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Floating Oral *in situ* Gel, An Approach of Gastro-Retentive Drug Delivery System: A Review

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Abstract

The Floating Drug Delivery System (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The Main work of FDDS is making the dosage form less dense than the gastric fluids to make it float on them. This research is directed towards overcoming physiological adversities such as short gastric residence time (GRT) & unpredictable gastric emptying time (GET). The main contribution of this work lies in the study of Floating Drug delivery System with its types and mechanisms. This study shall help to learn about gastric retention, various approaches to produce gastro retention of drug delivery system with special discussion on floating in-situ gel. This offers various advantages like prolonged and sustained action in comparison to conventional drug delivery system.

Keywords

Bioavailability, Floating *in situ* gel, Gastric retention time.

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INTRODUCTION [1,2,3,4,5]

Oral drug delivery system is the most popular route administration due to versatility, ease of administration and most importantly patient compliance. Oral controlled release drug delivery has 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. Since oral sustained drug delivery formulation show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into absorption window leading to diminished efficacy of the administered dose. Drugs with half-short life and drug that easily absorbed from gastrointestinal track (GIT) and eliminated quickly from the systemic circulation. Several drug delivery systems with prolonged gastric retention time have been investigated to overcome this problem. It is evident from the recent research and patent literature that an increased interest in novel dosage form that are retained in the stomach for a prolonged and predictable period of time exist today. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer duration, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner. Gastro retentive drug delivery system

(GRDDS) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and improves solubility of drugs that are less soluble in high pH environment. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape system or by the administration of pharmacological agents that delaying gastric emptying. Based on these approaches, floating drug delivery system seems to be the promising delivery system for control release of drugs. Floating oral drug delivery system (FDDS) are retained in the stomach and are useful for drugs that are poorly water soluble or unstable in intestinal fluid. If drug is poorly soluble in intestine due to alkaline pH and then its retention in gastric region may increase the solubility before they are emptied. Floating Drug Delivery System have a bulky density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on gastric content, the drug is released slowly at the desired rate from the system.

The successful development of oral controlled drug delivery system requires an understanding of the 3 aspects of the system, namely

1. The physiochemical characteristic of drug.
2. Anatomy and physiology of GIT and
3. Characteristic of dosage form.

Basic Physiology of The Gastrointestinal Tract [6,34]

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. The primary aim of the stomach is processing and transporting of food. The stomach has proteins in which the primary substantial metabolism of enzyme is promoted. Anatomically the stomach is divided into 3 regions: fundus, body and antrum. The proximal part made of fundus and body acts as a reservior for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

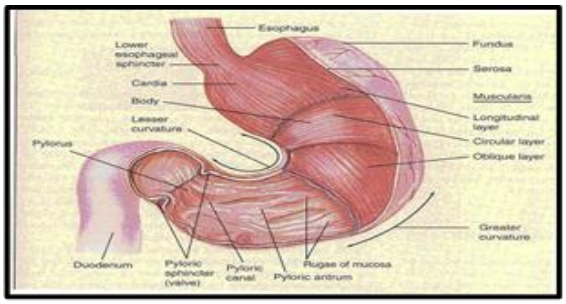

Figure 1: Location of stomach in human body

During fasting as well as fed states gastric emptying can be occurs. During the fasting state an inter digestive series of electrical events take place, through stomach and intestine every 2 to 3 hours, which is called as the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC). It is further divided into 4 phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phase III and I of 2 consecutive cycles. The pattern of contractions can be changed from fasted to that of fed state, after the ingestion of a mixed meal. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (less than 1mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed which results in slowdown of gastric emptying rate.

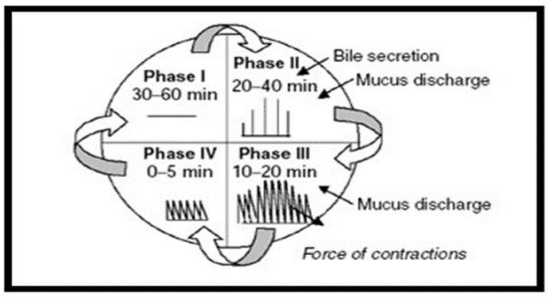

Figure 2: Migrating Myloelectric Cycle (MMC)

CURRENT APPROACHES TO GRDDS [8,9,11,18,19,30,32]

This drug delivery system aims at enhancing bioavailability of drugs by prolonging their retention in the stomach. Various approaches have been procured by experiments aiming at formulating gastro retentive drug delivery systems. Design and Development of several gastro retentive drug delivery approaches including,

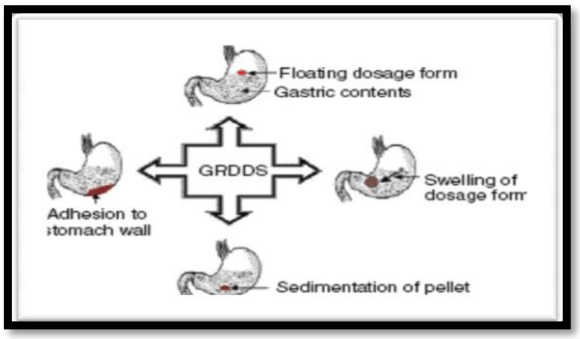

Figure 3: GRDDS Technology

A. Floating drug delivery system (FDDS)

Floating drug delivery system (FDDS) have a bulk density lower than the gastric fluid and thus remain buoyant in the stomach for a prolong period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. The residual system is emptied from the stomach after the release of the drug. This results in an increase in the GRT and a better control of fluctuation in the plasma drug concentrations.

A minimal gastric content needed to allow the proper achievement of the buoyancy retention; a minimal 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 reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object floating. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations

$F = F_{buoyancy} - F_{gravity} = (D_f - D_s)\, gv$

Where, F = total variance force, D_f = fluid density, D_s = object density, V = volume and g = acceleration due to gravity.

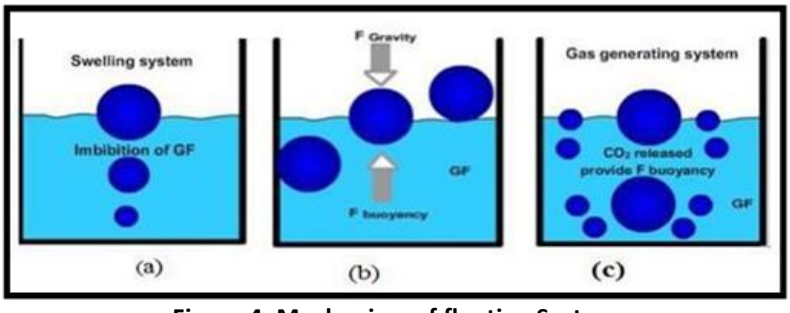

Figure 4: Mechanism of floating System

Floating system can be classified into two distinct categories:- Non effervescent systems and effervescent systems.

1. Effervescent systems:-

These are matrix type of systems prepared with the help of swellable polymers such as methyl cellulose and chitosan and various effervescent compounds, eg. Sodium bicarbonate, tartaric acid and citric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas is reported to be 0.76:1. Effervescence systems are classified into two types i) Gas generating systems ii) volatile liquid systems.

i) **Gas generating systems:** These are matrix type of systems prepared with the help of swellable polymers such as methyl cellulose and chitosan and various effervescent compounds, eg. Sodium bicarbonate, tartaric acid and citric acid.

ii) **Volatile liquid systems:** The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid eg. Ether, cyclopentane, that gasifie at body temperature to cause inflatation of chamber in the stomach.

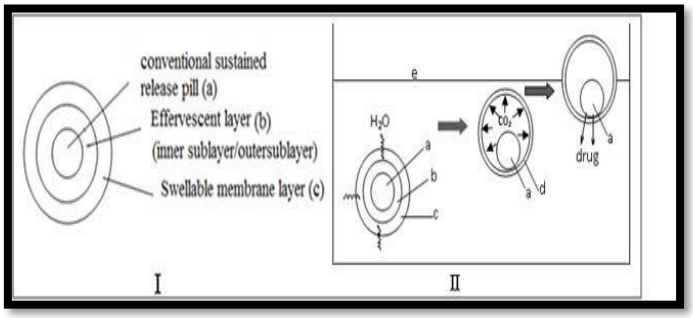

Figure 5

(i) A multiple unit oral floating dosage form
(ii) Stages of floating mechanism
(a) Penetration of water
(b) Generation of CO_2 and floating
(c) Dissolution of drug
(d) Expanded swellable membrane layer

2. Non effervescent systems:-

One or more gel forming, highly swellable cellulosic hydrocolloids Hydroxy ethyl cellulose, hydroxyl propyl cellulose, hydroxy propyl methyl cellulose (HPMC) and sodium carboxy methyl cellulose, polysaccharides or matrix forming polymers (eg, Polycarbophil and polystyrene) are incorporated in high level (20-75%) to tablets or capsules.

The air trapped by the swollen polymer achieves buoyancy to these type of dosage forms. This system can be further divided into the sub-types:

(a) Hydrodynamically balanced systems

These systems were first designed by sheth and Tossounian. These are single unit dosage form which contains one or more gel forming hydrophilic polymers. In these systems Hydroxy propyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), polycarbophil, polyacrylate, agar, carrageenans or alginic acid excipients are most commonly used. The polymer is mixed with drugs and administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. For the improvement of these systems many strategies have been tried and investigated.

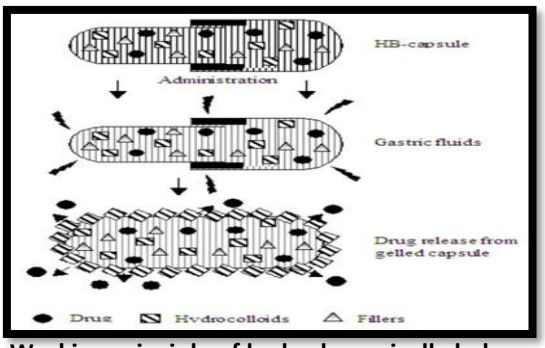

Figure 6: Working principle of hydrodynamically balanced system

(b) Alginate beads

Talukdar and Fassihi developed a multiple unit dosage floating system based on cross-linked beads. The beads were made by using Ca^{++} and low methoxylated pectin or Ca^{++} low methoxylated pectin and sodium alginate. In this system, sodium alginate solution is dropped into aqueous solution of calcium chloride and which causes the penetration of calcium alginate. These beads are separated and dried by air convocation and freeze drying (-40ºC) for 24 hrs, which leads to the formation of a porous system maintaining a floating force for over 12 hrs. These beads improve gastric retention time more than 5.5 hrs.

(c) Microballons/Hollow microspheres

Microballons were prepared by simple solvent evaporation or solvent diffusion/ evaporation methods. Polymers used in these systems are cellulose acetate, calcium alginate, polycarbonate, Eudragit S, agar and low methoxylated pectin. The drug release and buoyancy from dosage form are dependent on quantity of polymers, polymer plasticizer ratio and the solvent used for formulation. The microballons can float continuously over the surface of an acidic dissolution media for >12 hrs. The microballons are good floating multiple-unit dosage form so they are most promising buoyant.

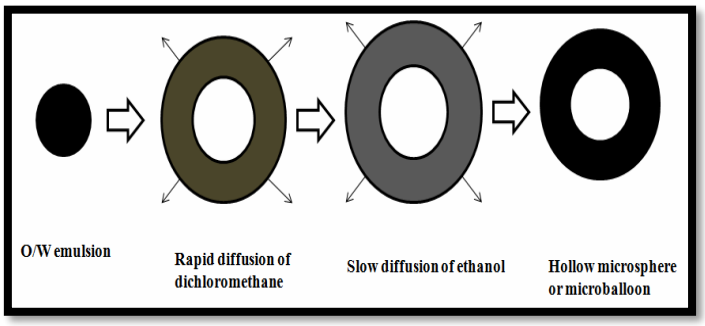

Figure 7: Formulation of floating hollow microsphere

(d) Microporous compartment system

This approach is based on the principle of the encapsulation of a drug reservior inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

B. Bio/Mucoadhesive systems

Bio/Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and as a potential means of extending the GRT of drug delivery system in the stomach, by increase the intimate and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bioadhesive/mucoadhesive polymers. The ability to provide adhesion of a drug to the GI walls provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

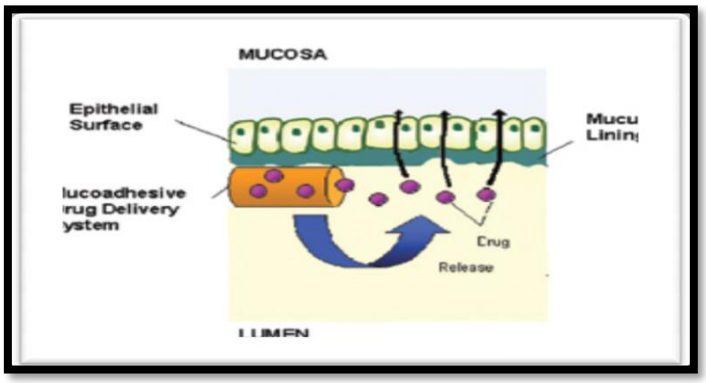

Figure 8: Bioadhesive system

C. Swelling and Expanding systems

These are dosage forms, which after swallowing swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type systems," since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity for several hours even in the fed state. The 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.

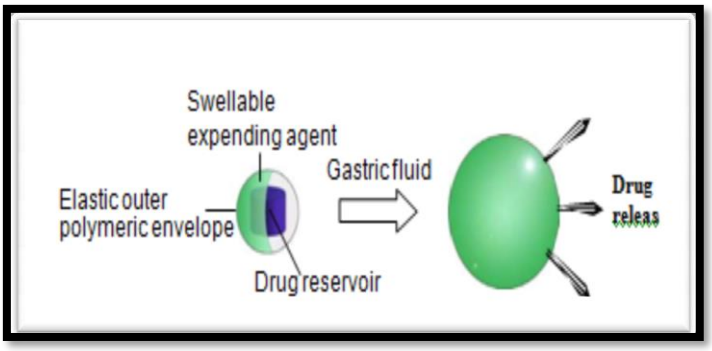

Figure 9: Swelling system

D. High density system

These system with a density of about 3 g/cm^3 are retained in the rogue of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such system can be retained in the lower part of the stomach. High density formulation includes coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

E. Low density systems

To avoid premature evacuation of drug through the pyloric sphincter low density systems with immediate buoyancy have been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called microballoons because of low density core.

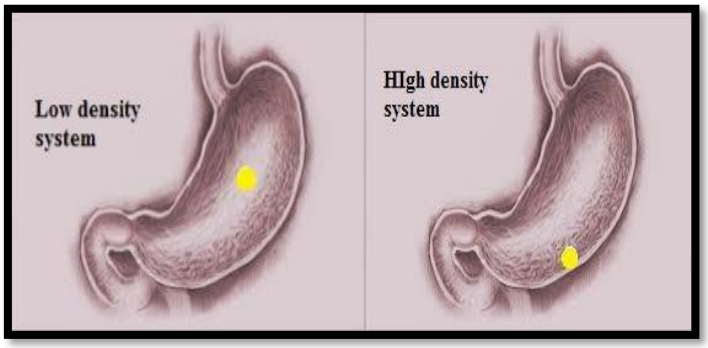

Figure 10: Low and High density system

F. Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formulation of CO_2 and acts as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the oesophagus. Usually, the system contains a gel forming agents and alkaline bicarbonate responsible for the formation of to make the system less dense and floats on the gastric fluids.

G. Magnetic systems

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet is placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet

must be positioned with migit compromise patient compliance. The technological approach in rabbits with bioadhesive granules containing ultra-fine ferrite. They guided them to oesophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2 hours.

FACTORS AFFECTING GASTRIC RETENTION [14,16]

To increase the retention time, various attempts have been made to retain the dosage form in the stomach. These attempts include the 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. These factors are as follows.

Density:- Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density. The density of the dosage form should be less than the gastric contents (1.004 gm/ml).

Size: - Dosage form units with a diameter of more than 7.5 mm are reported to have 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 are reported to have a better GRT 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 compared with single unit dosage forms.

Fed or unfed state: - Under fasting conditions, gastrointestinal motility is characterized by periods of strong motor activity that occurs every 1.5 to 2 hours. The GRT of the unit can be expected to be very short if the timing of administration of the formulation coincides with that of the MMC.

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.

Caloric content: - GRT can be increased by 4 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.

PATIENT RELATED FACTORS:

Gender & Age: Gastric emptying rate may differ in the male & female. Generally, the gastric emptying in women is slower than in men. Especially those over 70 years have a longer gastro-retentive time. Thus, gastric emptying time is slowed down.

Body Posture: Gastric retention times are different in supine and upright patient states. In the upright position, the floating systems floated to the top of the gastric fluid and remained for a longer time, showing prolonged GRT. However, in the supine position, the floating units are emptied faster than the non-floating units of similar size.

Disease State: In the case of partial or total gastrostomy and duodenal ulcers there is a decrease in gastric residence time. Diseases like gastroenteritis, pyloric stenosis, and diabetes show an increase in gastric residence time.

The volume of the GI Fluid: The volume of liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster. The cold fluids delay gastric emptying while warmer fluids fasten gastric emptying.

Effect of Gastrointestinal Fluid: On comparison between the floating and non-floating dosage form, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents protected from the peristaltic waves during the digestive phase, while the non-floating units stayed close to the pylorus and were sink; thus, they are subjected to propelling by the digestive phase for emptying.

NEED OF FDDS [10,23]

Frequency of drug administration is increased in case of drug with regional action in stomach get quickly emptied and don't get enough retention period in stomach similarly rapid gastric transition from stomach produce low bioavailability for oral dosage form especially in case of API which shows their local action to avoid this problem floating system are produced. The tablet/capsule floating formulation is needed to swallow as the whole unit. For the dose adjustment, it cannot break into half as they are designed for control or sustain release and floating ability also depends on the tablet dimension. The liquid floating formulation is not stable in comparison with tablet/capsule floating formulation. Some children, elder patients, adult patient, and patients with certain state suffer from dysphasia. Hence tablet/capsule floating system are difficult to swallow. The tablet/capsule floating system is needed to available in different strengths for the dose adjustment. Hence the in-situ gel formulation orally administered in aqueous solution form and

gets converted into gel under certain polymeric conformation. Thus, viscous gel of lower-density buoyant on gastric layer produces continuous and slow drug release for a longer duration of time. The low-density gel formation is called a raft.

ADVANTAGES OF FDDS [7,11,22]

- Enhance the bioavailability.
- Enhance first- pass biotransformation.
- Sustained drug delivery/Reduced.
- Frequency of dosing.
- Targeted therapy for local aliments in the upper GIT.
- Reduced drug fluctuation of drug concentration.
- Improved selectivity in receptor activation.
- Reduced counter activity of body.
- Extended time over critical concentration.
- Minimized adverse activity at the colon.
- Site specific drug delivery.
- Improved patient compliance.
- Maintenance of constant therapeutic level over longer period.

DISADVATAGES OF FDDS [12]

- Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS. E.g. NSAIDs, some antibiotics, digoxin, corticosteroid, iron (ferrous sulphate), oral contraceptive and tricyclic.
- Drugs which are absorbed along the entire GIT and which undergo 1st pass metabolism may not be desirable. E.g. nifedipine.
- They are not suitable candidates for drugs with stability and solubility problem in stomach. E.g. ranolazine
- Single unit floating capsules or tablets are associated with an "all or none concept" but this can be overcome by formulating multiple unit systems like floating microsphere or micro balloons.
- FDDS required sufficiently high level of fluids in stomach so that the system can float and thus sufficient amount of water (200-250 ml) to be taken together with FDDS.

INTRODUCTION TO FLOATING ORAL *IN SITU* GEL [13]

Gels: Gels are an intermediate state of matter which contains both liquid and solid components. It consists of three-dimensional solid networks. As it has three dimensional solid networks, gels are classified into two types based on the nature of the bonds. They are:

Physical gels which arise, when weak bonds like hydrogen bonds, electrostatic bonds and Vander Waal bonds constitute together to maintain the gel network.

Chemical gels arise when strong covalent bonds constitute to maintain the gel network. The gel network indicates the presence of cross-linking which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.

Hydrogels: Hydrogels are the three-dimensional structures that has polymeric networks which has the capacity to absorb and retain large amounts of water and biological fluids to swell.

Classification of hydrogels: Hydrogels are of two types. They are Preformed hydrogels are defined as simple viscous solutions which do not undergo any modification after administration. In-situ gels are the solutions or suspensions that undergo gelation after reaching the site due to physicochemical changes.

***In-situ* gelling system:** In-situ gelling system has become one of the most prominent among novel drug delivery systems due to many advantages such as improved patient compliance, reduced frequency of drug administration. 'In-situ' is a Latin word which means 'in position'.

There are many triggering mechanisms in in-situ gel formation some of them are pH change, temperature modification and solvent exchange. As the gel formed from in-situ gelling system, being lighter than gastric fluids float over stomach contents due to the presence of bio adhesive nature of polymers resulting in prolonged gastric retention time. In-situ gels are the formulations that are in sol form before administration in the body, but once administration undergo gelation to form gel. Various routes administration of in-situ gelling systems is oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal and rectal route.

ADVANTAGES OF *IN SITU* GEL [10]

1) Reduced dosing frequency.
2) Decreased occurrence of toxicity and intensity of adverse effect.
3) Increase patient compliance.
4) More uniform blood concentration.
5) More consistent and prolonged therapeutic effect.
6) To maintain continuous concentration of drugs in the blood.
7) Greater selectivity of pharmacological activity.
8) Reduced dose dumping.
9) Improved stomach retention with the slow release of drugs.

CRITERIA FOR SELCTING DRUG CANDIDATE FOR *IN SITU* GEL FLOATING SYSTEM [14,16]

- The right selection of drugs for oral in-situ drug delivery systems are drugs that have poor colonic absorption and Drugs that having better absorption properties at the upper parts of the GIT, so the following few points are taken into consideration:

- ❖ Drug acting locally in the stomach like Antacids and drugs for H. pylori, e.g. Misoprostol
- ❖ Drugs that are maximum absorbed from the stomach like chlordiazepoxide and cinnarizine.
- ❖ Drugs those are poorly soluble at alkaline pH like verapamil HCl and diazepam.
- ❖ Drugs with a narrow window of absorption like levodopa and riboflavin.
- ❖ Drugs which are rapidly absorbed from the GIT. Like Tetracycline.
- ❖ Drugs that degrade in the colon. like ranitidine and metronidazole.
- ❖ Drugs that disturb normal colonic microbes like ampicillin.
- ❖ Poor soluble of drugs at alkaline pH e.g. Furosemide, Diazepam, Verapamil, etc.

VARIOUS APPROCHES TO PRODUCE *IN SITU* GELATION [17]

There are various mechanisms for the in- Situ gel formulation: physical changes in biomaterials (e.g. Diffusion of solvent and swelling), Chemical reactions (e.g. Ionic cross linking, enzymatic crosslinking), physiologically stimuli (e.g. Temperature and pH)

a) By Physical Change (Swelling and Diffusion): By this approach physical change like swelling or diffusion may take place. In swelling, polymer in the system absorbs water from the surrounding environment and swells to form a viscous gel. 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.

b) By Chemical Change: Change in chemical environment leads to polymeric cross linking thereby formation of gel. Ion sensitive polymer (sodium alginate, calcium alginate, gellan gum, pectin) undergo phase transition in present of various monovalent and divalent cation (ca^{+2}, mg^{+2}, Na^{+}, k^{+}) for the formation of gel. For e.g.: gelation of low methoxy pectin in present of divalent cation (ca^{+2}). Alginate contain molecule (sodium alginate) undergo gelation in presence of di/polyvalent cation e.g.ca^{+2} interact with guluronic acid block in alginate side chain.

c) By Physiologically Changes:

(i) pH dependent gelling- Another formation of *in situ* gel based on pH dependent. For these purpose various pH sensitive polymers are use such as PAA (carbomer) or its derivatives, polyvinyl acetyl dimethyl amino acetate (AEA), mixture of poly (methyl acrylic acid) (PMA), and poly (ethylene glycol) (PEG) shows change from sol to gel when changes in pH. at higher pH range weakly acidic group shows gel formation and vice-versa. Triggered floating *in situ* gel of levetiracetam.

(ii) Temperature Dependent Gelling - Dosage form is solution at room temperature (20 – 25 ˚c) but when in contact with body temperature (35 – 37◦c) they convert into gel. Some of the polymer have drastic changes in solubility in response to increase in environmental temperature (lower critical solution temperature) LCST. At the LCST the interaction between polymer and water is unfavourable as compared to polymer-polymer and water-water. So, molecule becomes dehydrated and produce hydrophobic structure polymer such as pluronic (poly (ethylene oxide)-poly (propylene oxide poly (ethylene oxide) (PEO-PPO PEO) triblock), polymer network of poly (acrylic acid) (PAA) and poly acryl amine (PAAM) or poly (acrylamide-co-butyl methacrylate). Below the upper critical solution temperature (UCST) hydrogel contracts upon cooling they form hydrogel this called positive temperature sensitive hydrogel. Polymer used such as poly acrylic acid, poly acryl amide and co-butyl methacrylate. Eg: *In situ* gelling formulation based on the methylcellulose / pectin systems for oral sustain drug release to dysphagia patient.

d) Dilution-Sensitive: In this approach, a polymer that undergoes phase transition in presence of higher amount of water may lead to formation of gel. E.g. Lutrol.

e) Electrical Signal Sensitive hydrogels: Hydrogels sensitive to electric current undergo shrinking or swelling in the presence of an applied electric field.

f) Light-Sensitive hydrogels: Light-sensitive hydrogels can be used in the development of *in situ* forming gels for cartilage tissue engineering. E.g. Quinone can be injected into a tissue and applied electromagnetic radiation is used to form a gel by enzymatic processes. For that long ultraviolet wavelengths are used.

g) Glucose-Sensitive hydrogels: Delivery systems which are responsive to stimuli 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, so it will functioning as a self-regulating insulin delivery system.

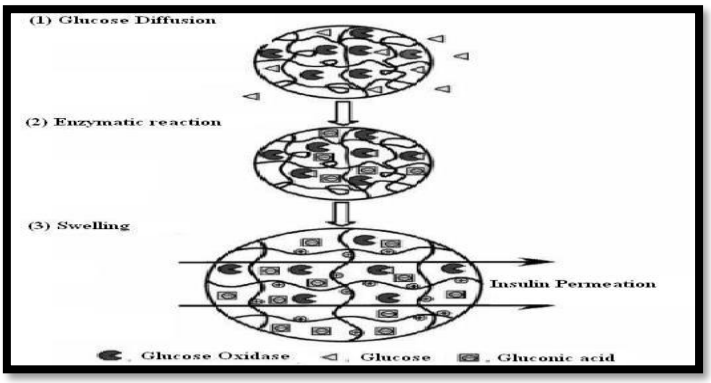

Figure 11: Glucose Sensitive Mechanism

APPLICABILITY OF *IN SITU* POLYMERIC DRUG DELIVERY SYSTEM [20]

1. 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 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.

2. 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 its efficacy for the treatment of allergic rhinitis. 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%).

3. 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-pass effect.

4. 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, progestin, oestrogens, peptides and proteins62. 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.

5. Injectable drug delivery system:-One of the most obvious ways to provide sustained release medication is to place the drug in delivery system and inject or implant the system into the body tissue. Thermo reversible gels mainly prepared from poloxamers are predominantly used. The suitability of poloxamer gel alone or with the addition of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran was studied for epidural administration of drugs in vitro.

6. Dermal and transdermal drug delivery system:- Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin. 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 insulin73. The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

7. Oral drug delivery system:-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. Advantages of pectin is water soluble so, no need to add organic solvent. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectin, 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 complexes calcium ions that undergo

gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was studied. Hydrogels made of varying proportions of PAA derivatives and cross-linked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastro protective property.

POLYMERS FREQUENTLY USED FOR *IN SITU* GELLING FOR FDDS [18,19,31]

Polymers that undergo solution to gel transition in aqueous solution at body temperature were used in the preparation of floating in-situ gel. Some of them are:

Pectin:

Pectin is originated from plant origin; it is an anionic polysaccharide isolated from the cell wall of most plants comprising mainly esterified D-galacturonic acid residues in a-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated. Pectin gelation characteristics can be divided into two types: high-methoxy and lowmethoxy gelation. Gelation of high methoxypectin 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 solid content.

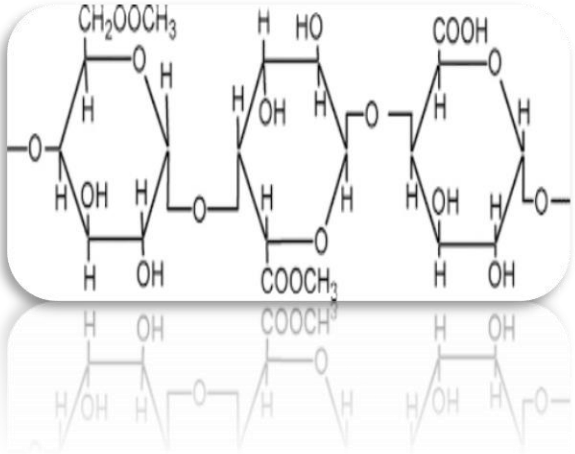

Figure 12: Chemical Structure of pectin

Gellan Gum:

a) Gellan gum secreted by Sphingomonas elodea (Pseudomonas elodea) is an anionic deacetylated polysaccharide with repeating tetra saccharide units composed of -D-glucuronic acid (1 unit), -L-ramose (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+, Ca 2+).

b) Gellan gum secreted by Pseudomonas elodea is an anionic deacetylated exocellular polysaccharide with a tetra saccharide 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 crosslinking.

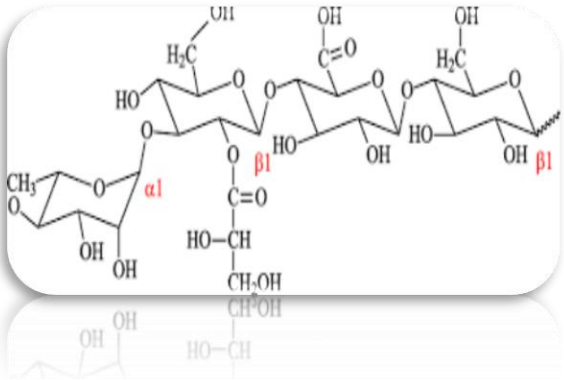

Figure 13: Chemical Structure of Gellan Gum

Sodium Alginate: (Alginic Acid)

Alginic acid is a polysaccharide consisting of β-D-mannuronic acid (M) and L-guluronic acid (G) residues joined by 1,4-glycosidic linkage. Alginate is a well-known polysaccharide which is widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent counter ions, such as calcium, lead, and copper. It is also possible to obtain an alginic acid gel by lowering the environmental pH value. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.

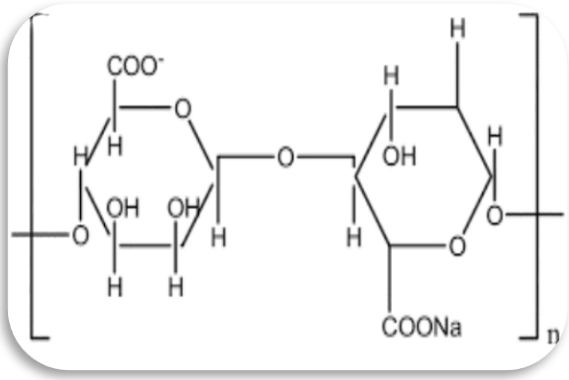

Figure 14: Chemical Structure of Sodium alginate

Pluronic Acid F127:

The Poloxamers or pluronic consist of more than 30 different non-ionic surface active agents. Poloxamers, commercially available as Pluronic R, are the most commonly used thermal setting polymers. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Pluronic F-127 gives colourless transparent gels which is most commonly used polymer in pharmaceutical technology. Pluronic F-127 was used as an *in situ* gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methyl cellulose to ensure long residence time at the application site.

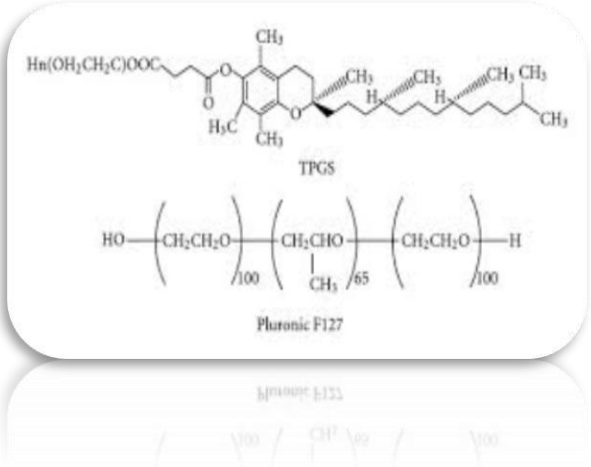

Figure 15: Chemical Structure of Pluronic Acid F 127

Xanthum Gum:

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (βD-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 pyruvic acid groups in the side chain.

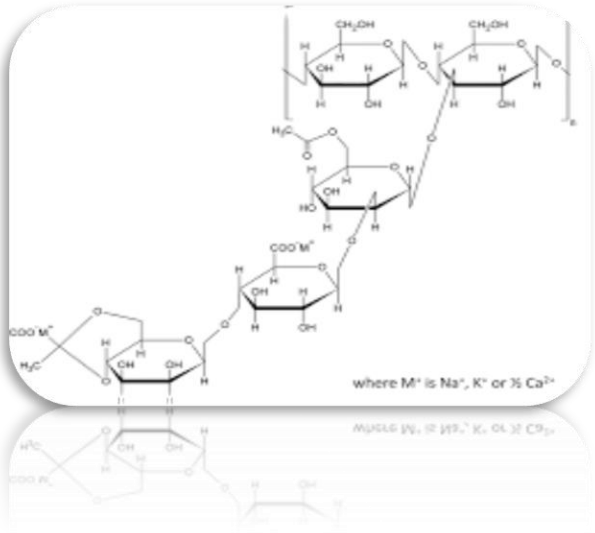

Figure 16: Chemical Structure of Xanthan gum

Xyloglucan:

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.

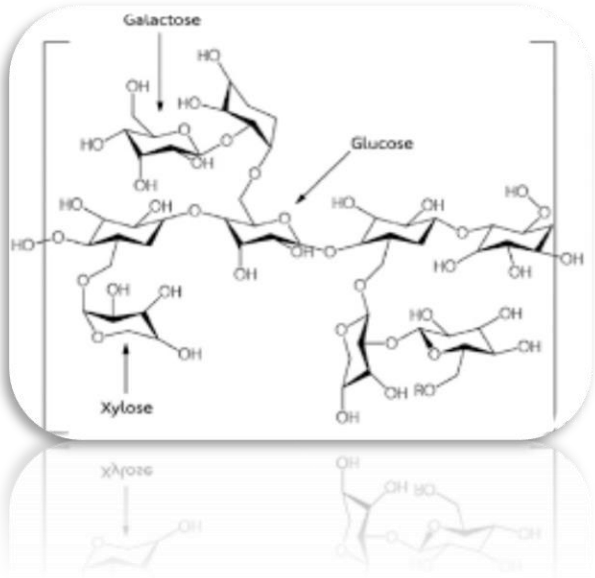

Figure 17: Chemical Structure of Xyloglucan

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. A 25-40% aqueous solution of this material will become gel at body temperature, and drug release from such a gel occurs over a period of up to one week.

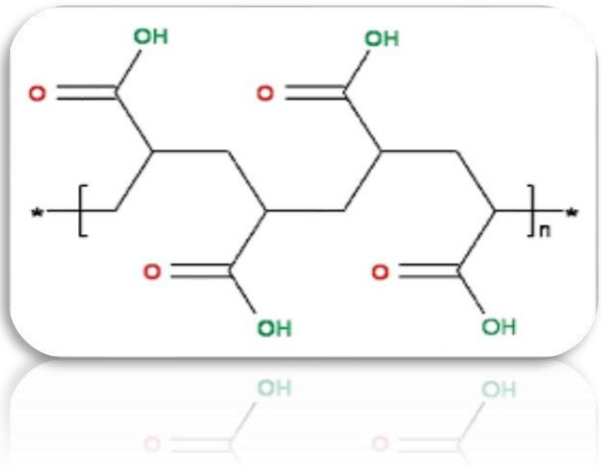

Figure 18: Chemical Structure of Carbopol

EVALUATION OF *IN SITU* GELLING SYSTEM [21,24,25,26,27,28,29,33,35]

Clarity

The clarity of formulated solutions can be determined by visual inspection under black and white background.

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-situ gelling capacity was cauterized in three class based on gelation time and time period at they remain as it.

(+) gel after few minutes, dispersed rapidly

(++) gelation immediate, remain for 12 hrs

(+++) gelation immediate, remain for more than 12 hrs.

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°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.

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 remoter with a specified amount of solution form gel were prepared in a beaker. This beaker is raised so pushing the probe of remoter 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.

Swelling Index

The swelling indexes of the gel of the selected formulations were determined by a simple method. The in-situ gel formed in 40 ml of 0.1 N HCl was used. From each formulation the gel portion from the 0.1 N HCl was separated and the excess HCl solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 50 ml of distilled water was added. After 12 hrs the water was decanted and the weight of the gel was recorded. The difference in the weight was calculated and reported.

Table 1: Commercially available marketed Products [17,18,32]

Dosage Forms	Drugs
Tablets	Acetyl salicylic acid, Amoxycillin trihydrate, Acetaminophen, Ampicillin, Ciprofloxacin, Captopril, Diltiazem, Nimodipine, Prednisolone, Riboflavine-5-Phosphate, Theophylline, Verapamil HCl
Capsules	Benserazie, Diazepam, Frusemide, L-Dopa, Misoprostol, Nicardipine, Propranolol, Urodeoxycholic acid
Microspheres	Aspirin, Griseofulvin, Ibuprofen, Ketoprofen, Terfenadine, Tramilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Films	Drug delivery devices, Cinnarizine
Powders	Several basic drugs

Table 2: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery System [17,18]

Name	Drug	Manufacturer	Remarks
valrelease	Diazepam	Hoffmann La Roche USA	Floating Capsules
Madopar	Benserazide	Roche Products USA	Floating CR Capsules
Prolopa	L. Dopa	Roche Products USA	
Liquid gaviscon	Aluminium Hydroxide Magnesium Carbonate	Glaxo Smith Kline	Effervescent floating alginate preparation
Topalkan	Al-Mg Antacid	Pirerre Fabre Drug France	Floating liquid alginate
Almagate	Al-Mg Antacid		
Floatcoat	Ferrous Sulphate	Ranbaxy India	
Conviron	Ferrous Sulphate	Ranbaxy India	Colloidal gel forming FDDS
Cytotech	Misoprostol	Pharma acia USA	Bilayer floating capsule
Cifron OD	Ciprofloxacin	Ranbaxy India	Gas generating floating form

CONCLUSION

The literature searched during the review of the topic reviled that gastro retentive drug delivery have various prospective advantages for drugs with poor bioavailability due to rapid transition and small absorption window at the upper gastrointestinal tract (GIT). It greatly improves the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which is sustained over a longer period. As in-situ gel can be the potential tools towards the treatment of diseases like chronic gastritis and peptic ulcers caused by H. pylori. It is not only helpful for sustained drug delivery of oral liquid dosage form but also become convenient for paediatric and geriatric patients having a swallowing problem. The polymeric in-situ gels for controlled release of various drugs may provide several advantages over conventional dosage forms. Good stability and biocompatibility characteristics also make the in-situ gel dosage forms very reliable. The application of these tools for the delivery of herbal medicaments will be the subject of research in the future.

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