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REVIEW ARTICLES

An Overview on Floating Drug Delivery Systems (FDDS); Conventional and New Approaches for Preparation and *In Vitro –In Vivo* Evaluation

Fatemeh SHARIAT RAZAVI[*], Maryam KOUCHAK [**°], Fatemeh FEIZOLESLAM[***], Maryam VEYSI [****]

An Overview on Floating Drug Delivery Systems (FDDS); Conventional and New Approaches for Preparation and In Vitro –In Vivo Evaluation

SUMMARY

Floating drug delivery systems (FDDS) are oral dosage forms that are able to float on the contents of the stomach and remain in the stomach for a long time. They offer an opportunity to prevail over the short gastric residence time of the usual dosage forms of the drug and play an important role in slowly delivering drug substances to the upper part of the gastrointestinal tract over a continuous period. Two methods have been proposed for the development of FDDS, including non-effervescent and effervescent systems. The present review briefly explains various technologies and their mechanism to design FDDS along with in vitro - in vivo tests for evaluation of them. In addition, new approaches to their preparation have been introduced.

Key Words: *Floating drug delivery systems, Gastro retentive, Effervescent, Non-effervescent, Novel floating drug delivery systems.*

Yüzer İlaç Salım Sistemlerine (FDDS) Genel Bir Bakış; Hazırlık ve İn Vitro - İn Vivo Değerlendirmede Geleneksel ve Yeni Yaklaşımlar

ÖZ

Yüzen ilaç taşıyıcı sistemler (FDDS) mide içeriği üzerinde yüzebilen ve midede uzun süre kalabilen oral dozaj formlarıdır. İlacın geleneksel dozaj formlarının kısa midede kalma süresine üstün gelme fırsatı sunarlar ve ilaç maddelerinin sürekli bir süre boyunca gastrointestinal sistemin üst kısmına yavaşça verilmesinde önemli bir rol oynarlar. FDDS'nin geliştirilmesi için efervesan olmayan ve efervesan sistemler dahil olmak üzere iki yöntem önerilmiştir. Bu inceleme, kısaca çeşitli teknolojileri ve bunların FDDS tasarım mekanizmalarını, bunların değerlendirilmesi için in vitro - in vivo testlerle birlikte açıklamaktadır. Ayrıca bunların hazırlanmasına yönelik yeni yaklaşımlar tanıtılmaktadır.

Anahtar Kelimeler: *Yüzer ilaç Salım sistemleri, Gastro retentif, Efervesan, Efervesan olmayan, Yeni yüzen ilaç salım sistemleri.*

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[*] ORCID: 0000-0002-5324-8267, Nanotechnology Research Center, Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[**] ORCID: 0000-0002-1399-7335, Nanotechnology Research Center, Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[***] ORCID: 0000-0002-2558-9777, Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[****] ORCID: 0000-0003-1358-6963, Department of Pharmaceutics, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

[°] Corresponding Author; Maryam KOUCHAK,
Tel: 00989163130204, email: koochekm@yahoo.com

INTRODUCTION

To maximize the therapeutic effectiveness and reduce the side effects of drugs, multiple delivery systems are applied. Oral administration of medicinal drugs is currently the most effective route of administration owing to its various advantages, such as low treatment cost, high patient compliance, dosage form flexibility, and ease of administration (Shivakumar, Gowda, & Kumar, 2004). One of the problems of oral delivery systems is the short drug residence at the site of absorption. Gastro retentive drug delivery systems (GRDDS) can prolong drug residence to several hours in the gastric area. GRDDS have valuable characteristics, including high therapeutic efficacy and bioavailability for narrow absorption window drugs and solubility improvement of less soluble drugs in environments with high pH. Different methods, including floating drug delivery systems (FDDS), have been introduced for improving the gastric residence of drugs (Garg & Gupta, 2008). This review aims to describe different techniques used in developing floating dosage forms, identify their mechanisms of action and introduce *in vitro* and *in vivo* evaluation methods for them.

Floating drug delivery systems (FDDS)

Davis first introduced FDDS in 1968. These systems are known to have lower densities than the gastric fluid, remaining buoyant for a long time in the stomach. They are recognized as an important means of achieving adequate gastric retention and drug bioavailability(Badoni, Ojha, Gnanarajan, & Kothiyal, 2012). In addition, they are appropriate systems for the delivery of drugs, which have a narrow absorption window in the upper small intestine or stomach (Singh & Kim, 2000). In view of the buoyancy mechanisms, non-effervescent systems and effervescent systems, have been applied to develop FDDS (Figure 1).

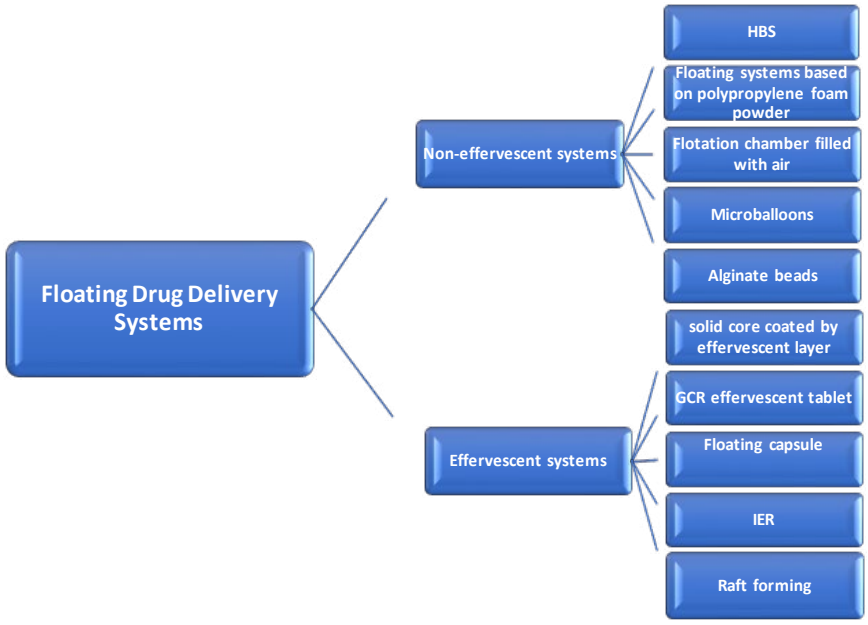

Figure 1. Classification of Floating Drug Delivery Systems

Non-effervescent systems

Such systems are generally composed of a highly swellable hydrocolloid in a matrix-forming polymer such as polycarbonate, polystyrene, polymethacrylate, or polyacrylate. Typically a polysaccharide or a cellulosic compound is used as the swellable part. Upon contact with gastric fluids, the hydrocolloid is hydrated and forms a low-density gel network that entraps the air and can be floated on stomach fluid. The release of the drug is directly controlled by these colloidal gels. Hydrophilic drugs are mainly released

by diffusion mechanism, while hydrophobic drugs are released by erosion of the outer surface of the system.

Hydrodynamically balanced systems (HBS)

HBS, with gel-forming hydrophilic polymers, are single-unit dosage forms. The most common excipient is hydroxypropyl methylcellulose (HPMC), although sodium carboxymethyl cellulose (NaCMC), carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and alginic acid have also been applied. Administration of the drug-mixed polymer is mainly done in a gelatin capsule, which dissolves in the gastric fluid rapidly. A floating mass is produced by hydration and swelling of the polymer's surface **(Figure 2**) (Makwana, Sameja, Parekh, & Pandya, 2012; Rastogi, 2016).

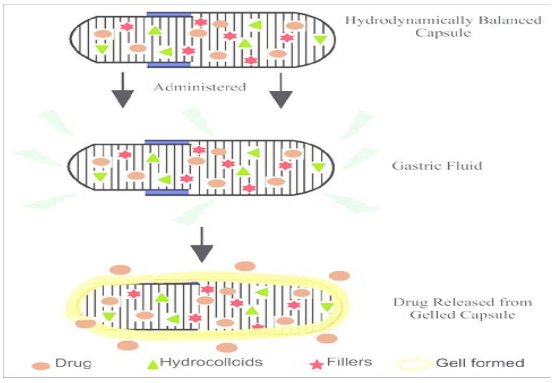

Figure 2. Hydro dynamically Balanced capsule *(Rastogi, Kumar, Yadav, Hegde, & Rastogi, 2016).* Thanks to Dr. Vaibhav Rastogi for permitting us to use this figure.

Sustained-release HBS tablets (containing hydrophilic hydrocolloids) were first developed by Sheth and Tossounian. Following contact with the gastric fluid, a soft gelatin mass was formed on the tablet surface, creating a water-impermeable barrier. The slowly released drug from the gelatin mass surface remained buoyant on the gastric fluid (Sheth & Tossounian, 1979). In order to prepare ofloxacin HBS capsules, liquid paraffin, lactose, HPMC K4M, and polyvinylpyrrolidone K30 (PVP K30) were used. The capsules were floated without any lag time for more than six hours. Sustained drug release was reported in this period ,and its rate was reliant on the amounts of PVP K30, HPMC K4M, and liquid paraffin content (A. K. Nayak, Das, & Maji, 2013).

Bomma et al. prepared floating matrix tablets of norfloxacin, using polymers such as xanthan gum, HPMC K199M, and HPMC K4M in the wet granulation technique. Prolonged drug release was indicated by the tablets while floating over the dissolution medium (Bomma, Naidu, Yamsani, & Veerabrahma, 2009). In addition, Ali J et al. introduced a single-unit floating capsule to deliver metformin using the HBS technology. In this system, different low-density polymers were used. During five hours of examination, the formulation was found to be buoyant on the gastric fluid in rabbits. The plasma level-time AUC increased in the optimized HBS metformin capsules compared to the immediate-release formulation (Ali et al., 2007).

Floating systems based on polypropylene foam powder

Streuble et al. prepared floating microparticles using polypropylene foam powder and investigated their performance *in vitro.* An oil-in-water solvent extraction method was used to prepare the floating microparticles, which consisted of polypropylene foam powder. Verapamil HCl was used as a drug, along with a controlled release polymer (polymethyl methacrylate, Eudragit® RS, or ethyl cellulose). All formulations displayed appropriate buoyancy behavior with a wide range of dissolution profiles (Streubel, Siepmann, & Bodmeier, 2002). The researchers also developed the floating tablets based on polypropylene foam powder in a matrix-forming polymer. The highly porous foam powder presented inherently low-density systems capable of floating for at least 8 hours at 0.1 N HCl at 37 ° C. The release properties were strongly related to drug chemistry and could be modified according to the ratio of the polymer matrix to the foam powder(Streubel, Siepmann, & Bodmeier, 2003).

Flotation chamber filled with air or harmless gas

Microporous compartment systems are designed by the principle of drug encapsulation in a compartment with pores on its walls (top and bottom) attached to an air-containing chamber (Harrigan, 1977). For preventing any interactions between the

undissolved drug and gastric mucus, the peripheral walls were sealed in the device completely. Using a low density of microporous chambers, the delivery system can float on the gastric fluid (Atyabi, Sharma, Mohammad, & Fell, 1996a). When a limited amount of gastric juice enters the pores, the drug dissolves and leaves the dosage form, and is continuously delivered throughout the intestine. (Hafeez, Maurya, Singh, Mittal, & Rana, 2013).

Micro balloons or hollow microspheres

Emulsification-solvent diffusion or simple solvent evaporation method was applied to prepare drug-loaded micro balloons (A. Michaels, 1974). In developing these systems, cellulose acetate, Eudragit S, polycarbonate, low methoxy pectin, and calcium alginate are used (Kawashima, Niwa, Takeuchi, Hino, & Itoh, 1992). In this regard, Kouchak and Badrian applied the emulsification-solvent diffusion method to prepare a multiple-unit oral floating system for theophylline. After dissolving dibutyl phthalate, theophylline, and ethyl cellulose in the dichloromethane-alcohol mixture, the compounds were added to an aqueous medium. Rapid alcohol diffusion in the aqueous medium and dichloromethane evaporation while stirring accounted for the formation of an interfacial polymer and drug deposition, resulting in the generation of low-density hollow microspheres with pores in the shells (**Figure 3).**

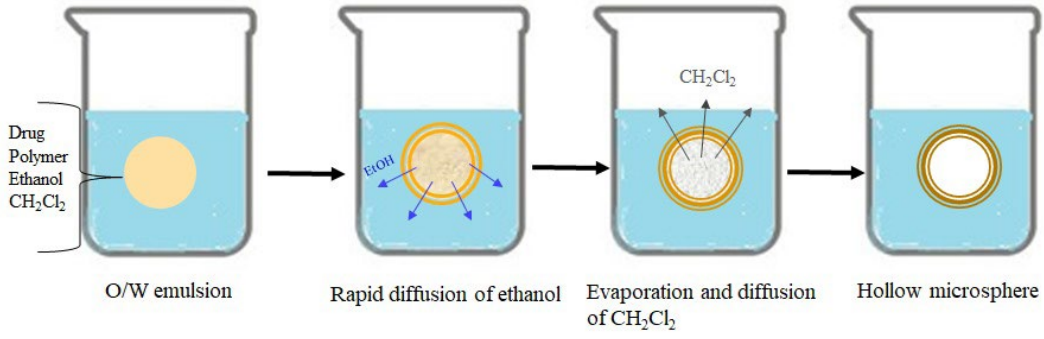

Figure 3. Hollow microsphere formation

The produced microspheres showed a spherical porous shape, which tended to float on the simulated gastric medium for 12 hours or more. In the scanning electronic micrograph (SEM), the hollow porous structure of the micro balloon is indicated. One of the problems in preparation of micro balloons with high drug content is the solubility of the drug in an aqueous phase in the process of microsphere formation. One of the problems in preparing high-drug micro balloons is the solubility of the drug in an aqueous phase in the process of forming microspheres. Kouchak and Badrian succeed in increasing theophylline loading of the micro balloons by adding NaCl 20% to the aqueous phase. The saturated solubility of theophylline decreased considerably at high concentrations of NaCl, which increased the encapsulation efficiency of theophylline (Kouchak & Badrian, 2007). Kouchak et al. used the mentioned emulsification-solvent diffusion method to prepare micro-balloon systems containing diclofenac to increase its gastric emptying time. In this study, the solubility of diclofenac decreased by adding HCl 0.1 M into the aqueous phase, resulting in enhanced loading efficiency (Kouchak & Moghimipour, 2007; Nayak, Malakar, & Sen, 2010). Rishikesh Gupta et al. introduced an oral multiple-unit famotidine microsphere to target stomach ulcers, using the modified solvent evaporation method. They used the Eudragit S-100 as polymer and dichloromethane and ethanol as solvents. The SEM images indicated the floating cavity and porous surface of the microsphere loaded with famotidine (Figure 4) (Gupta, Prajapati, Pattnaik, & Bhardwaj, 2014).

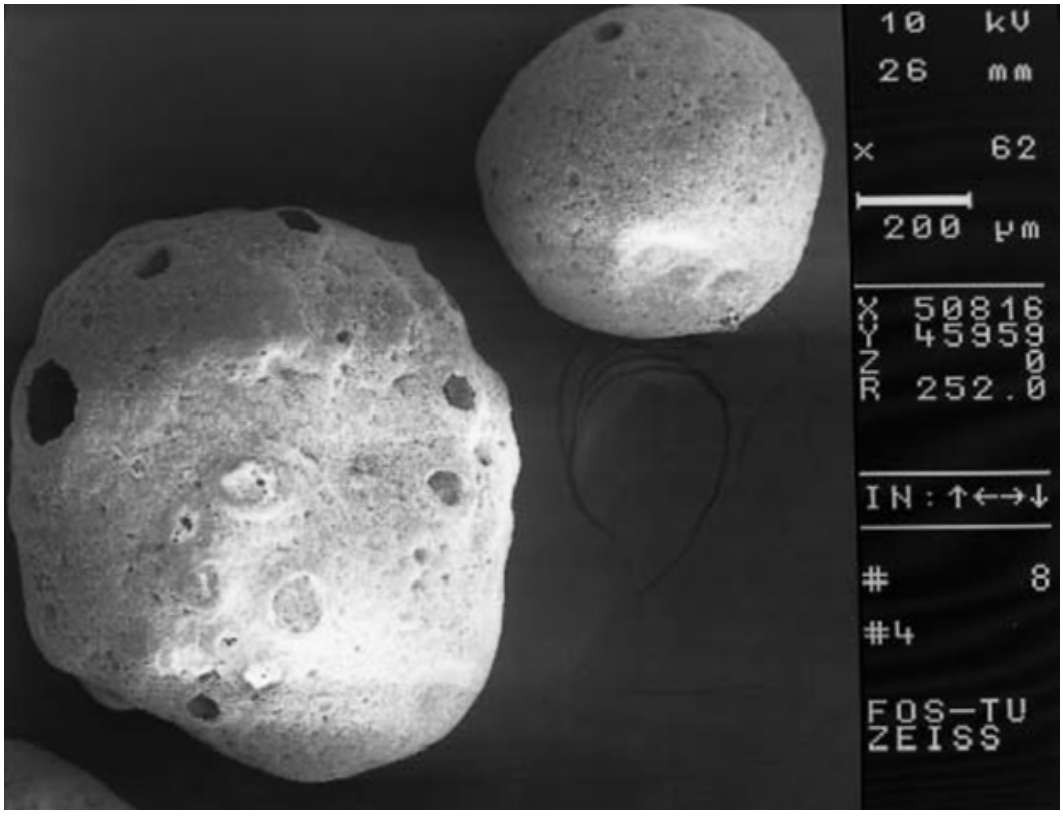

Figure 4. SEM image of hollow microspheres (Kouchak & Badrian, 2007).

Joseph et al. using hollow polycarbonate microspheres, designed a floating dosage form of piroxicam. In *in vivo* studies on healthy rabbits, the pharmacokinetic data revealed that piroxicam-loaded polycarbonate microsphere systems could increase bioavailability and sustained drug delivery over an extended period. In addition (Joseph, Lakshmi, & Jayakrishnan, 2002), Thanoo et al. used polycarbonate in the solvent evaporation method to develop sustained-release floating microspheres. In their study, griseofulvin, aspirin, and p-nitroaniline were applied as the model drugs (Thanoo, Sunny, & Jayakrishnan, 1993).

For the preparation of hollow microspheres, Sato et al. used mixtures of Eudragit S with other hydrophobic or hydrophilic polymers (e.g., HPMC or EC) to improve riboflavin release. An increase in the content of HPMC increased the release of riboflavin, while the floating features of the microspheres reduced. γ-scintigraphy was applied to evaluate riboflavin-containing micro-balloon. Also, urinary riboflavin excretion was assessed. The floating system showed a significantly higher bioavailability, compared to the non-floating formulation (Sato, Kawashima, Takeuchi, & Yamamoto, 2004a, 2004b; Sato, Kawashima, Takeuchi, Yamamoto, & Fujibayashi, 2004).

Alginate beads

For designing a multiple-unit floating system, Talukdar and Fassihi used cross-linked beads, which consisted of Ca^{2+} ions, an anionic polysaccharide, and sodium alginate. The buoyancy was maintained for more than 12 hours by using the beads (Talukder & Fassihi, 2004). Sodium alginate solution was added to an aqueous calcium chloride solution in this method, resulting in calcium alginate precipitation. After separation and drying the beads via air convection and freeze-drying, a porous system was created (Figure 4) (Kaushik, Chaurasia, Chaurasia, Mishra, & Bhardwaj, 2011; Mahajan, Gupta, & Sharma, 2010). Malleswari

prepared alginate beads of stavudine using the ionotropic gelation method with HPMC and sodium alginate. The beads showed extended drug release (almost 12 hours) and remained buoyant for nearly 12 hours (Malleswari K, 2016). Moreover, Mishra et al. formulated controlled-release gastro retentive floating gel beads of loratadine using pectin and sodium alginate, accompanied by oil (mineral or castor oil), by the emulsion gelation method. They used calcium chloride solution as the cross-linking agent (Mishra & Pathak, 2008).

Additionally, Fell et al. prepared floating alginate beads containing amoxicillin through dropwise addition of alginate to the $CaCl_2$ solution and freeze-drying the prepared gel beads. The buoyancy of beads with high drug loadings persisted for 20 hours (Whitehead, Collett, & Fell, 2000). Kumar Dey et al. developed amoxicillin-loaded floating mucoadhesive beads containing sunflower oil using sodium alginate and HPMC as matrix polymers and Chitosan as a coating polymer. They used ionotropic gelation method to prepare the beads. Firstly, an aqueous solution of sodium alginate, HPMC, and amoxicillin trihydrate in demineralized water was prepared, and sunflower oil was added dropwise. The emulsion was extruded through 5% (w/v) calcium chloride solution, and the formed beads transferred to chitosan solution to be coated. All beads were able to float for >24 h with a maximum lag time of 46.3 ± 3.2 s. X-ray study in rabbit stomach confirmed the gastric retention of optimized formulation(Dey et al., 2016).

Effervescent systems

Effervescent floating systems can produce CO_2 and decrease device density. These systems remain buoyant for a long time in the stomach. Some of the FDDS that use an effervescent mechanism in their design are given in the following sections.

Solid core coated by the effervescent layer

Gas-producing agents (such as citric acid and tartaric acid) are utilized as internal effervescent layers in these systems for gas generation (Figure 5). The stoichiometric citric acid ratio to sodium bicarbonate is reported to be optimally 0.76:1 (Michaels, Bashwa, & Zaffaroni, 1975).

In this regard, Elsamaligy and Bodmeier designed a multiple unit effervescent extended-release drug delivery system. In addition to adequately controlling the release of drugs with different solubility, this system showed fast and long buoyancy. Fluidized bed-coating methods were applied for preparing the pellet systems, and were evaluated from the points of drug release, floatation, medium uptake, and swelling in HCl 0.1 M. In addition, two pellet systems were studied. The first system included drug-layered sugar cores, $NaHCO_3$ layer, and polymeric top coating. The second pellet system was coated by three layers, including Eudragit® RL 30D top coating, $NaHCO_3$ layer, and drug-containing Eudragit® RS 30D coating. The Eudragit® RL coating led to adequate medium penetration into the pellet and high CO_2 entrapment efficiency (Elsamaligy & Bodmeier, 2015).

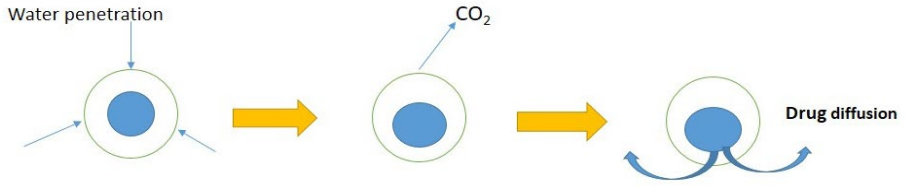

Figure 5. Gas generation of a solid core coated by effervescent layer after placing in water.

Gastro retentive controlled-release (GCR) effervescent tablets

Tadros developed ten gastro retentive formulations, using HPMC K15M and, or sodium alginate as release-retarding polymers, along with $NaHCO_3$ or $CaCO_3$ as gas formers. The tablets showed acceptable swelling, floating, and adhesive properties (Tadros, 2010). In addition, Goole et al. developed 3-mm floating mini tablets containing glyceryl palmitostearate as a meltable binder and tartaric acid, $NaHCO_3$, and $CaCO_3$ as effervescent agents. After preparing the tablets via melt granulation and compression, the coating was done with Eudragit® RL 30D and a flexible membrane was produced. The buoyancy of mini-tablets was independent of the medium pH; it occurred within 10 minutes and continued for more than 13 hours (Goole, Amighi, & Vanderbist, 2008; Goole, Deleuze, Vanderbist, & Amighi, 2008).

Floating capsules containing effervescent agents

Li et al. prepared floating capsules consisting of an effervescent mixture, Carbopol 934, and HPMC with different viscosity grades. They found that the presence of Carbopol, HPMC viscosity, and polymer-polymer interactions significantly influenced the buoyancy and release features of dosage forms (Li, Lin, Daggy, Mirchandani, & Chien, 2002, 2003).

Bicarbonate-loaded Ion exchange resin (IER) system

Bicarbonate-loaded IER beads can be used to formulate gastro retentive systems. For this purpose, an ionic drug and bicarbonate ions are attached to anionic resin beads, and the beads were coated with a semipermeable membrane. After reaching the acidic stomach environment, chloride and bicarbonate ions are exchanged. As carbon dioxide is released and trapped in the membrane, the density of the beads decreases and they move to the top of gastric fluid (Anand, Kandarapu, & Garg, 2001; Klausner, Eyal, Lavy, Friedman, & Hoffman, 2003).

Kouchak and Atyabi prepared a multiple-unit oral floating dosage system, using Amberlite-IRA900 as the IER system. It included loading IER beads with diclofenac and bicarbonate ions using a batch method and coating them with Eudragit RS or ethyl cellulose. In the batch method, the ion exchange resin beads and the solution containing the ion exchange candidate ions are mixed in a vessel and allowed to equilibrate. In contact with the simulated gastric fluid, the beads could generate CO_2, and the entrapped gas caused the coated beads to float (Kouchak & Atyabi, 2004). In this regard, Atyabi et al. introduced a similar system using Dowex as an ion exchange resin and loaded it with bicarbonate ions and theophylline (as the model drug). The beads were coated with a semipermeable membrane to overcome rapid CO_2 loss (Atyabi et al., 1996a; Atyabi, Sharma, Mohammad, & Fell, 1996b).

Raft forming system

The raft forming system consists of an effervescent liquid with in-situ gel properties and buoyancy capability(Ibrahim, 2009). In this system, the CO_2 is generated along with a viscous alginate gel in contact with gastric fluids.This continuous layer of gel, called raft, can remain intact and buoyant over the stomach contents for a long time to facilitate sustained release of drugs (Fayaz et al., 2018; Vinod et al., 2010). So, an antacid raft forming system acts as a barrier between the stomach and the esophagus and prevents the reflux of gastric content into the esophagus. In addition, the alginate layer can adhere to the gastric mucosa due to its bioadhesive nature (Fayaz et al., 2018).

Kerdsakundee et al. developed new raft forming systems containing solid dispersions of curcumin-Eudragit EPO to provide a long-acting gastric ulcer treatment. These formulations were composed of curcumin-Eudragit EPO solid dispersions, sodium alginate as a gelling polymer, and calcium carbonate for creating divalent Ca^{2+} ions and carbon dioxide gas. The solvent evaporation method was used to prepare the solid dispersions. These new raft forming formulations at 40 mg/kg once daily displayed a higher therapeutic effect on the gastric ulcer than the standard antisecretory agents: lansoprazole (1 mg/kg, twice daily) and a curcumin suspension (40 mg/kg, twice daily)(Kerdsakundee, Mahattanadul, & Wiwattanapatapee, 2015).

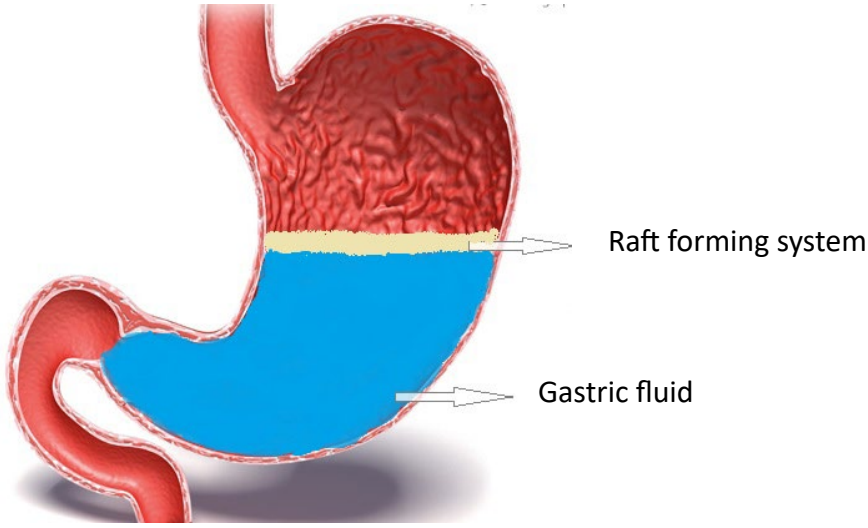

Figure 6. Schematic image of Raft forming system

Novel techniques for preparation of FFDS

Recently, researchers have used novel methods to design floating systems. Regardless of whether their mechanism is effervescent or non- effervescent, some of them are described in the following section (**Figure 7**).

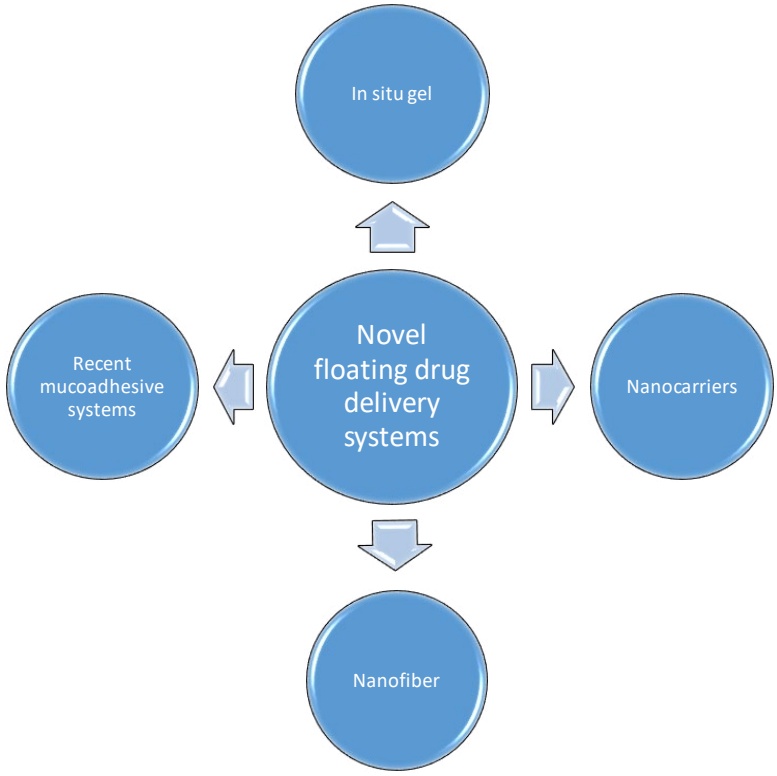

Figure 7. Some of the novel floating drug delivery systems

In situ gelling

Rajinikanth, et al. designed a gastric floating system based on in situ gelling mechanism for delivery of amoxicillin to eradicate *Helicobacter pylori*. Calcium carbonate and gellan were used as the gas-releasing agent and the gelling polymer, respectively. Dissolution of calcium carbonate in the acidic environment of the stomach produces calcium ions and leads to gelation of gellan gum. *In vivo* study showed ten times effectiveness of the floating system against Helicobacter pylori compared to the amoxicillin suspension (Rajinikanth, Balasubramaniam, & Mishra, 2007). This author, in another similar study, made a floating in situ gelling system of clarithromycin using gellan and calcium carbonate. The increased clarithromycin stability and prolonged gastrointestinal residence time led to eradication of *H. pylori* (Rajinikanth & Mishra, 2008).

Nanocarriers

Nana Chen, et al. prepared novel nanomicelles-loaded gastro retentive beads. At first, emodin-loaded nanomicelles were prepared by pluronic F127 and Tween 80 using the thin-film hydration method. The nanomicelles were coated with chitosan and tested against human gastric carcinoma. Secondly, nanomicelles-loaded floating mucoadhesive beads (NFM-Beads) were developed by ionotropic gelation method using sodium carboxymethylcellulose and aluminum chloride. NaHCO3 as a floating agent was trapped in this network. The release, swelling, degradation, mucoadhesion, and floating ability of the samples were investigated *in vitro*. Also, gastric retention was evaluated *in vivo*. They concluded that the NFM-Beads system could improve the therapeutic potency of emodin against gastric cancer (Chen et al., 2019).

The insertion of liquid crystalline (LC) monomers can give molecularly imprinted polymers (MIPs) reversible deformation properties in response to different environmental factors. Recently, it has been shown that liquid crystalline -molecularly imprinted polymers (LC-MIPs) have buoyancy behavior on the aqueous medium due to their solvent-responsive deformation. LC-MIPs have a much higher capacity compared to usual MIPs because of their low cross-linking structure. LC-MIPs were first used as an FDDS for S-amlodipine delivery (Zhang et al., 2017).

Li-Ping Zhang, et al. fabricated a novel floating interaction-controlled DDS using LC-MIP coated multiwalled carbon nanotubes (MWCNTs) and used levofloxacin as a model template. The levofloxacin-loaded MWCNT@LC-MIP showed a combination of buoyancy and controlled release properties, which provided high relative bioavailability (Zhang, Tan, Huang, & Liu, 2018).

Nanofiber-based effervescent pouches

Serdar Tort, et al. reported a nanofiber-based effervescent approach for producing FDDS. They embedded polyethylene oxide (PEO)/sodium bicarbonate ($NaHCO_3$) cast films into Pramipexole-loaded electrospun nanofibers fabricated from Eudragit RL and RS polymers. The PEO/ $NaHCO_3$ film released CO_2 gas after contact with gastric acid and produced self-inflating nanofiber pouches filled gas bubbles. Nanofiber formulations showed floating lag times lower than 1 second and total floating times more than 72 h. The system provided the sustained release of pramipexole more than overnight (Tort, Han, & Steckl, 2020).

Recent mucoadhesive systems in floating drug-delivery

Zn-pectinate-sterculia gum interpenetrating polymer network (IPN) beads were prepared by concurrent ionotropic gelation with zinc acetate and covalent crosslinking with glutaraldehyde. The pectinate-sterculia gum (SG) blend beads could enhance the duration of gastric retention, which was achieved by a combination of floatation mechanism and mucoadhesion. Bera, et al. utilized this system for intragastric ziprasidone HCl delivery. The density of ziprasidone HCl –loaded IPN beads was significantly lower than the density of gastric fluids (0.608 -0.911 ± 0.19 g/cm^3). The use of zinc acetate as an ionic crosslinker may be the cause of this low density. The optimized beads displayed a floating lag time of less than 2 min and buoyancy ability of more than 63% at eight h. They showed good mucoadhesive with the goat gas-

tric mucosa. (See **Table 1.**) (Bera, Boddupalli, & Nayak, 2015).

Evaluation Tests

Various parameters are usually evaluated for gastro retentive formulations, including floating duration, specific gravity, dissolution profile, content uniformity, and friability. Particle size, flow properties, mechanical properties, and surface morphology are also assessed in multiparticulate drug delivery systems (Arunachalam et al., 2011).

***In vitro* evaluation**

Size and shape measurements

The particle shape and size majorly influence the dissolution and bioavailability of drugs. Different methods, including air elutriation analysis, photo analysis, sieve analysis, optical microscopy, laser diffraction methods, colter counter, ultrasound attenuation spectroscopy, and sedimentation techniques, are used to measure the particle size (Narang, 2011).

Buoyancy test

This test is commonly carried out in simulated gastric fluid (SGF) at 37°C. The floating or buoyancy lag time refers to the time needed for the dosage form to float on the medium surface. Also, the total buoyancy time is the total quantity of time when the dosage form is buoyed on the dissolution medium (Prajapati, Jani, Khutliwala, & Zala, 2013).

Table 1.: polymers used in new floating dosage forms

Floating Dosage Form	polymer(s)	Drug	Ref.
In situ gelling solution	Gellan	Amoxicillin	(Kerdsakundee, 2015)
In situ gelling solution	Gellan	Clarithromycin	(Rajinikanth, 2007)
NFM-Beads [1]	Pluronic F127 Chitosan Sodium carboxymethylcellulose	Emodin	(Rajinikanth & Mishra, 2008)
(LC-MIP) particles [2]	Methacrylic acid Ethylene glycol dimethacrylate 4- Methyl phenyl dicyclohexyl ethylene	S-amlodipine	(Chen, 2019)
MWCNT@LC-MIP particles [3]	Methacrylic acid Ethylene glycol dimethacrylate 4-Methyl phenyl dicyclohexyl ethylene	Levofloxacin	(Zhang, 2017)
Electrospun nanofibers	Polyethylene oxide Eudragit RL Eudragit RS	Pramipexole	(Zhang, 2018)
IPN beads [4]	Sterculia gum LM-pectin	Ziprasidone HCl	(Tort, 2020)

Resultant weight

1 nanomicelles-loaded floating mucoadhesive beads
2 Liquid crystalline-molecularly imprinted polymer
3 Multiwalled carbon nanotubes (MWCNTs) coated LCMIP
4 Interpenetrating polymer network beads

To describe buoyancy, floating time and bulk density are considered the most critical parameters. However, mere measurement of density is insufficient for identifying buoyancy, as thickness varies in media with changes in the resultant weight through time (Narang, 2011; Rathee P, 2011).

Drug release

For *in vitro* evaluation of drug release, dissolution tests are carried out using a USP apparatus: apparatus I (Paddle), apparatus II (basket), apparatus III (modified disintegration testing apparatus), or apparatus IV (flow-through cell). These tests are performed in 0.1M HCl (900 mL) at a stirring rate of 50 or 100 rpm at 37±0.5°C(Jawale, Bairagi, Jaybhai, & Deshmukh, 2010).

Surface topography

Atomic force microscopy (AFM), SEM, and contact profilometer were used to determine the surface topography and structure (Arunachalam et al., 2011; Ichikawa, Watanabe, & Miyake, 1991; Sharma, Agarwal, Gupta, & Khinchi, 2011).

Moisture content measurement

The moisture content is seldom necessary. It indicates whether a product has standard features for production and trade. There are various techniques for determining the moisture content of formulations, such as freeze-drying, vacuum drying, Karl Fischer titration, thermogravimetric methods, and physical methods (Arunachalam et al., 2011; Klausner et al., 2003; Sato, Kawashima, et al., 2004a).

Swelling index

The swelling index is measured by evaluating water uptake (WU) or weight gain after submerging in an aqueous medium, especially 0.1 M HCl for a specific time. After removing the dosage form at regular intervals, weight changes are determined relative to time (Narang, 2011; Sharma et al., 2011). WU is determined based on the weight gain percentage:

$$WU = (Wt - Wo) * 100 / Wo$$

Where Wo and Wt are the initial weight of dosage form and weight at time t, respectively. Also, dimensional changes can be determined, considering the increase in the thickness and, or diameter of the tablet over time (Prajapati et al., 2013; Sharma et al., 2011).

Drug content assessment

The drug content represents the amount of drugs in each unit. It is measured using HPLC, HPTLC, spectroscopy, near-infrared spectroscopy, microtitrimetric methods, or inductively coupled plasma atomic emission spectrometer (Arunachalam et al., 2011; Tanwar, Naruka, & Ojha, 2007).

Encapsulation efficiency

A significant physicochemical feature of the dosage form is its encapsulation efficiency. Various methods, including ultrafiltration, gel filtration, dialysis bag diffusion, ultracentrifugation, and microdialysis, have been suggested to evaluate encapsulation efficiency (Arunachalam et al., 2011; Bajpai, Bajpai, & Sharma, 2007).

Fourier-transform infrared spectroscopy (FTIR)

FTIR is commonly applied to detect polymeric, organic, or inorganic materials and functional groups. The FTIR spectra of pure drugs, polymers (or other ingredients), and drug-loaded formulations are used to evaluate drug interactions with the polymer (Arunachalam et al., 2011; Sonar, Jain, & More, 2007).

***In vivo* Evaluation**

Radiology and scintigraphy

X-ray radiography and gamma scintigraphy can help determine the dosage form position in the gastrointestinal tract; therefore, it is possible to identify the dosage form passage in this tract and predict the gastric emptying time. By integrating a radio-opaque material in a solid dosage form, X-ray visualization will be enabled to evaluate gastric retention at different intervals. Barium sulfate is recognized as commonly radio-opaque marker. Also, indirect observation is facilitated by a scintiscanner using radionuclide γ-emission in a formulation. The emitting ma-

terial is mostly ^{99}Tc (Horton, Ross, & Darling, 1965; Shalaby, Blevins, & Park, 1992). However, Razavi et al. used samarium (III) oxide ($^{153}Sm_2O_3$) to radiolabel the metformin HCl-loaded floating tablet to trace the dosage form via gamma scintigraphy in the gastrointestinal tract. This study was performed on New Zealand white rabbits (Razavi et al., 2015).

Gastroscopy

Gastroscopy is an oral endoscopy, which uses video systems or fiber optics to visualize the effect of dosage form on residence time in the stomach. Moreover, it provides an accurate analysis of the gastro retentive system of drug delivery (Prajapati et al., 2013; Soni et al., 2011).

MRI imaging

MRI, as a relatively safe in vivo approach, is used to evaluate the gastro-retention of a system. It can be used to determine the site of ingested dosage form by radio waves and magnetic fields. In this method, compounds, which have optimal paramagnetic features (such as ferrous oxide), are integrated into the dosage form for imaging (Bagul, Patil, Shirsath, Nikam, & Gujar, 2012; Steingoetter et al., 2003).

^{13}C octanoic acid breath test

This test is used to measure the gastric emptying time of GRDDS systems. Octanoic acid is a medium-chain fatty acid, which is rapidly absorbed in the duodenum, with subsequent hepatic oxidation to $^{13}CO_2$. In this molecule, ^{13}C isotope replaces the carbon atom, which enters CO_2 and comes out in the breath. After oral administration of a floating system containing ^{13}C octanoic, the appearance of $^{13}CO_2$ in the breath is mainly associated with the gastric emptying of the dosage form in the duodenum (Perri, Pastore, & Annese, 2005). Its analysis requires the collection of several respiratory samples before the use of ^{13}C octanoic acid and then at regular intervals of 15 minutes and 4 hours later, the ratio of $^{13}CO_2/^{12}CO_2$ can also be determined by mass spectrometry (IRMS) or infrared spectrometry (IR)(Bruno et al., 2013). The breath test is a non-invasive, non-operator-dependent, reproducible method without any biological hazards. Moreover, this method is more cost-effective than other methods (Bagul et al., 2012; Jackson et al., 2004).

CONCLUSION

The inability to localize and restrain an oral dosage form in the upper gastrointestinal tract, i.e., stomach, duodenum, and jejunum and the highly variable nature of gastric emptying time result in unpredictable bioavailability. FDDS has been suggested as a potential approach for prolonging gastric retention, controlled delivery, and enhancing the bioavailability of a drug. In this study, we reviewed different floating systems, which have been developed so far. Two major classes, including effervescent and non-effervescent FDDS and also application of in situ gels, nanocarriers, nanofibers, and recent mucoadhesive systems in the fabrication of floating dosage forms, were described in detail. In addition, *in vitro* and *in vivo* evaluating methods for assessment of efficiency of floating systems were discussed.

CONFLICT OF INTEREST

All the authors of this article declared no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Developing hypothesis and experimenting (Kouchak M.), preparing the study text and literature Research (Feizoleslam F., Veisy M.), reviewing the text (Shariat Razavi F.), Analysis, interpretation of the data, and revising the final manuscript (Kouchak M.).

ABBREVIATIONS

Floating drug delivery systems (FDDS)
Gastro retentive drug delivery systems (GRDDS)
Hydro dynamically balanced systems (HBS)
Hydroxypropyl methylcellulose (HPMC)
Sodium carboxymethyl cellulose (NaCMC)
Carrageenan, hydroxyethyl cellulose (HEC)
Hydroxypropyl cellulose (HPC)

Polyvinylpyrrolidone K30 (PVP K30)

Gastro retentive controlled-release (GCR)

Bicarbonate-loaded Ion exchange resin (IER)

Nanomicelles-loaded floating mucoadhesive beads (NFM-Beads)

Liquid crystalline -molecularly imprinted polymers (LC-MIPs)

Multiwalled carbon nanotubes (MWCNTs) coated LCMIP (MWCNT@LC-MIP)

Polyethylene oxide (PEO)

Pectinate- sterculia gum (SG)

Interpenetrating polymer network beads (IPN beads)

Simulated gastric fluid (SGF)

Atomic force microscopy (AFM)

Water uptake (WU)

Fourier-transform infrared spectroscopy (FTIR)

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