensitive gelation property. In-situ gel possesses a potential application for rectal & vaginal route. Miyazaki et al. investigated the use of xyloglucan based thermo reversible gel for rectal drug delivery of Indomethacin.

Vaginal drug delivery system

The vagina, in addition to being an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermo-plastic graft copolymer that undergo in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins[36] Chang et al have recently reported a mucoadhesive thermo-sensitive gel(combination of poloxamers and polycarbophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

Injectable drug delivery system

One of the most obvious ways to provide sustainedrelease medication is to place the drug in delivery system and inject or implant the system into the body tissue.Thermoreversible gels mainly prepared from poloxamers are predominantly used.[38] The suitability of poloxamer gel alone or with the addition

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of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran was studied for epidural administration of drugs in vitro.[39] The compact gel depot acted as the rate limiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions. J. M. Barichello et al. evaluated Pluronic F127 gels, which contained either insulin or insulin-PLGA nanoparticles with conclusion, that these formulations could be useful for the preparation of a controlled delivery system. Likewise, poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone[42] or with the aim to develop a long acting single dose injection of lidocaine[39]

Dermal and transdermal drug delivery system

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin[46]. In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin.[47] The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

EVALUATION OF IN SITU GELLING SYSTEM [49-51]

Determination of drug content

Certain weight of formulation equivalent to an amount of drug has to be dissolved in a suitable medium, stirred for required time, filtered and analysed for drug content.

pH determination

The pH of solution can be determined using digital pH meter and the favourable conditions that facilitate in situ gelling can be identified. The influence of pH on the gelation of sol can be determined by using the medium of various pH values.

In-vitro gelling capacity

In general the gelling capacity of an *in situ* gel forming system can be determined by formulating a colour solution of *in situ* gelling system for visual observation. By adding the in-situ gelling formulation to a medium (simulating gastric fluid), various parameters like the time taken for *in situ* gel formation, its stiffness and the duration for which formed gel remains intact, can be estimated.

In-vitro buoyancy studies

After adding a fixed volume of *in situ* gelling formulation to a medium (simulating gastric fluid), the parameters like the time taken for the system to float over the surface of medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

In-vitro drug release studies

The release rate of drug from in situ gel can be determined using USP dissolution rate testing apparatus I (basket covered with muslin cloth) at 50 rpm. 900 ml of 0.1 N HCl can be used as dissolution medium and temperature of 37+0.5^{o}C can be maintained. 5 ml samples can be withdrawn at various time points for estimating the drug release using UV-Visible spectrophotometer. Same volume of fresh medium has to be replaced every time the sample is withdrawn. The drug release studies from in-situ gel can also be done using plastic dialysis cell.

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Measurement of rheological property of sol and gel

Viscosity of the solution prepared using various concentrations of gelling agents can be determined by viscometers like Brookfield viscometer, Cone & plate viscometer etc., Viscosity of the formed gel can also be determined to estimate the gel strength.

Water uptake study

Once the sol is converted to gel, it is collected from the medium and the excess medium was blotted using a tissue paper. The initial weight of thus formed gel has to be noted. Again the gel has to be exposed to the medium/distilled water and the same process is repeated for every 30 min to note down the weights of the gel at each interval after removing the excess amount of medium/distilled water, using filter paper. The weight gain due to water uptake has to be noted from time to time. Effect of pH, concentration of gelling agent/cross linking agent on viscosity, in-situ gelation character, floating ability and drug release can be studied for in-situ gelling type of floating formulations.

Gel strength

This parameter is evaluated by using rheometer with a specified amount of solution form gel were prepared in a beaker. This beaker is raised so pushing the probe of rheometer through the gel. The change in the load on the probe can be measured as a function depth of merge of the probe below the gel surface.

Spread ability

For the determination of spread ability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 min. Weight (50 g) was added to the pan and the time required for separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spread ability (S).

Spread ability (g.cm/s) (S)=M×L/T

Where M = weight tide to upper slide L = length moved on the glass slide T = time taken

Sol-gel transition temperature and gelling time

Sol-gel transition temperature is the temperature at which the phase transition of sol meniscus is first noted when it kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the required for first detection of gel formation of sol formulation.

MARKETED PRODUCTS[50]

Liquid Gaviscon - Al-hydroxide (95mg), Mg carbonate (385mg)

Topalkan - Al-Mg antacid

Conviron - Ferrous sulfate

COMMERCIAL FORMULATIONS OF *IN-SITU*Gel [51]

Timoptic-XE

It is a timolol maleate ophthalmic gel formulation of Merck and Co. Inc., This formulation is available in two dosage strengths 0.25% and 0.5% in market. The pH of thesolution is approximately 7.0, and the osmolarity is260-330 mOsm. Each ml of Timoptic-XE 0.25%contains 2.5 mg of timolol (3.4 mg of timolol maleate).Inactive ingredients include gellan gum, tromethamine,mannitol, and water for injection and the preservativeused is benzododecinium bromide 0.012%. Timoptic-XE, when applied topically on the eye, reduces theelevated, as well as normal intraocular pressure,whether or not accompanied by glaucoma.

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AzaSite:

AzaSite is a marketed product of InSite Vision. AzaSite is a topical ophthalmic solution of azithromycin formulated in DuraSite (polycarbophil,edetate disodium, sodium chloride). AzaSite is supplied as a sterile aqueous ophthalmicformulation designed for topical administration. The recommended initial dose of the drug isin still 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first two daysand then in still 1 drop in the affected eye (s) once daily for the next five days.

Pilopine HS:

Pilopine HS is a marketed product of Alcon Laboratories Inc. Pilopine HS (pilocarpinehydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel which containsmore than 90% water and employs Carbopol-940, a synthetic high molecular weight cross-linkedpolymer of acrylic acid, to impart a high viscosity.

Akten™:

Akten™ is an HPMC-based gel of lidocaine hydrochloride for ocular surface anesthesia. Akten™ contains 35 mg of lidocaine hydrochloride per mL as the active ingredient. Akten™also contains Hypromellose, Sodium Chloride, and Purified Water as inactive ingredients. ThepH may be adjusted to 5.5 to 7.5 with Hydrochloric Acid and/or Sodium Hydroxide. Therecommended dose of Akten™ is 2 drops applied to the ocular surface in the area of the plannedprocedure. Akten™ may be reapplied to maintain anesthetic effect.

Virgan:

Vigran is an ophthalmic antiviral that is indicated for the treatment of acute herpetickeratitis. The recommended dosing regimen for Virgan is 1 drop in the affected eye 5 times perday (approximately every 3 hours while awake) unti the corneal ulcer heals, and then 1 drop 3times per day for 7 days. Virgan (ganciclovir) contains carbomer 974. The carbomers arepolyacrylic acid derivatives that impart high viscosity to their aqueous solutions at neutral pH(above their pKa values) due to ionization and hydration of the carboxyl groups.

Cytoryn :

This is one of the Macromed's products, which is anovel, peritumoral, injectable depot formulation ofinterleukin-2 (IL-2) for cancer immunotherapy usingRegel drug delivery system. It is a free flowing liquidbelow room temperature that instantly forms a geldepot upon injection from which the drug is released ina controlled manner. Cytoryn enhances theimmunological response by safely delivering fourtimes the maximum tolerated dose allowed byconventional IL-2 therapy. Cytoryn also activates thesystemic antitumor immunity. Regel system stabilizesand releases IL-2 in its bioactive form.

FUTURE POTENTIAL

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoetin, vasopressin, insulin, low

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molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

FUTURE PROSPECTS WITH RESPECT TO HERBAL DRUGS

Herbal drug delivery is the emerging field in the pharmacy. The use of FDDS for herbal medicament is the novel approach for the better delivery. The drug release profile has been a major focusing area for the pharmaceutical research scientists for the past two decades. The scientists are finding it a great opportunity to work on GI transit profiles. This has given rise to new products with substantial benefits to the patients. Now with the advent of FDDS the products have been designed which could release drug for upto 24 hrs. Some herbals that can be delivered as floating drug delivery systems:

BLACK MYROBALAN

The aqueous extract of black myrobalan (Terminalia chebula Retz) has been shown to have uniform antibacterial activity against ten clinical strains of H. pylori.

GINGER

Ginger root (Zingiber officinale Rosc.) has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum, and is also reported to have chemopreventative activity in animal models. The gingerols are a group of structurally related polyphenolic compounds isolated from ginger and known to be the active constituents.

TURMERIC

Curcumin, a polyphenolic chemical constituent derived from turmeric (Curcuma longa L.), has been shown to prevent gastric and colon cancers in rodents. Many mechanisms had been proposed for the chemopreventative effects, although the effect of curcumin on the growth of H. pylori has not been reported.

LICORIC

In a recent study at the Institute of Medical Microbiology and Virology, Germany, researchers found that licorice extract produced a potent effect against strains of H. pylori that are resistant against clarithromycin, one of the antibiotics typically used in the three antibiotic treatment regimens.

BERBERINE

Berberine is a plant alkaloid isolated from the roots and bark of several plants including golden seal, barberry,Coptis chinensis Franch. and Yerba mansa. Berberine-containing plants have been used medicinally in ayurvedic and Chinese medicine, and are known to have antimicrobial activity against a variety of organisms including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. More recently, berberine had been demonstrated to be effective against H. pylori. All these herbal drugs can be prepared as gastroretentive drug delivery system.[49]

RECENT RESEARCHES IN FLOATING DRUG DELIVERY SYSTEMS

Stubbing et al investigated the mechanism of floating and drug release behaviour of poly (vinyl acetate)- based floating tablets with membrane controlled

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drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollicoat ® SR 30 D/Kollicoat® IR coats varying from 10 to 20 mg polymer/cm2 were investigated regarding drug release in 0.1 mole.lit-1 HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined. In addition, benchtop MRI studies of selected samples were performed. Coated tablets with 10 mg polymer/cm2 SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release and floating onset, the fastest increase in and highest maximum values of floating strength. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.[57]

Jang et al has prepared a gastro-retentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA- 6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizer and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastro-protective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.[58]

Rajinikanth and Mishra have developed a floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori. Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionised water to which varying concentrations of drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant anti-H. pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared H.pylori more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of H. pylori was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of H. Pylori.[59]

2. Conclusion

In conclusion, the primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in situ* gel offers. Exploitation of polymeric in- situ gel for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the *in situ* gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the *in situ* gel formulations can make them more acceptable and excellent drug delivery systems.

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References

1. Miyazaki S, Aoyama H, Kawasaki N, Kubo W, Attwood D. In situ-gelling gellan formulations as vehicles for oral drug delivery. J Control Rel. 1999; 60:287-95
2. Miyazaki S, Endo K,Kawasaki N, Kubo W, Watanabe H, Attwood D. Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations. Drug Dev Ind. Pharm. 2003; 29 (2):113-9.
3. Peppas N, Langer R. New challenges in biomaterials. Science1994; 263:17152
4. A. Rozier, C. Mazuel, J. Grove, B. Plazonnet, Gelrite: A novel, ionactivated, in situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. Int. J. Pharm. 1989; 57 163–168.
5. S. Cohen, E. Lobel, A. Trevgoda, Y. Peled. A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J. Control. Release. 1997; 44 201–208.
6. B. Srividya, R.M. Cardoza, P.D. Amin. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J. Control Release. 2001;73: 205–211.
7. S. Miyazaki, N. Kawasaki, K. Endo, D. Attwood. Oral sustained delivery of theophylline from thermally reversible xyloglucan gels in rabbits. J. Pharm. Pharmacol. 2001; 53: 1185–1191.
8. S. Miyazaki, S. Suzuki, N. Kawasaki, K. Endo, A. Takahashi, D. Attwood. In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int. J. Pharm. 2001; 229: 29–36.
9. S. Miyazaki, F. Suisha, N. Kawasaki, M. Shirakawa, K. Yamatoya, D. Attwood. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J. Control. Release. 1998; 56:75–83.
10. Himanshu Gupta , Aarti Sharma. Ion activated bioadhesive in situ gel of clindamycin for vaginal application. International Journal of Drug Delivery. 2009; 1: 32-40
11. U.V. Singh, N. Udupa, R. Kamath, P. Umadevi, Enhanced Biodegradable in situ forming implants and methods of antitumor efficacy of methoteraxate poly(lactic-co-glycolic) producing the same, US Pat. 4938763, 3 July 1990. acid injectable gel implants in mice bearing sarcoma-180, 136.
12. F. Suisha, N. Kawasaki, S. Miyazaki, M. Shirakawa, K. Yamatoya, M. Sasaki, D. Attwood, Xyloglucan gels as sustained release vehicles for the intraperitoneal administration ofmitomycin C. Int. J. Pharm. 1998 ; 172: 27–32
13. Lathori S.R, Syed Iftequar M, Dehghan M.H, Shoaib S, Mohiuddin S, An Overview of gastroretentive drug delivery system research. International Research Journal of Pharmacy,2(11),2011,50-57.
14. Nayak Amitkumar, Maji Ruma, Das Biswarup, Gastroretentive drug delivery systems: A review. Asian Journal of Pharmaceutical and Clinical Research, Vol.3, Issue 1, January-March 2010, 1-10.61-63
15. Patel Nirav, Nagesh C, Chandrashekhar S, Patel jinal, Jani Devdatt, Floating drug delivery system: An innovative acceptable approach in Gastro retentive drug delivery. Asian J. Pharm. Res, 2012, Vol 2,Issue I, 7-18
16. Ramdas T. Dolas, Dr. Avanish Hosmani, Dr. Anil Bhandari, Novel sustained release gastroretentive drug delivery system: A review. International Journal of Pharma. Research & Development, Vol-2,Issue-II, 2011, 26-41.
17. R. Vinod, Vasal Santhosh, Anbuazaghan, Banjil David, A. Padmasri, Approaches for gastroretentive drug delivery systems. International Journal of Applied Biology and Pharmaceutical technology,Vol-1,Issue-2, Aug-Oct-2010,589-601
18. Wu, C., H. Qi, W. Chen, C. Huang, C. Su, W. Li andS. Hou, Preparation and evaluation of a carbopol/hpmc based *in situ* gelling ophthalmic system for puerarin. Yakugaku Zasshi, Pharmaceutical Society of Japan, 127(1): 2007. 183-191
19. H.V.Rathod, H., V. Patel and M. Modasia, *In situ* gel as a novel approach of gastroretentive drug delivery. International Journal Of Pharmacy and Life Sciences,1(8): 2010. 440-447.

Innovational Publishers
www.innovationalpublishers.com

20. Seth SD.Text book of pharmacology, Reed Elsevier Ltd.2005
21. Shah, D.P. and G.K. Jani, A newer application of physically modified gellan gum in tablet formulation using factorial design. ARS Pharmaceutica, 51(1): 2010. 28-40.
22. Patel, J.K., J.R. Chavda and M.K. Modasiya, Floating *in situ* gel based on alginate as carrier for stomach-specific drug delivery of famotidine International Journal Of Pharmaceutical Sciences, 3(3): 2010.1092-1104.
23. Ganapati, R., K.S. Bhimagoni and S. Anegundha,. Floating drug delivery of a locally acting H2-antagonist: an approach using an *in situ* gelling liquid formulation. Acta Pharmceutica, 59: 2007345-354.
24. Nagarwal, R.C., A. Srinatha and J.K. Pandit, *In situ* forming formulation: development, evaluation and optimization using 33 factorial design. AAPS Pharmscitech, 10(3): 2009 977-984.
25. Rajinikanth, P.S., J. Balasubramaniam and B. Mishra Development and evaluation of a novel floating *in situ* gelling system of amoxicillin for eradication of Helicobacter pylori. International Journal of Pharmaceutics, 335: 2007.114-122.
26. Shah, D.P. and G.K. Jani,. A newer application of physically modified gellan gum in tablet formulation using factorial design. ARS Pharmaceutica, 51(1): 2010.28-40.
27. Schmolka IR, Artificial skin, Preparation and properties of pluronic F127 gels for the treatment of burns, J.Biomed. Mater. Res, 1972, 6, 571-582
28. Kabanov A, Batraoka E, Alakhov V, Pluronic block copolymers as novel polymer therapeutics for oral and gene Delivery, J. Control. Rel, 2002, 82, 189- 212.
29. Carelli V, Coltelli S, Di Colo G, Nannipieri E, Serafini MF,Silicone microspheres for PH controlled gastrointestinal drug Delivery, Int J Pharm, 1999, 17, 73-83
30. Kubo W, Miyazaki S, Attwood D, Oral sustained delivery of paracetamol from in situ gelling gellan and sodium alginate Formulations, Int J Pharm., 2003, 258, 55-64 56.
31. Schoenwala RD, Smlen VF, Drug absorption analysis from Pharmacological data: Transcorneal biophasic availability of tropicamide, J Pharm Sci, 1971, 60, 1039-1045
32. Durrani A.M, Davies N.M, 33.Thomas M, Kellaway I.W, Pilocarpine bioavailability from a mucoadhesive liposomal ophthalmic drug deli. Sys, International Journal of Pharmaceutics, 1992, 88, 409, Chrai S.S et al, J.Pharm. Sci, 1973, 62,1112-1121
33. Alder, C.A, Maurice, D.M & Paterson, M. EExp. Eye Res, 1971,11, 34-42
34. Patton T.F, Robinson J.R, J. Pharm. Sci, 1975, 64, 1312-1315
35. Choi HG, Oh YK, Kim CK., In situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability, Int J Pharm, 1998, 165, 23-32
36. Liaw, J, Robinson J, Rin mitra, A.K. ed, ophthalmic drug delivery system, 1993, 369-381
37. Vermani K, Garg S, The scope and potential of vaginal drug delivery, Pharm Sci & Technol Today, 2000, 3, 359-364
38. Chang JY, Oh YK, Kong HS, Kim EU, Jang DD, Nam KT,Prolonged antifungal effects of clotrimazolecontaining Mucoadhesive thermosensitive gels on vaginitis, J Control Release, 2002, 82, 39-50
39. Ricci EJ, Bentley MV, Farah M, Bretas RES, Marchetti JM, Rheological characterization of Poloxamer 407 lidocaine hydrochloride gels, Eur J Pharm Sci, 2007, 17, 161-167
40. Paavola AY, liruusi J, Rosenberg P, Controlled release and dura mater permeability of lidocaine and ibuprofen from Injectable poloxamer-based gels, J Control Release, 1998, 52, 169-178
41. Barichello JM, Morishita M, Takayama K, Nagai T, Absorption of insulin from Pluronic F-127 gels following subcutaneous administration in rats, Int J Pharm, 1999, 184, 189- 198
42. Katakam M, Ravis WR, Banga AK., Controlled release of human growth hormone in rats following parenteral administration of poloxamer gels, J Control Release, 1997, 49, 21-26

Innovational Publishers
www.innovationalpublishers.com

43. DesNoyer JR, McHugh AJ, The effect of Pluronic on the proteinrelease kinetics of an Injectable drug delivery system,J Control Release, 2003, 86, 15-24
44. Kim YJ, Choi S, Kohl JJ, Lee M, Kim SW. Controlled release of insulin from Injectable biodegradable triblock Copolymer, Pharm. Res, 2001; 18:548-550
45. Jeong B, Bae YH, Lee DS, Kim SW, Biodegradable block copolymers as injectable drug delivery systems, Nature,1997, 388, 860-862
46. Miyazaki S, Tobiyama T, Takada M, Attwood D, Percutaneous absorption of indomethacin from pluronic F127 gels in rats, J Pharm Pharmacol, 1995, 47, 455-457
47. Pillai O, Panchagnula R, Transdermal delivery of insulin from poloxamer gel: ex vivo and in vivo skin permeationstudies in rat using iontophoresis and chemical enhancers, J Control Release, 2003, 89, 127-140
48. Kashyap N., Viswanad B., Sharma G., Bhardwaj V., Ramarao P. and Kumar M.N. Design and evaluation of biodegradable, biosensitive in situ gelling systems for pulsatile delivery of insulin. Biomaterials, 2007, 28:2051 2060.
49. Shah SH, Patel JK, Patel NV. Gastroretentive floating drug delivery systems with potential herbal drugs for Helicobacter pylori eradication: a review J Chin Integr Med. 2009; 7(10): 976-982
50. Bhimani RD, Patel JK, Patel VP.Devlopment and evalutionfloting in situ gel of clarithromycin.Int J of Pharm Res, 2011, 3, 32-35
51. Shreeraj Shah, Pratik Upadhyay, Darsh Parikh, Jinal Shah.In Situ Gel: A Novel Approach of gastro retentive Drug Delivery. Asian Journal of Biomedical and Pharmaceutical Sciences, 2012,2, 01-08
52. Asfaw, Bruktawit T.Jackson, John C.Lu, ZhihuaZhai, XiaowenShums, SameerHirt, ThomasHu, Xianbo René, Claude-raymond, In situ forming hydrogel wound dressing containing antimicrobial agents, USpatent 0009275, Jun 28, 2011. 25-263
53. Gillian Eccleston, Ronald Paterson, Gastric raft composition, USpatent 0063980, Oct 29, 2002.
54. Yawei Ni, Kenneth M. Yates In situ gelation of pectin substance, US patent 01199941, February 28, 2001.
55. Claire Haug, Stephane Jonat, In situ gelling systems as sustained delivery for front of eye, US patent 0082221, Jun 11, 2009.
56. Garg S. and Sharma S. Gastroretentive Drug Delivery System, Business Briefing: *Pharmatech*, 2003, 160-166 .
57. Strübing S, Abbouda T, Renata C, Metza H. New insights on poly (vinyl acetate)-based coated floating tablets: Characterisation of hydration and CO2 generation by benchtop MRI and its relation to drug release and floating strength. *European J.Pharm.and Biopharm,* 69, 2008, 708-717.
58. Janga S, Lee J, Park S. Gastroretentive drug delivery system of DA-6034, a new flavonoid derivative, for the treatment of gastritis. *Int.J.Pharm*, 356, 2008, 88-94.
59. Rajinikanth P. and Mishra B. Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H.pylori. *J.Cont.Rel*, 25, 2008, 33-41.
60. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006. p.197-217.
61. Chawla G, Gupta P, Bansal AK. Gastroretentive drug delivery systems. In: Jain NK (Ed). Progress in controlled and novel drug delivery systems. CBS Publishers and Distributors. New Delhi. 2004. p.76-97.