Oral *in situ* Gel System as an Approach to Floating Drug Delivery Technology[1]

Shahad Myasar Alfaris, Amina Mudhafar Al-Nima, Rasha Khalid Dhahir

Department of Pharmaceutics, College of Pharmacy
University of Mosul, Nineveh, Iraq

Date of Receiving: 22 July 2022, Date of Acceptance: 20 August 2022, Date of Publication: 21 August 2022

ABSTRACT

The discovery of floating depended technology has yielded the chances to overcome many challenges as physiological problems, like unstable emptying of stomach and short residence interval that all affect medication availability inside body. drug formulation as controlled release gastro- retentive dosage form that could be trapped in gastric area for several hours would significantly prolong the gastric residence time, improve bioavailability, reduce drug waste, and enhance the solubility of the drug. Regarding floating technology; the oral in situ gel or environment- sensitive gel is a novel dosage forms which can be formulated as a floating system. It is a liquid at the begin but converts into a floating gel as it contacting the gastric content. gel transformations are due to mechanisms such as physiological activation (e. g., temperature and pH), biomaterials physical alterations (e. g., diffusion of solvent and swelling), and chemical reactions (e.g., enzymatic, ionic and photo polymerization). These systems have been utilizes for delivering many medications in the stomach either locally or systemically to overcome the problems of short gastric residence time and immediate drug release. This review gives a brief explanation of floating technology in general and detailed information about the floating oral in-situ gel formulation, its mechanisms of action, formulation methods, in vitro and in vivo evaluation and research done by different researchers on a number of drugs and polymers.

Key words: *floating drug delivery systems, oral in situ gel, increased residence, sustained release.*

INTRODUCTION

The oral administration considers the most important routes of drug delivery as it is easily administered, low-cost, flexibility in handling and formulation, and usually result in high patient compliance. Unfortunately, this route is often associated with a variable and incomplete drug release from a different region of the gastrointestinal tract. Therefore, attempts had been made toward developing a new approach that can retain the drug within the gastrointestinal tract for the longer time than conventional therapy [1,2]. Controlled release preparations are designed for delivering the drug in an extended time thus reduce dosing frequency and provide more stable plasma concentration. Any way this approach fails to localize the drug at a certain site of the alimentary tract due to the variability in gastric emptying and motility. Floating drug delivery system (FDDS) have been delivered to keep the drug in stomach for the required period of time and exhibited low solubility at elevated pH level. This system depends on powder, granules, laminated film, capsules, and hollow microsphere[1,3–5]. The environmentally sensitive gel, is a polymeric dosage form which has been utilized recently in the delivery of the drug. It is administered as low viscosity solutions that change to gel matter under physiological conditions and this make the drug delivering to be continuously and extending of the retention time of the drug in the stomach and therefore FDDS is useful for chronic conditions[6]. Example of such formulation; the phase transition which may be induced by temperature change such as thermo gelling xyloglucan or cations availability as for sodium alginate, gellan gum, pectin [7–11]. In addition to other stimuli like solvent exchange, ultra violet irradiation,

[1] *How to cite the article:* Alfaris S.M., Al-Nima A.M., Dhahir R.K., Oral in situ Gel System as an Approach to Floating Drug Delivery Technology, *IJPPS*, Jul-Sep 2022, Vol 6, Issue 3, 7-19

pH change, and the existence of certain molecules. these systems may be used to prepare a sustainable delivery vehicle for various active pharmaceutical ingredients (APIs) which share the advantages of simple application, reduced frequency of administration, improved patient compliance and protection of the drug against changes in surrounding conditions [10, 12-14]. However, this review discusses the different aspects of oral floating system in general and in particular oral *insitu* gel system.

BASIC GASTROINTESTINAL PHYSIOLOGY

The stomach lies between the esophagus and the small intestine; and divided anatomically into three main parts: Fundus, Body, and Antrum (Figure 1). The first two parts act as container for undigested materials, whereas the last one can be regarded as the pump for gastric emptying which occurs when the stomach is full or empty [15,16]. There are certain types of electrical events that occur during fasting state called inter digestive myoelectric cycle that can be divided into 4 main phases: basic phase, pre burst phase, burst phase and the last phase that occur between the second phase and one of two consecutive cycles [17].

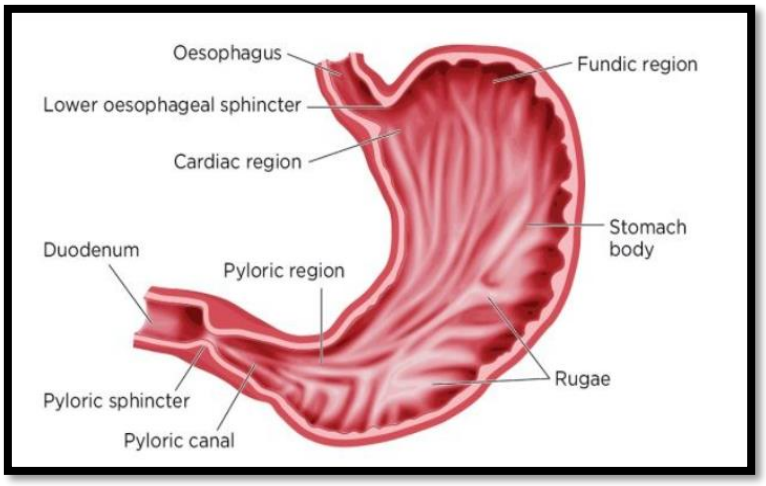


Figure 1: Parts of the stomach [15]

AFFECTING FACTORS ON FDDS

Density is the most important factor; because floating is a function of buoyancy, therefore density has a great influence. The form of dosage form is also an affecting factor; as the tetrahedron and ring shaped devices are preferred over other shapes [4]. Another factor is concomitant drug administration; as the anticholinergic, opiates, and prokinetic drugs can effect on the floating time. In addition to the fed or unfed state because more vigorous contraction of the stomach occurs under the fasting state. On the other hand, nature of meal for example fatty meal and indigestible polymer can prolong gastric emptying rate. Age also can affect FDDS, as older people, have a longer stomach stay than young people. Moreover, the posture has an influence because upright and supine position can effect on the floating time. Finally, the caloric content and diet frequency as fat and protein in the diet can increase floating time from 4 -10 hours [18,19].

CLASSIFICATION OF FDDS

FDDS can be divided into three main types:

Single unit: Balanced hydrodynamics system or non-effervescent system: These systems depend on certain types of polymers (gel forming hydrophilic polymers) like hydroxypropylmethylcellulose (HPMC), other polymers like hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), agar, and carrageen. It contains a high level of such polymers (20-75%) and floats when the polymer comes in contact with gastric fluid, in which the gel barrier controls the fluid penetration rate into the device and the release of the drug. These polymers should be mixed with the drug

components then enclosed within a capsule shell; continuous hydration and erosion of the surface allow drug release[20].

Gas-generating systems*:* In this system, the reaction between sodium bicarbonate and tartaric acid or citric acid results in carbon dioxide and bubbles forming which causes the drug to float within the gastric fluid [21].

Multiunit dosage form*:* This system consists of hollow microsphere with high loading capacity that made up of certain types of polymers such as albumin, gelatin, starch, polymethacrylate. It is referred as micro balloons that provide excellent floatability [18].

Raft forming systems: This system depends on certain types of gel forming agents like alginic bicarbonates, calcium carbonates, and mannitol, in addition to citric acid and sweetener. These gel forming agents depend on the presence of cohesive viscous gel with gastric fluid to form continuous layer when swells known as raft. However, as carbon dioxide emerged in the reaction between bicarbonates and citric acid, the raft floated to the surface. This system plays an important role for local treatment of gastric inflammation and for antacids [18].

ADVANTAGES OF FLOATING-BASED DRUG FORMULATIONS

FDDS provides many advantages, including that FDDS can remain in the gastric fluid for a long period of time. they are applicable to locally acting drugs such as antacids and can withstand strong bowel movements to remain floating in the stomach. These systems also provide a great advantage for those drugs that act directly on the stomach and cause irritation like aspirin , and for those directly absorbed by the stomach such as iron salts. Floating systems can reduce the mucosal irritation through controlling the drug release. They are also important for the treatment of gastroesophageal backflow. Lastly, they have the advantage of improving patient compliance. [22–24]

LIMITATIONS OR DISADVANTAGES OF FDDS

The FDDS are not useful for those drugs that irritate the gastric mucosa, unstable in gastric fluid like erythromycin, and also for those like Nifedipine that undergoes significant first pass effect and absorbed from the entire gastro intestinal tract [22,25]. On the other hand, one of the important requirements of FDDS is that sufficient fluid within the stomach should be present to work in a proper way, and it is better to give the drug in a full stomach putting in mind that other factors like pH, gastric motility, fed status can influence the retention time of the stomach and therefor interference with FDDS work. Furthermore, the supine position may affect these systems, so it is best not to give the medication before going to bed [22].

DIFFERENT APPROACHES TO DESIGN GASTRO RETENTIVE DELIVERY SYSTEMS

High-density systems: The drug remains within the stomach in these systems and can resist intestinal movement. the main drawbacks of this system are that manufacturing a large amount of medicine is difficult for this system, and also it is difficult to get such density. Examples of diluents that are used to obtain high density are titanium oxide, barium sulfate, zinc oxide, and iron powder [25,26] (figure 2).

Expanding and Swelling Systems: These systems are prepared from certain types of polymers that can swell up when they come in contact with gastric fluid. They are called plug-type systems because they can be retained inside pyloric sphincters, even in feeding condition[26,27] (Figure 3).

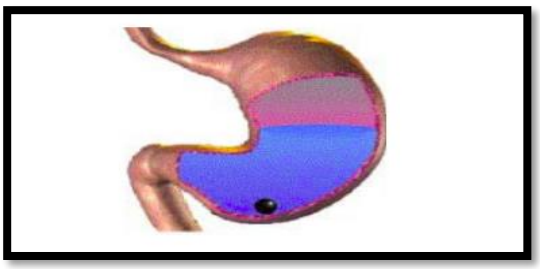


Figure (2) High density system[28]

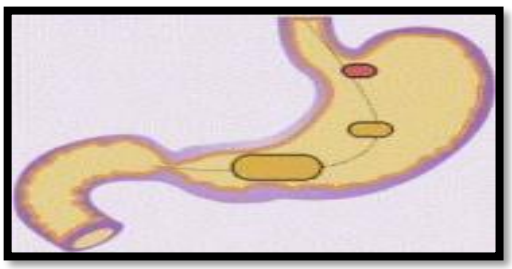


Figure (3) swelling system[28]

Incorporating retardant excipients: These systems consist of the incorporation of digestible polymers, or fatty acids that can change the motility of the stomach in the feeding state, such as triethanolamine myristate[23,25,26**].**

Modified systems: These systems have the non-disintegrating geometric shape resulted from polyethylene blend which can delay stomach emptying depending on the size, shape and flexion modules of the systems or manufactured from plastic elastomers.

Muco-adhesive and bioadhesive systems: These systems depend on the use of certain kinds of polymers that can adhere to the stomach epithelium and produce a local pharmaceutical effect (Figure4) [26,29].

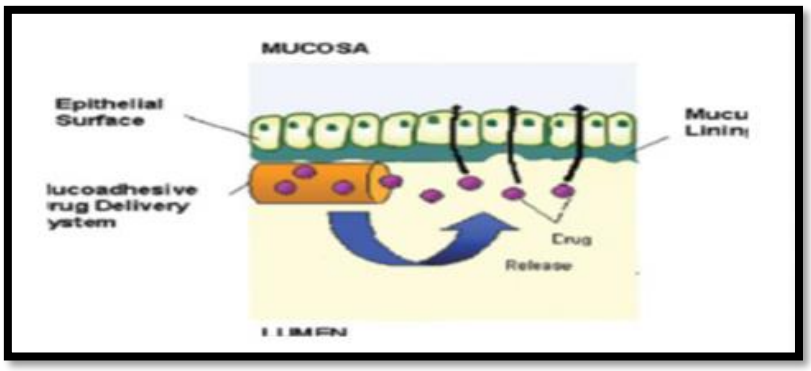
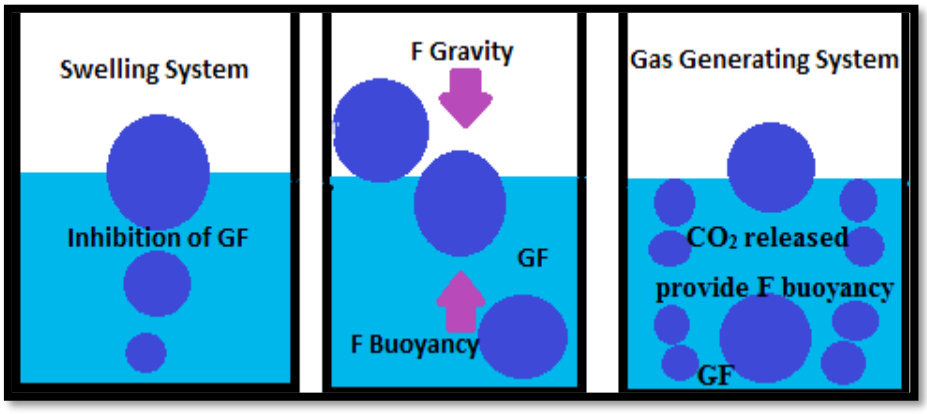


Figure 4: Bioadhesive system[30]

Floating Drug Delivery Systems: These systems are dependent on the drug floating on the surface of the stomach fluid in order to release the drug slowly due to its low density, and the remaining parts can be emptied later [25–27].

FDDS MECHANISM OF ACTION

Different mechanisms can be employed to prolong the residence time of drug in the stomach, like floating dosage form, in addition to various other methods like, mucoadhesive systems, high-density systems, modified shape systems, and gastric emptying delaying devises. FDDS can be regarded as the most common one, they remain buoyant in the stomach with no effect on gastric emptying rate as they have lower density than stomach fluid [31,32]. This is the reason behind the constant plasma concentration achieved by these systems (Figure 5). The floating force can be measured by certain



apparatus, and the dosage form has better buoyancy if the force of floating (F) is maintained high [31].

F=F buoyancy- F gravity , F is the total vertical force.

Figure 5: Diagram representing the mechanism of floating system, (GF=gastric fluid) [33,34]

PREPARATION OF FDDS

Polymers and other ingredients:

Polymers: like Eudragit RL, Eudragit RS, Eudragit S100, Edragit S, Propylene foam Ethylene cellulose, HPMC K4 M, HPMC 4000, HPMC 100, HPMC K15, HPMC K4, Calcium alginate, Polycarbonate, Beta cyclodextrene, Poly

methyl methacrylate, Methocel K4M, Poly ethylene oxide, CMC, Polyethylene glycol, polycarbonate, Sodium alginate, PVA, HPC-L, CP 934P, HPC, , Polyox, Acrylic polymer, E4 M, and Carbapol [35].

Inert fatty materials (5% -75%): These agents are inactive and can be eaten with specific gravity of less than one. It can be used to increase buoyancy through its ability to decrease the hydrophilic characteristic of the formulation for example: long chain fatty alcohols, fatty acids, gelucires 39/01, and bees wax.

Effervescent agents: These agents are capable of producing carbon dioxide through the the reaction between citric acid, sodium bicarbonate, and other agents like disodium glycerin carbonate and citroglycerine.

Release rate accelerants (5%-60%): such as manitol and lactose.

Release rate retardants (5%-60%): Such as magnesium stearate and dicalcium phosphate.

Bouncy increasing agents: Ethyl cellulose is an example of such agents.

Low density material: such as poly propylene foam paper [25,35].

DRUGS EXPLORED FOR FDDS

Microspheres tablets/pills: aspirin, piretanide, theophylline, chlorpheniramine maleate, acetaminophen, grisofulvin, aetylsalicylic acid, amoxicillinetrihydrate, p-nitroaniline, terfenadine, tranilast, atenolol, captopril, isosorbide dinitrate, sotalol, ibuprofen, isosorbide mononitrate, prednisolone,and isosorbide dinitrate.

Films: Amino benzoic acid, quinidine gluconate, and cinnarizine.

Granules: Cinnarizine, diltiazem, diclofenac sodium, fluorouracil, prednisolone, isosorbide mononitrate , isosorbide dinitrate, and indomethacin.

Powder: Riboflavin phosphate, theophylline, and sotalol.

Capsules: Chlordiazepoxide HCl, diazepam, Verapamil HCl, misoprostol, furosemide, propranolol HCl, ursodeoxycholic acid, L-opa and benserazide,and nicardipine[34,35].

Oral in-situ gel: Cinnerazine, riboflavin and levodopa, amoxicillin trihydrate antacids and misoprostol , ranitidine HCl and metronidazole [3,34,35].

EVALUATION PARAMETERS OF STOMACH SPECIFIC FDDS

In-vitro floating behavior is not sufficient indicator for *in-vivo* floating, therefore *in-vivo* evaluations can be regarded as an important guide for getting an extended gastric residence time.

FLOATING LAG TIME AND TOTAL FLOATING TIME DETERMINATION

Floating lag time can be defined as “the time that is required for the dosage form to rise to the upper one third of the dissolution vessel after its introduction into the medium”. While floating time can be defined as “the time that is needed for the dosage form to float on the face of the medium”. This test can be performed by using USP dissolution apparatus, using HCL or simultaneous gastric fluid as dissolution medium [36].

DRUG RELEASE

This examination is carried out by USP apparatus for determination the medication release rate. Periodical sample withdrawal is performed from medium with replacement the withdrawal volume each time Then drug content can be determined after appropriate dilution.

DRUG LOADING, PARTICLE SIZE ANALYSIS, SURFACE CHARACTERIZATION, DRUG ENTRAPMENT EFFICIENCY, MICROMETRICS STUDIES AND RESULTED PERCENTAGE

A drug loading test can be determined by pulverization a certain amount of microspheres or beads then added to a certain amount of dissolution medium. The percentage of drug loading can be obtained by division of the measured medication amount present in the sample by the whole amount of beads or microspheres. While optical microscopy method can be

used for measuring the particle size and size distribution; whereas external and transverse morphology can be determined using a scanning electron microscopy [19].

RESULTANT WEIGHT DETERMINATION

Bulk density and flotation time are the primary endpoints used in determining the buoyancy capacity of the dosage form. The content of the drug is released after the reaction between the dry material of the formulation and stomach contents; therefore, floating force evolution does not depend on single density only. It can therefore be determined by some type of force equal to that required for the object to be fully flooded in the gastric environment [37].

WEIGHT GAIN AND WATER UPTAKE

Swelling behavior is an important indicator of the weight gain of the dosage form. It can be determined through submerging the dosage form in simulated gastric fluid then measuring the changes of tablet dimensions [18].

X-RAY/ GAMMA SCINTIGRAPHY

The X-Ray scintigraphy, can be done on animal to visualize the floating tablet. The animal should undergo overnight fasting, and X-Ray should be done before taking the floated tablet, to visualize any radio-opaque material, before examining the animal, the distance between the animal and source of the radiation should be adjusted in order to visualize any movement of the floated tablet. While in Gamma scintigraphy, introducing the radio-isotope allow the imaging of the movement of the dosage form from its site of delivery [38].

PHARMACOKINETIC STUDIES

These studies include calculating the maximum plasma concentration and the duration it takes to achieve the maximum plasma concentration, as well as the area under the curve. All can be done using computer or statistical analysis [18].

SPECIFIC GRAVITY

Specific gravity can be measured using displacement methods, with the aid of benzene as displacement medium [18].

FDDS APPLICATION

Extended drug release is achieved by FDD: the short stomach residency time is the most significant problem associated with the conventional release formulation, thus FDDS is used in place of those conventional formulations to resolve the problem. So, the drug can float on the gastrointestinal tract surface because of its low density. Also it will be captured in the gastric fluid due to its large size so it will not pass through the pyloric opening. [31,39,40]
Site specific drug delivery systems: those are important for medications that absorbing locally from the stomach or the approximate section of the small intestine, and therefore minimize the amount of medication reach to the circulation. In addition to that the frequency of the drug administration is also reduced, example furosemide and riboflavin.

Absorption enhancement: Maximization of drug absorption can be achieved through FDDS for those drugs that have low bioavailability due to their site specific absorption.

Reduce unwanted effects at the colon: Gastro retentive drug delivery systems can reduce the colonic adverse effects like microorganism resistance that results from certain types of drugs that are absorbed from intestine only, like beta lactam antibiotics.

Reduced fluctuation of drug concentration: This property is of particular importance for those drugs that have a narrow therapeutic index, because continuous drug release produces narrow range of plasma concentration compared with immediate release preparation[39–41].

PRINCIPLE OF IN-SITU GEL FORMATION

In general, the in situ oral formulation of the gel system requires a gelling agent that will form a stable solution with scattered medication and other excipients (Figure 6). Achieving gelification of this system in the gastric fluid is stimulated by ionic complexation that caused by pH change. Sodium alginate (SA) serves as a gelling agent. The formulation acquired is a SA solution containing calcium carbonate (as a source of Ca^{2+}) and sodium citrate, which forms a complex with the free Ca^{2+} ions and liberates them in the acidic stomach medium. The free Ca^{2+} ions start to entrap in sodium alginate polymeric chains causing cross-linking of polymer chains to construct matrix structure. This gelling need the formation of double helical junction zones that lead to the recomposition of double helical segments forming a 3D lattice with cations. as well as hydrogen bonding with water [42,43].

$$\text{Sodium citrate} + \text{Ca-Carbonate } (Ca^{2+}) \rightarrow \text{Ca-Citrate complex} \xrightarrow{\text{Acidic environment}} Ca^{2+} + COO^{-}$$

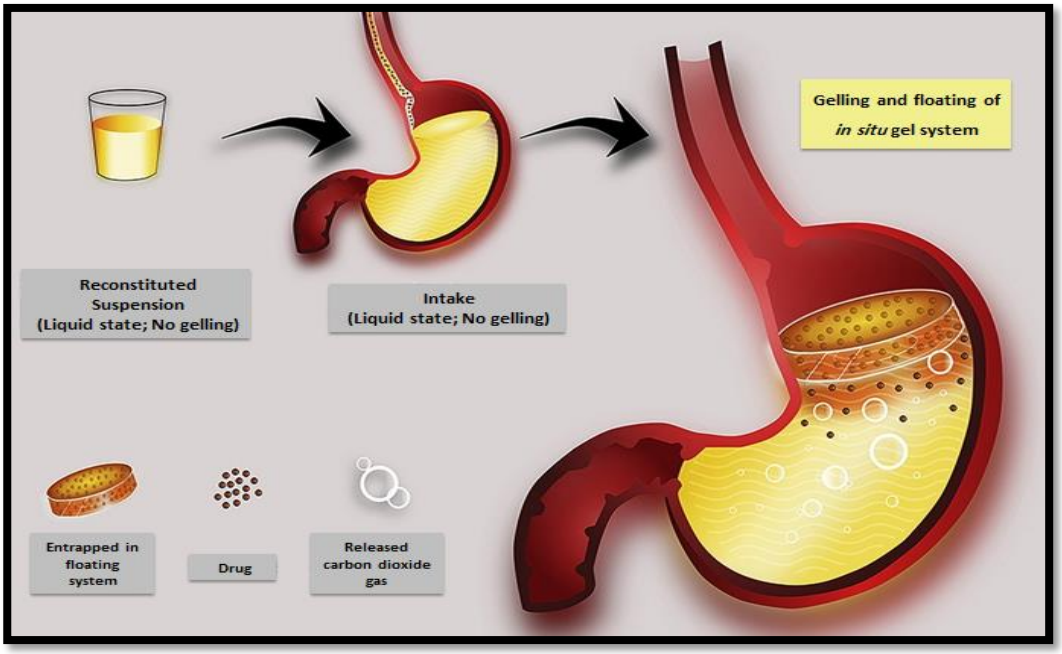


Figure 6: Floating *in situ* gelling system [44]

NECESSITY FOR THE ORAL IN-SITU GEL SYSTEM

In situ oral gel accounts for the commercially appealing dosage form due to its various benefits including its stability, biocompatibility, reproducibility, ease of application, decrease the administration frequency that could improve patient comfort and adherence, and finally provide controlled intake and elimination rates that allow for an accepted safety limit [45,46].

COMMONLY USED POLYMERS IN THE PREPARATION OF THE IN SITU ORAL GEL SYSTEM.

Polymers is an important part of in *situ gel* system, which should be safe, has changeable viscosity, compatible and has pseudo plastic characteristics[6]. The polymers used may be natural or synthetics. Some of the natural polymers include: Pectin, gellan gum, xyloglucan, and alginic acid [34]. Pectin gelation needs calcium ions, in the stomach, gel formation occurs when pectin is administered orally because of the divalent cations [9]. The thermally reversible gelation of Xyloglucan occurs with body temperature if it is included within the oral drug delivery then aggregating complex twin-helical segments with cations to form a 3-D network in addition to the formation of hydrogen bonding with water. There were many papers previously examined the applicability of utilizing gellan formulas for the oral sustained FDDS. The

suggested formula was a gellan solution containing sodium citrate and calcium carbonate (Ca^{2+}ions), that forming a complex with Ca^{2+} free ions releasing them in the stomach in the presence of high acidic environment. By this mechanism, the formula remained in form of solution until it reached the stomach in which spontaneous gelation takes place [47–50]. Chitosan has a very stable crystalline or alkaline pH, however, in diluted acids where the pH is near or below 5.0, the free amino groups are protonated (RNH3) and water solubility increases. Anyway, molecular weight of chitosan also affect its solubility in the acidic medium. Acid solutions of chitosan under alkaline pH lose this load and form viscous gels in an acidic environment. This *in-situ* gel system formation of chitosan has been used for sustaining the release of many drugs. Chitosan has positive charges that can result in high electrostatic interaction with the negatively charged mucus or mucous surfaces. The property of mucoadhesion of chitosan is affirmed to extended residence time of drug in the alimentary tract in order to improve drug absorption and bioavailability[51]. Diluted aqueous alginate solutions form firm gels because of the addition of di- and trivalent metallic ions. The formation of covalent bonds leading to the approach of intractable crosslinked alginate hydrogels reduces the immersion of dispersed medicines in alginate matrices [3,43]. The HPMC-K100M can also be used in-situ gelling formulations. Carbopol-934 and Pluronic F-127 were also utilized as polymer as by Akshay Kumar S *et al* for fungal treatment within mouth cavity [52]. Various commercial formulations of *in-situ* polymeric systems are shown in table (1).

Table 1: Commercial Formulations of In Situ Polymeric Systems [53]

Dosage form	Drug	Brand name	Company country
Opthalmic	Timolol maleate	Timoptic-XE	Merck and Co
Regel:depot-technology	Paclitaxel	Oncogel	Macromed's drug delivery
Injectable depot formulation	Interleukin -2	Cytoryn	Macromed's drug delivery
Ophthalmic solution	Azithromycin	Azasite	Insite Vision

CANDIDATE MEDICINES FOR GEL FORMULATION IN SITU.

1. Narrow absorbing window dug into the digestive tract e.g., riboflavin and levodopa, celecoxib.
2. Drugs that possess pH-dependent solubility having the highest solubility at the acidic environment as itraconazole [54,55]
3. Drugs that degrade at pH value more than 1.2 such as captopril [56]
4. Absorbed primarily from stomach and upper part of GI tract, e.g., cinnarizine.
5. medications that have a local action in the stomach, e.g., misoprostol and antacids
6. medications that break down in the colon, for instance metronidazole and ranitidine HCl
7. medications that disrupt the normal bacteria flora of the colon, e.g. amoxicillin trihydrate [3,30,57]

Table 2, displays various preparations of FDDS that marketed as gel formulation.

Table 2: Preparations marketed for use as floating gel medications [58]

Name	Type and Drug	Company-Country	Remarks
Amalgate Float Coat	Floating antacid, floating gel		Floating dosage form
Madopar HBS	Floating capsule, levodopa and beneserazide	Roche products,USA	Foating CR capsules

(Propal HBS)			
Valrelease	Floating capsule, diazepam	Hoffmann-LaRoche, USA	Floating capsules
Liquid Gaviscone	mixture of alginate	Claxo Smith Kline India	Suppress gastro-esophageal reflux and alleviate heart burn
Topalkan	Floating antiacid, aluminum and magnesium mixture	Pierre Fabre drug, France	Effervescent floating liquid alginate preparation
Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
Citran OD	Ciprofloxacin (1g)	Ranbaxy, India	Gas generating floating form

EVALUATION OF IN-SITU GEL DRUG FORMULATIONS

***Chemical evaluation*:** It is done to determine if the drug can meet the needed criterion and to ensure that the it is safe in terms of contaminants [59] .

Physical assessment: Such as color, taste and smell that has been detected by the sense [60].

***Diffusion**:* This test can be performed by using diffusion cell, that can be assessed using the medicine concentration at fixed interval [59].

Viscosity: The rheological research should be performed to ensure that the gel shows thixotropic behavior. The preparations viscosity can be evaluated using Brookfield digital Viscometer [59,61].

***In-vitro* floating study:** This test can be done by recording floating lag time and floating duration[60,62].

Dissolution study: Data from the in vitro release study provide information about the system under test conditions. *In-vitro* test conditions should be calibrated to be similar to those *in-vivo* [59]. This test is carried out in triplicate with the aid of dissolution devices; the agitation speed must be adjusted. Agitation must be sufficient slow to ensure that the gelled formulation does not break. At fixed intervals, samples should be collected and replaced with fresh dissolving medium, filtered and determined using a UV-visible spectrophotometer [60].

pH Measurement: A calibrated digital pH meter is utilized for PH measurement of the prepared formulations at 27˚C. The pH should be around neutral or slightly alkali to avoid irritation to the throat [62,63].

Drug assay: Drug content can be determined using UV spectrophotometer [59,64]**.**

In vitro gelation study: This test is conducted to determine the in vitro gelification capability of the formulation, by adding a certain amount of the coloured formulation to a gelation solution. in test tube with mild agitation. And the gelling capacity can be graded into three classes (+) gels dispersed rapidly within minutes; (++) gelling immediately which sustains for few hours; and (+++) gelation quickly that stays for long duration [9,60,65].

***Measurement of water uptake*:** the medication is releasing concomitantly with liquid penetration into the matrix, however, the quantity of water uptake can be measured by recording the primary weight of the in-situ gel formed, then recording the weight after distilled water addition at fixed interval [60].

Many researches works have been published dealing with the formulation of in-situ gel formulation, Hani *et al.* have formulated and assessed piroxicam in situ oral gel, a three-factor, two-stage factor model was applied to determine the effects of three factors against sodium bicarbonate, sodium alginate, and sodium citrate on the dependent variables like *in-vitro* floating, *in-vitro* gelation, percentage water uptake, and percentage drug release. *In-vitro* gelation was instantaneous, which remained intact for a prolonged time. The optimized formulation remained floated for 12 h and resulted in maximum release of 90% within 8 h [66].

Karemore and Avari have developed and optimized *in-situ* gel of nifedipine for sustained delivery by ion sensitive mechanism and studied its *in-vitro* and *in-vivo* assessment. Full factorial design was done to assess gellan gum andaction of HPMC K4M on medicine libration and viscosity. One percent of the 55.12 drug release at 6h with a viscosity of 195.66 cps was registered for the optimized preparation and a gamma camera was used for monitoring *in-vivo* gastro retentive ability in which discovered that gel could stay in gastric environment more than 8 h [67].

Kathpalia, Salunkhe and Juvekar have formulated a novel dry suspension based on floating *in-situ* gel formulation of curcumin to help in local treatment of stomach ulcerations. Studies of solubility enhancement for curcumin were employed because of its sparing solubility in both lipophilic solvents and water. The soy lecithin complexation technique was established to enhance curcumin solubility from 0.05µg/ml to130.9 µg/ml in a buffer of 1.2 PH. This complex was joined into a gelling system consisting of calcium carbonate, gellan gum and sodium citrate that formed the basis of a floating *in-situ* gel formula ,in which prolonged curcumin liberation in pH 1.2 buffer up to 12 h [44].

Narita et al. evaluated the benefits of using collagen–genipin solutions in endoscopic therapy of digestive tract ulcerations. Genipin acted as cross-linking polymer. Collagen–genipin solutions had a depressed viscosity value at 23°C which facilitate endoscopic using. However, solution converted to gel that deposit locally on ulcer at physiological temperature and in phosphate buffer (pH 7) [68].

CONTEMPORARY PROGRESS

Over the last decade, much works has been don on the in situ gel system that demonstrates increase efficiency by prolonging their presence at the site of action/absorption[69].

Biodegradable polymer was involved in situ gel formula that have manufacturing problems, processing difficulties, need organic solvents for their preparation, the shattering effect and non-producible drugs release. while, the natural one comply with features of perfect polymer except reproducible batch one.

Recent advancements in biotechnology have developed labile macromolecular treating products that need complicated preparations for effective administration. [39,69,70].

CONCLUSION

FDDS is now available to solve the problem of the highly variable drug absorption throughout the gastro intestinal tract, by extending the time for drug absorption, thus provides constant drug delivery. It also results in controlled drug release, reduces the flocculation in drug concentration, minimizes the drug side effect, and improves bioavailability and patient compliance. Different approaches can be employed to design various types of such system that can achieve many advantages and some limitations. Floating *in-situ* gel provides liquid oral for prolonged drug release, by using various polymers of either natural or synthetic origin. This In-situ drug system could be regarded as a suitable approach for drugs showing local effect or low intake window in gastric area, also for medications that degrade in the colon. Optimal dosage form for certain drugs can be achieved through different types of *in-vivo* studies. Now a day, there are many marketed preparations of FDDS with promises for increasing the product numbers in future.

Financial Support and Sponsorship: Nil

Conflict of Interest: None

REFERENCES

[1] Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. Aaps PharmSciTech. 2005;6(3):E372–90.
[2] Uchegbu IF. Introduction. Fundam Pharm Nanosci. 2013;1–5.
[3] Neha K, Sl H. Review Article Insitu Gelling System : a Review. J Drug Deliv Ther. 2014;4(4):93–103.
[4] Bashir R, Majeed A, Ali T, Farooq S, Khan NA. Floating Oral In-Situ Gel: A Review. J Drug Deliv Ther. 2019;9(2):442–8.
[5] Rao MRP, Shelar SU, Yunusi A. Controlled release floating oral in situ gel of itopride hydrochloride using ph sensitive polymer. Int J Pharm Pharm Sci. 2014;6(11):338–43.
[6] Padmasri B, Nagaraju R, Prasanth D. A comprehensive review on in situ gels. Int J Appl Pharm. 2020;12(6):24–33.
[7] Fayaz MW, Chasta P, Sheikh TH, Rather MA, Kumar AH, Mustafa A. Gastroretentive Drug Delivery System. J Drug Discov Dev (ISSN 2581-6861). 2018;2(1):11–7.
[8] Kiassen N V, Marchington D, Mcgowant HCE. No Title. 1994;66(18):2921–5.
[9] Kiassen N V, Marchington D, Mcgowant HCE, Miyazaki S, Suzuki S, Kawasaki N, et al. No 主観的健康感を中心とした在宅高齢者における 健康関連指標に関する共分散構造分析Title. Int J Pharm Pharm Sci. 2016;3(3):1–11.
[10] Mukund JY, Kantilal BR, Sudhakar RN. Floating microspheres: a review. Brazilian J Pharm Sci. 2012;48(1):17–30.
[11] Fayaz W, Chasta P, Sheikh TH, Rather A, Kumar AH, Mustafa A, et al. review article. 2016;2(1):5–12.
[12] Sharma P, Malviya R. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery : Special Emphasis on Floating In situ Gel Systems A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery : Special Emphasis on Floating In situ. 2011;(July).
[13] Chaniyara S, Modi D, Patel R, Patel J, Desai R, Chaudhary S. American Journal of Advanced Drug Delivery Formulation & Evaluation of Floatable In-situ Gel for Stomach-specific Drug Delivery of Ofloxacin. Available from: www.ajadd.co.uk
[14] Mathews R, Prakash Rao B, Konde A, Sudarshan S, Taha NA, Suresh C. Statistical design and development of a liquid oral floating in situ gel of metformin hydrochloride for sustained release: Pharmacodynamic and toxicity (histopathology) studies. Int J Appl Pharm. 2019;11(5):96–104.
[15] Knight J, Williams N, Nigam Y. Gastrointestinal tract 2: the structure and function of the stomach. Nurs Times. 2019;115(7):43–7.
[16] Stillhart C, Vučićević K, Augustijns P, Basit AW, Batchelor H, Flanagan TR, et al. Impact of gastrointestinal physiology on drug absorption in special populations—An UNGAP review. Eur J Pharm Sci [Internet]. 2020;147(February):105280. Available from: https://doi.org/10.1016/j.ejps.2020.105280
[17] Sinica DP, Awale KB, Shah RR, Kondawar MS, Birnale A, Sangli VC. Pelagia Research Library Preparation and evaluation of herbal gel containing Clerodendrum serratum for anti-inflammatory activity. 2014;5(4):47–54.
[18] Neetika B, Manish G. Floating drug delivery system. IJPRAS. 2012;1(4):20–8.
[19] Kamalakkannan V, Puratchikody A, Prasanth VV, Masilamani K. Enhancement of drugs bioavailability by floating drug delivery system-A review. Int J Drug Deliv. 2011;3(4):558.
[20] Shariat Razavi F, Kouchak M, Feizoleslam F, Veysi M. An Overview on Floating Drug Delivery Systems (FDDS); Conventional and New Approaches for Preparation and In Vitro -In Vivo Evaluation. Fabad J Pharm Sci. 2021;46(3):345–62.
[21] Baumgartner S, Kristl J, Vrečer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000;195(1–2):125–35.
[22] Joseph NJ, Lakshmi S, Jayakrishnan A. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits. J Control release. 2002;79(1–3):71–9.
[23] Patle L, Rai G. An Emerging Trade in Floating Drug Delivery System-A Review. Res J Pharm Dos Forms Technol. 2013;5(6):371–7.
[24] Rathod HJ, Mehta DP, Yadav JS. A review on stomach specific floating in-situ gel. Int J Pharm Res.

2014;6(4):19–30.

[25] Lodh H, FR S, Chourasia PK, Pardhe HA. Floating Drug Delivery System: A Brief Review. Am J PharmTech Res. 2020;10(4):103–22.

[26] Devereux JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. J Pharm Pharmacol. 1990;42(7):500–1.

[27] Kouchak M, Atyabi F. Ion-exchange, an approach to prepare an oral floating drug delivery system for diclofenac. 2004;

[28] Narang N. An updated review on: Floating drug delivery system (FDDS). Int J Appl Pharm. 2011;3(1):1–7.

[29] Shah SH, Patel JK, Patel N V. Stomach specific floating drug delivery system: A review. Int J Pharm Tech Res. 2009;1(3):623–33.

[30] Prajapati DR, Prajapati RR, Jain HP. Floating Oral in situ Gel , An Approach of Gastro-Retentive Drug Delivery System : A Review. 2021;11:29–45.

[31] Janhavi ZS, Pradnya SL, Darekar AB, Saudagar RB. A Comprehensive Review on Gastro-Retentive Floating Drug Delivery Systems. Asian J Pharm Res. 2015;5(4):211–20.

[32] Munir R, Massud A, Inam S, Akram U. "Where improvisation meets innovation" Floating Drug Delivery System. 2013;1(8):1–7. Available from: www.ijopils.comwww.ijopils.com

[33] Kumar M. Floating drug delivery system: A innovative approach. J Drug Deliv Ther. 2012;2(6).

[34] Ninan S, I JW, Kumaran J, Aparna P, Jaghatha T. A review on floating drug delivery system. 2018;4(5):275–81.

[35] Dixit N. Floating drug delivery system. J Curr Pharm Res. 2011;7(1):6–20.

[36] Singh B, Rani A, Ahuja N, Kapil R. Formulation optimization of hydrodynamically balanced oral controlled release bioadhesive tablets of tramadol hydrochloride. Sci Pharm. 2010;78(2):303–24.

[37] Prajapati PH, Nakum V V, Patel CN. Formulation and evaluation of floating matrix tablet of stavudine. Int J Pharm Investig. 2012;2(2):83.

[38] Waterman KC. A critical review of gastric retentive controlled drug delivery. Pharm Dev Technol. 2007;12(1):1–10.

[39] Devi P, Rajamanickam V. The recent developments on gastric floating drug delivery systems: An overview. Int J Pharm Tech Res. 2010;2:524–34.

[40] Sneha SW, Trupti VK, Darekar AB, Saudagar RB. A review: Floatable gastroretentive drug delivery system. Asian J Pharm Res. 2015;5(1):51–60.

[41] Niharika MG, Krishnamoorthy K, Akkala M. Overview on floating drug delivery system. Int J Appl Pharm. 2018;10(6):65–71.

[42] Sinica DP, Kajale AD, Chandewar A V. Pelagia Research Library Formulation development and evaluation of oral floating insitu gel of Ilaprazole. 2016;7(4):51–63.

[43] Kouchak M. In situ gelling systems for drug delivery. Jundishapur J Nat Pharm Prod. 2014;9(3).

[44] Kathpalia H, Salunkhe S, Juvekar S. Formulation of gastroretentive sustained release floating in situ gelling drug delivery system of solubility enhanced curcumin-soy lecithin complex. J Drug Deliv Sci Technol. 2019;53:101205.

[45] Abdul Rasool BK, Khalifa A, Abu-Gharbieh E, Khan R. Employment of Alginate Floating In Situ Gel for Controlled Delivery of Celecoxib: Solubilization and Formulation Studies. Biomed Res Int. 2020;2020.

[46] Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm J. 2018;26(1):64–70.

[47] Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm. 2001;229(1–2):29–36.

[48] Xu D, Jin J, Yu H, Zhao Z, Ma D, Zhang C, et al. Chrysin inhibited tumor glycolysis and induced apoptosis in hepatocellular carcinoma by targeting hexokinase-2. J Exp Clin Cancer Res. 2017;36(1):1–11.

[49] Khare P, Chogale MM, Kakade P, Patravale VB. Gellan gum–based in situ gelling ophthalmic nanosuspension of Posaconazole. Drug Deliv Transl Res [Internet]. 2022;(0123456789). Available from: https://doi.org/10.1007/s13346-022-01155-0

[50] Zhu L, Ao J, Li P. A novel in situ gel base of deacetylase gellan gum for sustained ophthalmic drug delivery of ketotifen: In vitro and in vivo evaluation. Drug Des Devel Ther. 2015;9:3943–9.

[51] Ganguly S, Dash AK. A novel in situ gel for sustained drug delivery and targeting. Int J Pharm. 2004;276(1–2):83–92.
[52] S AK, N VG, Dv G, Sivadasu P. Formulation and development og in situ forming gel FOR the treatment of oral thrush. 2018;11(8).
[53] Bashir R, Majeed A, Ali T, Farooq S, Khan NA. Journal of Drug Delivery and Therapeutics Floating Oral In-Situ Gel : A Review. 2019;9(2).
[54] Basher TA, Al-akkam EJ. Formulation and in-vitro evaluation of itraconazole floating microparticle. 2020;29(1):236–46.
[55] 55. Abdul Rasool BK, Khalifa AZ, Abu-Gharbieh E, Khan R. Employment of alginate floating in situ gel for controlled delivery of celecoxib: Solubilization and formulation studies. Biomed Res Int. 2020;2020.
[56] Abed HN, Abdulrasool AA, Ghareeb MM. Controlled Release Floating Matrix Tablet of Captopril. 2011;20(2).
[57] Article R, Bhardwaj V, Harikumar SL. Pharmacophore. 2013;4(1):26–38.
[58] Pattan SR, Wani NP, Shelar MU, Nirmal SA, Chaudhari PD, Gude RS. Scope and significance of floating drug delivery system. Indian drugs. 2012;49(10):1–8.
[59] Praditya UMI. Application and characterization of in situ gel. 2018;10(6).
[60] Maheswaran A, Padmavathy J, Nandhini V, Saravanan D, Angel P. Formulation and evaluation of floating in situ gel of diltiazim hydrochloride. 2017;9(1):1–4.
[61] Madan JR, Adokar BR, Dua K. Development and evaluation of in situ gel of pregabalin. Int J Pharm Investig. 2015;5(4):226.
[62] Anyanwu N. Development and Evaluation of in Situ Gelling Gastroretentive Formulations of Meloxicam. Univers J Pharm Res. 2017;2(3):11–4.
[63] Thomas LM. Formulation and evaluation of floating oral in-situ gel of metronidazole. Int J Pharm Pharm Sci. 2014;6(10):265–9.
[64] Abbas Z. DEVELOPMENT AND IN VITRO EVALUATION OF AN IN SITU GELLING ORAL LIQUID SUSTAINED RELEASE FORMULATION OF NIZATIDINE Article in WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES · December 2013 CITATIONS 2 READS 92. 2016;(March 2016). Available from: www.wjpps.com
[65] Nair SS. Formulation and Evaluation of stomach specific floating in-situ gel of clarithromycin FORMULATION AND EVALUATION OF STOMACH SPECIFIC FLOATING IN-SITU GEL OF. 2021;(January 2020).
[66] Hani U, Osmani RAM, Alqahtani A, Ghazwani M, Rahamathulla M, Almordy SA, et al. 2 3 Full Factorial Design for Formulation and Evaluation of Floating Oral In Situ Gelling System of Piroxicam. 2020;
[67] Karemore MN, Avari JG. Journal of Drug Delivery Science and Technology In-situ gel of nifedipine for preeclampsia : Optimization , in-vitro and in-vivo evaluation. J Drug Deliv Sci Technol. 2019;50(January):78–89.
[68] Narita T, Yunoki S, Ohyabu Y, Yahagi N, Uraoka T. In situ gelation properties of a collagen–genipin sol with a potential for the treatment of gastrointestinal ulcers. Med Devices (Auckland, NZ). 2016;9:429.
[69] Vigani B, Rossi S, Sandri G, Bonferoni MC, Caramella CM, Ferrari F. Recent advances in the development of in situ gelling drug delivery systems for non-parenteral administration routes. Pharmaceutics. 2020;12(9):1–29.
[70] Bhardwaj L, Kumar Sharma P, Malviya R. A Short Review on Gastroretentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating In situ Gel Systems. African J Basic Appl Sci. 2011;3(6):300–12.