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FLOATING DRUG DELIVARY SYSTEM: A BETTER APPROACH

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of man drugs. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such system for drugs with bioavailability problems. In this review, current & recent developments of Stomach Specific FDDS are discussed.

KEY WORDS

Floating Drug Delivery System, Effervescent Systems, Non-Effervescent Systems, recent advancement, In vivo and In vitro evaluation.

INTRODUCTION

In1968, Davis First Inventor of Floating drug delivery system. The oral route is considered as the most favorable route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment. [1] This results in a significant variation in drug levels. Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could alter method of medication and provide a number of therapeutic benefits [2]. The most important objectives of these new drug delivery systems are: First, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limits of conventional drug delivery system, floating tablets have been developed.[2] To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system, low density raft systems incorporating alginate gels, low density systems[2] Swellable, floating and sustained release gel are developed by using a combination of hydrophilic polymer(hydroxypropyl methylcellulose), floating

gents (calcium carbonate)It is also useful for drugs which are introducing at acidic pH of stomach, Delivery system with higher density, initially settle down in stomach and then absorbed water, swell and then float due to decrease in density of the system. But, with such system, there may be a possibility of gastric emptying of system, before the floating starts. Low density of system, which leads to floating, rendered either by incorporation of low density excipients [3] Oral in situ gel forming system also known as stomach specific or raft forming systems have provided a suitable way of providing the controlled drug delivery within stomach with enhanced gastro-retention. The solid floating dosage forms are stable as compare to liquids but the difficulty with them is that they are needed to swallow as whole unit. In case of dosage adjustment these cannot be possible because of disturbing designed for controlled release and floating ability also depends on dimensions of solid dosage form .In addition to this, a wide variety of both natural and synthetic hydrophilic polyionic systems such as sodium alginates have been investigated for the preparation of multiple unit floating dosage forms. In the present study, a multiple-unit FDF was designed keeping in view the 'all or nothing response of single-unit systems. Literature review indicates a widespread use of sodium alginate for achieving the sustained release of drugs as it targets the gastric mucosa and increases the bioavailability of the drugs because of its ability to form a stable and bioadhesive gel with calcium ions. Hydroxy propyl methyl cellulose (HPMC) has been reported to enhance the sustained release properties of alginate by providing a denser inner matrix[4]Drug having short half-life and easy absorb from stomach, in chronic disease condition orally administration is convenient for long period and quickly eliminated from blood circulation, An shortened release of the drug and shorter residence time of the dosage form in the upper gastro intestinal tract a major site for the absorption of the many drugs, will show to lower bioavailability. Therefore, prolonged gastric retention is must for achieving control over the gastro retention time because this helps to maintain the controlled release system in the stomach for a longer and predicted time [5]

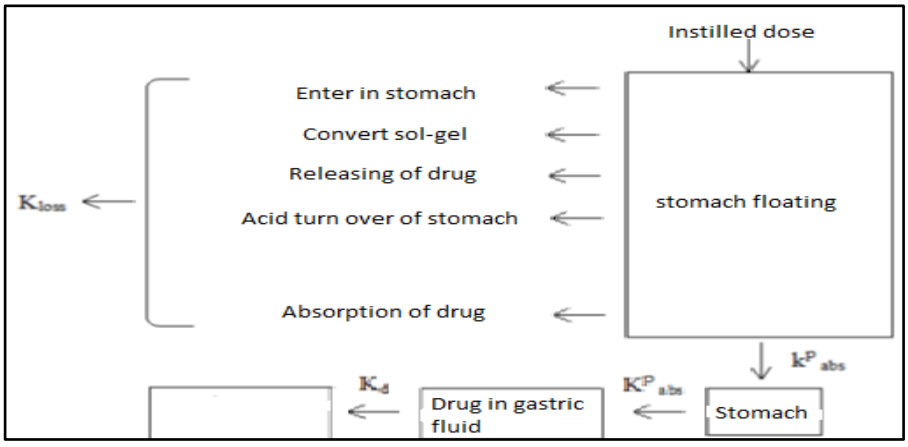
OBJECTIVE

These have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems, recently. The study highlights these advantages with reference to the various types of gastroretentive drug delivery systems, as well as provides a general idea of the recent advances that have taken place in this arena. [2]

SELECTION CRITERIA FOR DRUG

-Drug that disturb normal colonic microbe.
-At high PH low solubility candidate suitable for these system
-Drug which have low solubility in intestinal and colonic environment e.g.Captopril, Metronidazole
-Locally active in stomach.
-Fine absorption window in G.I.T

Figure 1 Amount of drug available



IN SITU GEL

In the early 1980s in situ gel suggested as new invention for sustained drug delivery. In situ gel forming systems have been widely scrutinized as vehicles for sustained drug delivery. This interest has been generated by the good advantages shown by in situ gel as polymeric delivery systems such as ease of administration and improved patient compliance, reduced frequency of administration and improves comfort. In situ gel formation occurs due to one or more polymer combination with different stimuli like pH change, temperature modulation and solvent exchange. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, sodium alginate, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone are used for formulation development of in situ forming drug delivery systems. Stomach floating in situ gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gel formed by in situ gelling system, being lighter as compare to gastric fluids, floats over the stomach contents or adhere to gastric mucosa, adherence due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and improve gastric residence time resulting in sustained drug delivery in gastrointestinal tract.[18]In-situ gel forming drug delivery systems are a revolution in oral drug delivery system. The insitu are liquid at room temperature but undergo gelation when in expose with body fluids or change in pH. This gelation involves formation of double helical junction zones followed by aggregation of the double helical segments to form three dimensional network complexes with cations by cross linking. [7]The main purposes of the present study were to prepare sol-gel system of respective drug using gellan gum and to study the effect of polymer and Ca2+ ion concentrations on the release and floating behavior of the gel formed in-situ. The sol is formulated as the solution of gellan gum (Gelrite®) which is an anionic polymer sensitive to presence of cations that triggers its gelation Drug is dispersed in this sol along with the cation source in the form of Calcium Carbonate. The resulting sol when comes in contact with the Gastric environment, the cations (Ca2+) released triggers gelation of gellan gum and the floating agent released CO_2 gets entrapped in the gel thereby forming a buoyant gel matrix which further controls the drug release The floating characteristics and the drug release are the function of polymer and cation concentration.[8] Solutions that undergo sol-gel transformation when they full fill physiological conditions may serve as an in situ gelling drug delivery system In situ is a Latin phrase meaning in the place. It is widely accepted that increasing the viscosity of a drug formulation in the gastric / precorneal region will lead to an increased bioavailability, due to slower and situ specific. Gels are transparent or translucent, non-greasy, semisolid preparations in vitro body. These are also termed jellies consisting of either suspensions made up of small inorganic particles, or large organic molecules interpenetrated by a liquid Hydrogel is three-dimensional hydrophilic polymeric networks capable of imbibing large quantities of water have generated a lot of interest recently as delivery system for pharmaceutically active agents . One of the main characteristics of stomach floating in situ gel is that they contain ingredients that are dispersible as colloids or are water-soluble .The stomach floating in situ gel of environmentally sensitive can be affected by many stimulus, these are: temperature, ionic concentration, electrical field, inflammation, solvent concentration, and glucose concentration. According to the mechanism by which sol-gel phase transition occur, the following three types of systems can be recognized

1- pH triggered systems.
2- Temperature sensitive system.
3- Ion activated system.

From the point of view of patient compliance, a liquid dosage form that can sustain drug release and remains in contact for extended period of time, improving the bioavailability, decreasing the dose concentration and frequency may be achieved by in situ gelling formulations. Gelation of the orally administered liquid formulations (Ion activated system) was ensured by the inclusion of calcium ions in the formulation as a soluble complex designed to break down to release free calcium ions on encountering the acidic environment of the stomach. The gelation was takes place after the orally

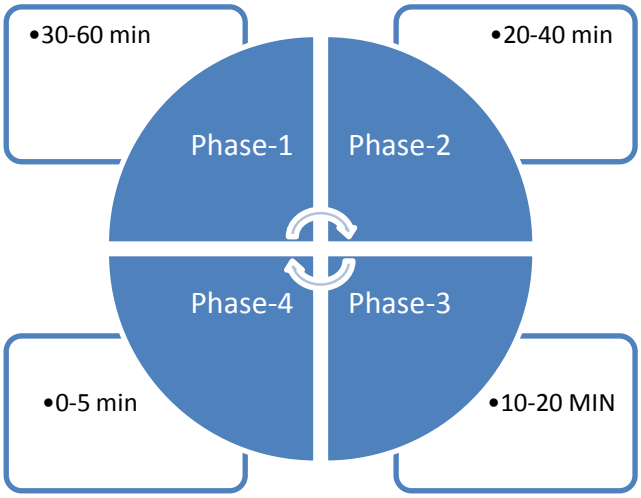
administered solution reached the stomach by complexing the calcium with sodium [9].

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY:

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [10]Gastric emptying occurs during fasting as well as fed states The pattern of motility is however distinct in the 2 states. Electrical events take place during the fasting state an interdigestive series, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (**MMC**), which is further divided into

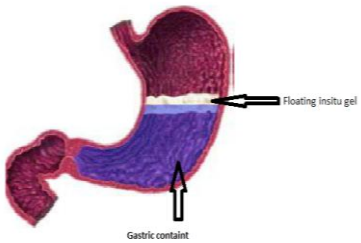
Following 4 phases as described by Wilson and Washington.

Figure 2: Gastro intestinal motility pattern



1. Phase I (basal phase) lasts from 30 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 10 to 20 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

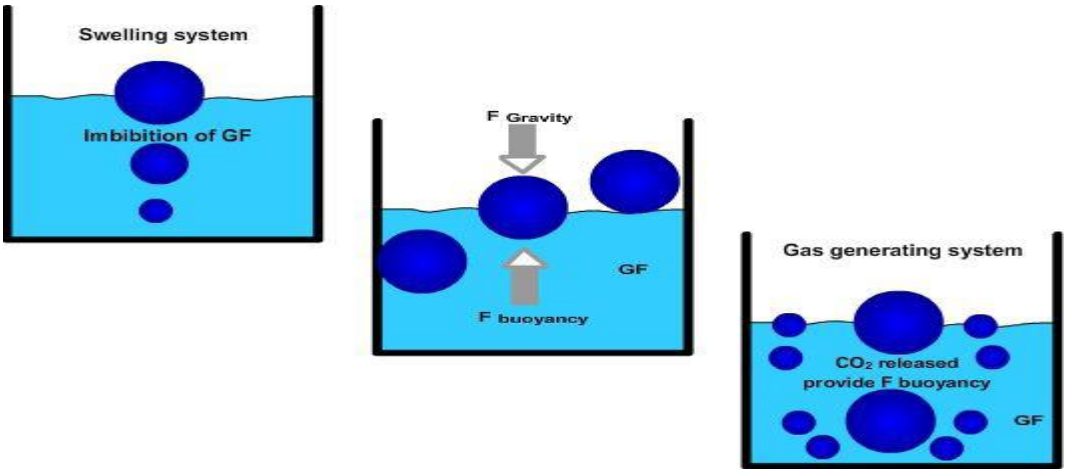
Figure 3: Stomach contain floating in situ gel



After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. 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 (to less than 1 mm), which are

propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[11] Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically complications, that of short gastric residence time and unpredictable gastric emptying rate.[11]

Figure 4: Mechanism of floating in situ gel [5]



1. IN SITU FORMATION BASED ON PHYSICAL MECHANISM:

Swelling and Diffusion:

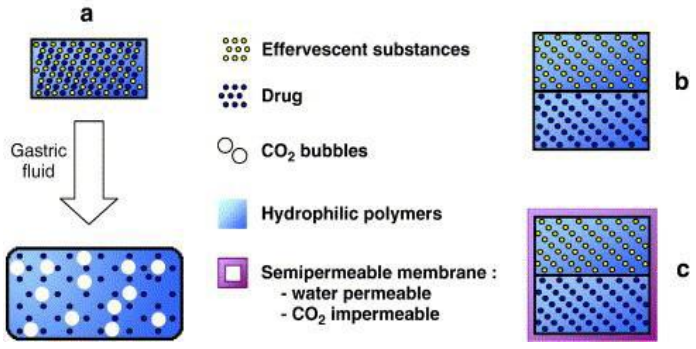
Stomach floating in situ gel systems, since they exhibit the tendency to remain extended at the pyloric sphincter. Swelling of polymer happen after absorption of water causes formation of gel certain biodegradable lipid substance such as myverol (glycerol mono-oleate) forms in situ gel under such phenomenon. Swelling is maintained by the degree of cross-linking between the polymeric chains on coming in contact with gastric fluid, the polymer absorbs water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-linkers in the hydrophilic polymer network. Solution of polymer such as N – methyl pyrrolidone (NMP) involves diffusion of solvent from Polymer solution into surrounding tissue and results in solidification of polymer matrix. [12] These cross links minimize the dissolution of the polymer and hence maintain the physical integrity of the dosage form.[13]

2. IN SITU GELLING BASED ON CHEMICAL STIMULI:

Ionic crosslinking:

Certain ion ph sensitive polysaccharides such as carrageenan, Gellan gum (Gelrite®), Pectin, Sodium Alginate undergo phase transition In presence of various ions such as Ca+2, Mg+2, Na+. For e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca2+ due to the interaction with guluronic acid block in alginate chain

Figure 5: Ionic crosslinking [19].



Enzymatic cross linking:

Certain natural enzymes which operate efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation in situ.

3IN SITU GEL FORMATION BASED ON PHYSIOLOGICAL STIMULI:

Temperature dependant in situ gelling:

In this approach, temperature dependent phase transition from less viscous solution to relatively high viscosity gel is seen. Polymer-polymer interaction occurs to form a solvated Change in temperature causes sudden change in the solubility of polymer within system, 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. Before administration these are present in liquid form, transfer in to gel at body temperature. These in situ gel are liquid at room temperature (20 ^{o}C-25 ^{o}C) and after exposure to body fluid goes in gelation phase (35^{o}C-37^{o}C), due to an increase in temperature this approach exploits temperature-induced phase transition. Some polymers undergo sudden changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST). At the LCST, hydrogen bonding between the polymer and water becomes adverse, compared to polymer–polymer and water–water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature. A positive temperature- sensitive in situ has an upper critical solution temperature (UCST), such insitu gel contracts upon cooling below the UCST. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling. [13,14].

PREPARATION OF THE IN-SITU GELLING SOLUTIONS:

Sodium alginate solutions of different concentrations were prepared in deionized water containing 0.25% of sodium citrate. Low concentrations of cations in solution were sufficient to hold the molecular chains together and inhibit hydration. Sodium alginate solution was heated to 75^{0}C with stirring. After cooling to below 40^{0}C, different concentrations of calcium bicarbonate and the drug were added and dispersed well with continuous stirring with magnetic stirrer. The resulting sodium alginate in-situ gelling solution containing respective drug was finally stored in amber bottles until further use. [15]

Table 1: Natural polymer use in preparation of in situ gel[16]

Natural polymer	Basic chain	Solubility	Source
Psyllium husk	ß-(1-4)-linked D-xylopyranosyl	Swells in water	Seed coats of Plantagoovata
Pectin	α-(1,4)- linked Dgalacturonic acid	Soluble in water, insoluble in ethanol (95%) & organic solvents	Citrus peel, apple pomace, sugar beet pulp etc.
Xanthum gum	α-(1,4)-linked D-glucose	Soluble in hot/cold water and acid/alkane conditions	Fermentation of glucose by Xanthomonascampestris
Chitosan	Deacetylated P-1, 4-Nacetyl-1-D glucosamine	Insoluble in neutral and alkaline pH	Shell of marine invertebrates
Gellan gum	D-glucose, D-glucuronic acid and rhamnose in ß-1, 4 linkage	Soluble in hot water	Pseudomonas elodea
Karaya gum	Mixture of d-galactose&Lrhamnose	Insoluble but swells in water (most of	Plant (Sterculiaurens)

	and Dgalacturonic acid	all gums)	
Starch	(1,4)-linked D-glucose and β-(1,6)-linked Dglucose	Amylose is soluble in boiling water but amylopectin is insoluble	Storage polysaccharide in plants
Alginates	1-4'- ß –D-mannuronic acid and α-L-glucuronic acid	Insoluble in ethanol (95%), ether, chloroform and slowly soluble in water, forming viscous colloidal solution	Laminariahyperborea, Ascophyllum, nodosum, Macrocystispyriferaetc
Guar gum	α-D-mannopyranose	Swells in water, insoluble in organic solvents	Endosperm of the seeds of Cyamopsis tetragonolobus

APRROACH STOMACH FLOATING IN SITU GEL: [17]

1) Floating dosage form

A) Non effervescent system

Colloidal gel barrier system

Alginate beads

Hollow micro sphere

B) Effervescent system

a) Gas generating

b) Volatile liquid/Vacuum system

-Intra gastric gastrointestinal drug deliverysystem

-Inflatable gastrointestinal drug delivery system

-Intragastricosmotically controlled drug delivery system

2) Raft forming system

3) High density system

1) Floating dosage form:

A)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 gastric fluidic environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms and releasing co2 which causing floating over gastric fluid excipients used most commonly in these systems include hydroxyl propyl methyl cellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, Calcium carbonate polyethylene oxide and polycarbonates.[13]

B) Effervescent systems (gas generating systems):

These buoyant systems utilized matrices prepared with swellable polymers like HPMC K (100) M, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid convert in to gas at body temperature. The stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing float gel in the stomach Excipients used most commonly in these some of the polymers used are hydroxypropylcellulose, hydroxypropyl methylcellulose, cross povidone, sodium carboxy methyl cellulose, and ethyl cellulose. [18]

2) Raft forming system:

The basic mechanism involve in raft formation include the conversion of sol-gel in contact with gastric fluid where in each portion of liquid swells forming continuous layer called as raft The raft float because of buoyancy created by the formation of CO_2 and act as barrier to prevent reflux gastric content like HCl

and enzyme in to esophagus usually system contain a gel forming agent and alkaline bicarbonate or carbonate responsible for the formation of to make system less dense and float on gastric fluid Reckitt and colman product limited have useful in the treatment of H.pylori infection of GIT.[17]

3) High density systems:

It is a well-known fact, that the density of the gastric content is approximately similar to water. So, when the density of the dosage form is higher than water, it tends to deposit or sink at the bottom of the stomach, near pyloric region. The density of these systems should at least be 1.004 g/ml. 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. [13] These sinked dosage forms, there withstand against peristaltic contractions and do not get emptied from the stomach. Retarded gastrointestinal transit, in case of such dosage form has been reported to extend gastric retention time up to 6 to 24 hours Commonly used excipients in such dosage forms are barium sulphate, titanium oxide etc., which raises the density of system up to 1.4 to 2.5 gram per cubic centimeter.[14]

FACTOR AFFECTING GASTRIC RETENTION:

Gastric residence time of an oral dosage form is affected by several factors. The rate of gastric retention of GRFDDS depends mainly on-

A. Volume of GI fluid: The resting volume of the stomach is 25 to 50 ml. When volume is large then the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

B. Meals: The rate of gastric emptying depends mainly on nature of meal and caloric content of meals.

Nature of meal: Feeding of indigestible polymers or fatty acid salts that can change the motility pattern of the stomach during fed state, thus minimizing the gastric emptying rate and prolonging drug release.

Caloric content of meal: GRT can be increased by 4 to 10hrs in the presence of higher protein meals and fat contains.

C. Dosage form related factors:

Density: A buoyant dosage form has low density than gastric fluid floats.Since it is left from the pyloric sphincter; the dosage unit is retained in the stomach for an extended period.

Size: In case ofDosage form units with a diameter of more than 7.5mm are reported to have an increase GRT compared with those with a diameter of 9.9mm. Small size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves,liquid dosage form by pass these effect.

Shape of dosage form: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5kilopounds per square inch (KSI) are reported to have better GRT~90% to 100% retension at 24 hrs. Compared with other shapes.

Single or multiple unit formulation: Multiple unit formulations show beneficial advantage than single unit dosage forms.

D. Fed Conditions

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.

Fed or unfed state: However in the fed state, MMC is delayed and GRT is considerably long.Under fasting condition, the GI motility is characterized by periods of strong motor activity or migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hrs

E. Patients related factors:

Gender: Mean ambulatory GRT in males (3.4±0.6hrs) is less compared with their age and race matched female counterparts (4.6±1.3hrs), regardless of the weight, height, and body surface.

Age: Elderly people, especially over 70 year age, have a significantly longer GIT.

Posture: GRT can differ between supine and upright ambulatory states of the
Patients

Concominant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

F. Biological factors: Diabees and Crohn's disease etc. [13]

Table 2: Marketed product of GRDDS [17]

Brand name	Delivery system	Drug (dose)	Company name
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India
AlmagateFlot coat®	Floating dosage form	Al – Mg antacid	
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India

Table 3: Recent activities on stomach specific floating in situ gel.

Author	Drugs	Category	Reference No.
Rajinikanth et al	Clarithromycin	Anti-H. pylori	1
Rajinikanth et al	Levofloxacin Hemihydrate	Anti-H. pylori	2
Jayswal et al	Cimetidine	Antihistaminic	3
Itoh et al	Paracetamol	NSAID	4
Patel et al	Chlordiazapoxide	Antidepressant	5
Rathod et al	Ambroxolhydrocloride	Secretolytic agent	6
Patel. et al	Famotidine	Antihistaminic	7
Lahoti et al	Ofloxacin	Antibiotics	8
Wamorkar et al	Metoclopramide	Anti-emetic	9
Jivani et al	Baclofen	Skeletal muscle relaxant	10
Patel et al	Ranitidine HCl	Antihistaminic	11
Patel et al	Hydrochlorothiazide	Antihypertensive/Diuretic	12

ADVANTAGES OF FLOATING DRUG DELIVERY:

1. Reduced fluctuations of drug concentration: The fluctuations in plasma drug concentration are minimized by sustained release and concentration-dependent adverse effects that can be prevented. Drugs have low therapeutic index this feature is of special importance.
2. Extended time over critical (effective) concentration: The sustained mode of administration give pharmacological action below

toxic level, thus enhances the pharmacological effects and improves the clinical outcomes.

3. Improved receptor activation selectivity: FDDS gives sustained release that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
4. Sustained drug delivery/reduced frequency of dosing: Those drugs having narrow biological half-life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved therapy and thus improves the patient compliance
5. Enhanced bioavailability: Some drugs have good bioavailability (e.g. riboflavin and levodopa) CR-GRDF is considerably enhanced as comparison to administration of non- GRDF CR polymeric formulations.
6. Targeted therapy for local ailments in the upper GIT: The prolonged and sustained administration of the drug through FDDS to the stomach may be helpful only for local therapy in the stomach.
7. Enhanced first-pass biotransformation: When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input.
8. Reduced counter-activity of the body: Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.
9. Site specific drug delivery: A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine. [29]
10. Improve efficiency:-The efficiency of the medicaments can be increased utilizing the sustained release.
11. Enhancement of therapeutic efficacy: Floating systems are particularly useful for acid soluble drugs that are poorly soluble or unstable in intestinal fluids. For example bromocriptine used in the treatment of Parkinson's disease have low absorption potential that can be improved by HBS dosage form and thus its therapeutic efficacy could be enhanced.
12. The Gastric floating are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs act by local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
13. In some type of diarrhea there is vigorous intestinal movement and a short transit time, poor absorption is expected under such circumstances it may be advantage drug in gastroretention to get a relatively better response.
14. Reduction in the variability in transit performance: Floating dosage forms with sustained release characteristics are useful in reducing the variability in transit performance. For example formulating tacrine as HBS dosage form reduces its gastrointestinal side effects in Alzheimer's patients.
15. This bacterium is highly sensitive to most antibiotics, and its eradication from patients requires high concentrations of drug to be maintained within gastric mucosa which could be achieved by floating system. Eradication of Helicobacter pylori: H.pylori is responsible for chronic gastritis and peptic ulcers. [23]

DISADVANTAGE FLOATING IN SITU GEL:

1) Unpredictable or in vitro and in vivo correlation.
2) Dose dumping.
3) Poor systemic availability in general.
4) Reduced potential for dosage adjustment.
5) Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
6) Not applicable to drugs which are irritant to gastric mucosa.
7) Drugs which undergo first pass metabolism may not be useful candidate for stomach floating insitu gel.
8) They require a sufficiently high level of fluids in the stomach for the drug delivery to float therein and to work efficiently. [30]
9) Drugs which undergo equal absorption through all regions or sites of the gastrointestinal tract are not desirable candidate. [25]

EVALUATION OF STOMACH SPECIFIC FLOATING IN SITU GEL SYSTEM:

1) Determination of Floating Lag Time:

Floating lag times for all the formulations are depicted in Table. Sodium alginate showed instantaneous floating when came in contact with stimulated gastric fluid. The basic mechanism behind floating was calcium carbonate is present in the formulation as insoluble dispersion and became soluble in the acidic medium. Released calcium ions and CO2 gas, caused gelation of polymer and released gas get entrapped in gel matrix, which caused the matrix system to float. [31]

Table 4: Floating lag time

Formulation Parameters	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Gelation	+++	++	++	+++	++	++	+++	++
Floting Lag Time (min)	< 4	< 4	< 4	< 4	< 4	< 4	< 4	< 4
Floating Duration (hrs)	> 8	> 8	> 8	> 8	> 8	> 8	> 8	> 8

2) Gelling Capacity:

The gelling capacity was determined by placing10 ml of solution in 100 ml of stimulated gastric fluid (pH 1.2) freshly prepared and equilibrated at37 ± 0.5°C and visually assessing the gel formation and noting the time for gelation and the time taken for the gel formed to dissolve. Different weights were allotted as per the gel integrity, weight and rate of formation of gel with respect to time [19]

3) In-vitro gelling capacity:

To evaluate the formulations for their in-vitro gelling capacity by visual method, colored solutions of in situ gel forming drug delivery system were prepared. The in-vitro gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37±1ºC temperature. One ml of colored formulation solution was added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which they formed gel remains as such. Color was incorporate to give visualized appearance to formed gel. The in-vitro gelling capacity was graded in three categories on the basis of gelation time and time period for which they formed gel remains.

(+) Gels after few minutes, dispersed rapidly

(++) Gelation immediate remains for 12 hours

(+++) Gelation immediate remains for more than 12 hours [19]

4) Measurement of water uptake by the gel:

The water uptakes by the gel of the selected formulations of sodium alginate were determined by a simple method. In this study the in situ gel formed in 40 ml of 0.1 N HCl (pH 1.2) 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 10 ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated and reported.[19]

5) In Vitro Drug Release Study:

The in vitro release rate of levetiracetam from sustained release in situ gel was performed using USP apparatus (model TDT-08L, Electrolab, Mumbai, India) fitted with paddle over disk (50 r/min) at 37± 0.50C using 500 ml of 0.1 N HCl as a dissolution medium. This speed was slow enough to avoid the breaking of gelled formulation and was maintaining the mild agitation conditions believed to exist in vivo. At the predetermined time intervals, 5 ml samples were withdrawn, filtered through a whatmann filter paper membrane filter, diluted, and assayed at given wavelength using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release (CPR) was calculated using an equation obtained from a calibration curve. [32]

6)pH measurement:

The pH was measured in each of the solution of sodium alginate based In situ solutions, using a calibrated digital pH meter at 27°C. [19]

7)Physical appearance:

All the prepared in situ gel was check for their clarity and the type of solution After administration of the prepared solution in ph 1.2 buffer also checked the time required for gel formation duration of floating and type of gel formed. The measurement of each data was in triplicate and average conclusion was taken. [33]

8)Determination of Drug Content:

Accurately, 10 ml of in-situ gel from different batches (equivalent to 20 mg of metoclopramideh HCl) were measured and transferred to 100 ml of volumetric flask. To this 50-70 ml of 0.1 N HCl was added and sonicated for 30 min. Volume was adjusted to 100 ml. Complete dispersion of contents were ensured, visually and filtered using Whatman Filter Paper. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1N HCl. Contents of metoclopramide HCl was determined spectrophotmeterically with using reference wavelength double beam UV-Visible spectrophotometer [18].

APPLICATION OF FLOATING DRUG DELIVERY SYSTEMS:

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1. Sustained Drug Delivery:

The generally problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Eg.Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

2. Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, furosemide and riboflavin.

Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating dosage was approximately 1.8 times those of conventional furosemide dosage form.

3. Absorption Enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the Gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby improving their absorption.

Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available dosage form [22]

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