Expert Opinion

Drug release kinetics and physicochemical characteristics of floating drug delivery systems

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Introduction: Absorption of drugs through the gastrointestinal tract poses a variety of limitations, making the *in vivo* performance of drug delivery systems uncertain. Following on from recent advances, in a time of increased consideration of floating drug delivery systems, it is as important as ever to continue the progress by studying different aspects of these systems. Moreover, it seems imperative to gain a deeper insight into drug release mechanisms, in order to design a more systematic and intellectual floating system.
Areas covered: This paper summarizes current approaches in the research and development of ideal floating drug delivery systems, from recent literature. Also, in order to have predictability and reproducibility in designing an efficient floating dosage form, some kinetic studies are mentioned, and the drug release mechanism from floating drug delivery systems is discussed.
Expert opinion: Developing an efficient floating dosage form is reliant on a better understanding of the relation between formulation variables and performance of the floating systems. Generally, the combination of two buoyancy mechanisms and gas-generating systems with swellable polymers would be beneficial for obtaining an appropriate floating lag time and duration of buoyancy, which in turn guarantees optimum efficiency of the pharmaceutical dosage form.

Keywords: buoyancy, drug release kinetics, effervescent and non-effervescent systems, floating drug delivery systems

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1. Introduction

Not surprisingly, the wide range of effective medicinal agents available today is one of the greatest scientific achievements. Regardless of the effectiveness and safety of the medicines embedded in dosage forms, the pharmaceutical concept of the latter is growing to be ever more important. Scientific and technological advancements have also been made in the research and development of different types of drug delivery system. Among the various routes of drug delivery to the systemic circulation, oral administration has excellent accessibility that offers painless administration, patient compliance and a preferred alternative for non-invasive delivery of drugs. Oral dosage forms possess several physiological restrictions, such as non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach [1]. The rate of transition of a dosage form through the gastrointestinal (GI) tract is highly affected by the physiological properties of the GI tract as well as the formulation properties. The transit time of a GI drug delivery system along the GI tract is the most limiting physiological factor in the development of controlled release GI drug delivery systems. The patterns of GI transit and gastric emptying depend on whether the person is in a fasted or fed state, and the physical state of the drug delivery system, either a solid or a liquid form.

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Article highlights.

- Very early on, floating drug delivery systems were considered to be one of the promising trends in enhancing drug residence in the gastrointestinal tract.
- Based on the mechanism of buoyancy, two markedly different technologies are used in the development of floating dosage forms: effervescent and non-effervescent systems.
- Despite the fact that interplay of the pharmacokinetic and pharmacodynamic parameters for a particular drug also has a noteworthy effect on the efficiency of the floating dosage form, *in vitro* evaluations are usually in line with the *in vivo* assessments.
- Combination of the gas-generating systems with swellable polymers will be beneficial for obtaining an appropriate floating lag time and duration of buoyancy.
- Different ingredients applied in the floating formulations appeared to be the key factor responsible for the multiplicity of the kinetic models fitting the dissolution data and also the differences in drugs.

This box summarizes key points contained in the article.

The gastric emptying of liquids in the fasted state is a function of the volume administered. Likewise, indigestible solids are emptied from the stomach as a function of their physical size [2,3]. Designing a suitable dosage form is an important basic principle of the drug delivery system to dominate these constraints and offer a proper delivery strategy that would function independent of the digestive state, clinical condition, or GI motility of the individual. As in this route of administration the bioavailability of drugs often depends on the GI transit rate of the dosage form, it appears necessary to establish an appropriate sustained release system for drug delivery [4].

Sustained release dosage forms have some benefit in safety and efficacy over normal release systems in that if the frequency of dosing could be reduced, drug efficacy would be prolonged and the incidence of adverse effects could be diminished. One of the advantages of the sustained release dosage forms is that medication is administered less often than in other dosage forms. Another advantage is that it reduces fluctuations of drug concentration in the blood. Thus, the patient is not repeatedly subjected to amounts of the drug that are less or more than adequate. Nor does the blood chemistry undergo repeated chemical imbalances, which might be detrimental to the patient's health [5,6]. The highly variable nature of the gastric emptying process makes the *in vivo* performance of these kinds of drug delivery system uncertain and can result in some bioavailability problems [7]. Nonetheless, retention of the dosage forms in the stomach prolongs the total GI transit time, leading to reduced drug concentration fluctuations in the blood. Drugs that have poor solubility in higher pH, that are absorbed from the stomach, requiring local delivery in the stomach, and also the ones that are susceptible to circadian variations, could be delivered ideally by slow release from the stomach [8]. In opposition, drugs that cause irritation to gastric mucosa and the ones that encounter first-pass metabolism or have stability problems in gastric fluids are not welcomed in these kinds of drug delivery system. For example, floating drug delivery systems are preferred in the case of drugs such as furosemide and theophylline with an absorption window in the stomach or in the upper small intestine. Floating systems are also suitable for antibiotic administration, such as metronidazole in eradicating *Helicobacter pylori* in the treatment of peptic ulcers that act locally in the proximal part of GI tract [9,10]. Also, drugs that are unstable in the intestinal fluid, such as captopril, and the ones with poor solubility in the intestinal tract, such as diazepam and verapamil, are candidates for these systems [11-17]. Despite the fact that oral controlled release dosage forms provide a constant drug release rate for longer periods of time, several groups of basic drugs do not have this benefit. A variety of drugs that: i) are locally active in the stomach, ii) have an absorption window in the stomach or in the small intestine, iii) are unstable in the intestinal or colonic environment, or iv) have low solubilities at high pH values, bring about methods for developing gastroretentive drug delivery systems [18,19]. Inadequate residency of drugs in the vicinity of the absorption site for the lifetime of drug delivery makes the utilization of all oral controlled release drug delivery systems restricted. The transit time from mouth to anus varies from one person to another. It also depends on the physical properties of the object ingested and the physiological conditions of the alimentary canal. Furthermore, there also exists an absorption surface in the upper small intestine region that is known to have a transit time of only 2 – 3 h. Several approaches have been developed recently to extend GI transit time by prolonging the residence time of drug delivery systems in the stomach [20]. One of the approaches is to develop a bio(muco)adhesive polymer-based drug delivery system [21]. In spite of various beneficial characteristics of the bioadhesive systems, the high turnover rate of gastric mucus and local irritation have remained challenging in this method [22].

2. Floating drug delivery systems

One of the thriving trends in enhancing drug residence in the stomach is designing floating dosage forms. Several approaches have been followed to encourage buoyancy of the dosage form in the stomach. The principal rule is constant in all techniques, and that is to provide a density lower than the gastric fluids so that they would be capable of floating on the gastric juice in the stomach [12]. Based on the mechanism of buoyancy, two markedly different technologies are used in the development of floating dosage forms: effervescent and non-effervescent systems [23,24].

2.1 Effervescent systems

Acid–base reactions have been utilized for years to produce diverse pharmaceutical preparations that effervesce on contact with water. As a result of effervesce and gas generation,

density of the system lessens and makes it float on the gastric fluid [11]. Three key sources in affording acidity in effervescent reactions are acids, acid anhydrides and acid salts. Along with this, organic acids, citric and acetic acids are the commonly used materials. On the other hand, carbonate sources that are used to provide carbon dioxide (CO_2) in contact with acids are carbonates and bicarbonates; the latter are most often used as CO_2-generating sources [14,25]. Addition of carbonates to the dosage form not only plays an important role in making the dosage form float but also provides the initial alkaline microenvironment for the polymers to gel. These materials usually react with gastric acid and produce CO_2, which is entrapped in the matrix of the dosage form, allowing it to float on the gastric fluid. Further, these effervescent systems are classified into two types: single-layered and multilayered dosage forms [11]. These systems are also prepared with swellable polymers and effervescent components so that the effervescent may be compressed in one hydrocolloid-containing layer and the drug in the other layer, and so on [26]. In total, the reaction is due to the CO_2 generated by neutralization in the effervescent layer with the diffusion of water through the swellable membrane layer; though the lag time relying on the duration of the gas generation reaction may end in gastric emptying before achieving floating. Subsequently, multiparticulate dosage forms consisting of small discrete units are pharmaceutical formulations in which the active substance is present as several small independent subunits. Multiparticulates are less dependent on gastric emptying, resulting in less inter- and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation. Recently, much emphasis has been laid on the development of multiparticulate dosage forms in preference to single-unit systems because of their potential benefits, such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [27-29].

Jiménez-Martínez *et al.* carried out an experiment in which they prolonged drug (captopril) release from floating matrix tablets using metolose SH 4000 SR/sodium bicarbonate in the formulations. Owing to the fact that captopril goes through a degradation reaction in higher pH and is stable in pH 1.2, it is essential to develop an appropriate delivery system for it. The presence of sodium bicarbonate in matrix tablets not only assured their buoyancy, but also demonstrated greater hydration volumes due to the matrix expansion produced by the evolution of carbon dioxide bubbles [30], whereas in metolose matrices floating depended on the porosity obtained after compaction. Carbon dioxide bubbles could increase the porosity of the formulations of metolose matrices with insufficient porosity. On the whole, expansion of the hydrated metolose matrices increased the surface area available for dissolution and the presence of gas bubbles hindered the diffusion path, decreasing the release constant values [30]. A matrix floating tablet along with gastroretentive delivery strategies was developed by Bani-Jaber *et al.* using interpolyelectrolyte (IPE) complexation between carrageenan (CG) and Eudragit E (EE). The effervescent tablets were prepared by including Na bicarbonate as an effervescent agent. Both CG and EE–CG effervescent matrices showed fast and prolonged floating with floating lag times < 30 s and floating duration > 10 h. The corresponding EE effervescent matrices showed delayed floating and rapid drug release, and completely dissolved after 3 h of dissolution [31]. In another study the design of the floating delivery system was based on the sustained release formulation, with floating and swelling features for ofloxacin. Different polymers, such as psyllium husk, HPMC K100M, betacyclodextrin crospovidone and its combinations with sodium bicarbonate as the effervescence agent were used in obtaining the desired sustained release profile over a period of 24 h with flotation lag time of < 25 s [32]. Tadros developed a gastroretentive controlled release drug delivery system with swelling, floating and adhesive properties for ciprofloxacin. The tablet formulations were designed using HPMC K15M and/or sodium alginate as the release-retarding polymer and sodium bicarbonate or calcium carbonate as a gas former. The findings of the study revealed that the promising controlled release floating tablets of ciprofloxacin were successfully formulated by the effervescent technique. Tablets containing HPMC K15M (21.42%, w/w), sodium alginate (7.14%, w/w) and sodium bicarbonate or calcium carbonate (20%, w/w) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability, adhesion retention period and sustained drug release rates [33].

2.2 Non-effervescent systems

There are several practical approaches in formulating such floating dosage forms without using gas-forming agents during the procedures.

2.2.1 Hydrodynamically balanced systems

Hydrodynamically balance systems, in contact with gastric fluid, form a hydrated gel layer in the outer exposed surface of the dosage form with a bulk density and buoyancy in the stomach. Hydrodynamically balanced system (HBS) formulations consist mainly of gel-forming or highly swellable cellulose-type hydrocolloids, for example, hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose, polysaccharides, matrix-forming polymers and a drug that is thoroughly mixed with gel-forming hydrocolloids [34,35]. Water penetration to the inner layers brings about surface hydration and a soft gelatinous barrier around the dosage form, which helps to sustain drug release through diffusing out of the gel structure. Therefore, the hydrated gel controls the rate of water penetration into the dosage form and the rate of drug release from the HBS. However, the major challenge for these systems is that they are not trustworthy enough owing to the all or none emptying process, which may cause high variability in bioavailability [36]. This necessitated the design and development of a floating drug delivery system

using multiple-unit devices, such as porous or hollow microspheres and alginate beads, which could distribute uniformly within the gastric contents and gradually pass through the GI tract without being affected by the gastric emptying processes [37]. As a result, bioavailability and the desired release profile are attained much more reliably than with mono-unit dosage forms.

A wide range of polymers are used in the floating drug delivery systems as well in the HBS. The effect of different excipients and polymers on floating behavior and drug release from floating matrices was studied by Kumar *et al.* They found that selection of suitable excipients depending on the polarity of drug could help to modulate the floatability and release profile where water uptake in the floating matrix increased with an increase in loading of polar drugs and decreased with nonpolar drugs. In the case of increased PEG in the formulations, the drug release increased up to a certain concentration and decreased thereafter, but drug release decreased linearly with concentration of the stearic acid [38]. Nakamichi *et al.* found that buoyancy of the floating dosage form composed of nicardipine hydrochloride (NH) and hydroxylpropyl methylcellulose acetate succinate (enteric polymer) could be controlled by varying the amount of calcium phosphate dehydrate, which showed excellent floating ability and mechanical strength in acid solution [39]. A combination of three polymers with different concentrations, sodium alginate rapidly hydrating a rate-controlling polymer, sodium carboxy methylcellulose a gel-forming agent, and magnesium alumino metasilicate, a swelling controlling agent, together with calcium sulfate dehydrate, a crosslinker and gel strength enhancer for sodium alginate, was used to design a new gastroretentive, floating, swellable, controlled release tablet of Metoprolol succinate [40]. A hydrodynamically balanced delivery system of clarithromycin was developed by Nama *et al.* to prolong gastric residence time with a desired *in vitro* release profile for localized action in the stomach, with the intention to treat *H. pylori*-mediated peptic ulcers. Different kinds of polymer with various possible concentrations were assessed to establish the optimum formulation; 66.2% clarithromycin, 12% HPMC K4M polymer, 8% sodium bicarbonate offered improved floating lag time < 3 min and 12 h duration of floating [41]. In general, use of a HBS is desirable, which swells to create a gel-like structure after administration and attains a density less than that of gastric fluids where prolonged drug delivery is required.

2.2.2 Porous systems

Owing to several useful features of the porous carriers, they have been playing a principal role in the pharmaceutical industries, including the development of new drug delivery systems such as floating and sustained drug delivery systems as well as improving the solubility of the poorly water-soluble drugs [42,43]. A porous structure for the low-density porous materials such as silica, porous ceramic, ethylene vinyl acetate, polypropylene foam powder and titanium dioxide was found to be essential for providing the applications mentioned [44]. These materials in porous dosage forms allow the inclusion of drugs inside a porous compartment that possess a relatively lower density than the gastric juice and remain buoyant in the stomach. Also, any other polymer that might be added to the dosage form would moderately cover the pores and trap air within the system. The trapped air in the formulation is gradually removed from the system on exposure to gastric medium, leading to extended floating times with a more reproducible and predictable drug release manner. After all, continued interest and notable surveys have been directed in recent years towards the porous carriers as controlled drug delivery matrices.

Jain *et al.* used calcium silicate, which has a characteristically porous structure with many pores and a large pore volume, in the formation of floating microspheres for gastroretentive delivery of repaglinide. The candidate drug, repaglinide, was chosen for further analysis owing to the fact that it has a very short half-life (1 h), low bioavailability (50%) and poor absorption in the upper intestinal tract. The designed system was convenient owing to the combination of excellent floating ability and a suitable drug release pattern in terms of increased bioavailability of repaglinide [45]. Elsewhere, floating matrix tablets were prepared based on low-density polypropylene foam powder, and the effects of formulation and processing parameters on drug release were evaluated by Streubel *et al.* The study stated that on contact with release medium the tablets eroded and the release patterns varied significantly with the type of matrix former by altering formulation parameters, matrix-forming polymer/foam powder ratio, drug loading, tablet height and diameter, type of matrix-forming polymer, and addition of water-soluble and water-insoluble fillers [46].

2.2.3 Alginate beads

Alginates are a remarkable family of natural polymers that are found in brown algae, which consist mainly of mannuronic acid, guluronic acid and mannuronic-guluronic blocks that have been studied for a variety of biomedical applications. This interest in alginates is primarily due to their high biocompatibility and non-toxic nature in oral administration, and they also demonstrate a protective effect on the mucous membranes of the upper GI tract. The alginate beads with a structure of spherical gels of ~ 2.5 mm in diameter are taken shape through dropwise addition of aqueous alginate solution to the aqueous solution containing calcium ions and/or other di- and polyvalent cations [9]. The pH-dependent reswelling property of dried alginate beads allowed them to be administered as a unique vehicle for a floating controlled release system in the GI tract as early as the 1980s [47-50]. Multi-unit floating dosage forms control the release of drugs that are loaded in the alginate beads as they are exposed to the gastric medium. Recently, oral controlled release systems involving alginate beads have been coated with chitosan to

improve their mechanical strength, as the crosslinked alginate gel beads have a relatively rigid and fragile nature [51]. Furthermore, the potential buoyancy of the hydrophilic drugs was limited owing to the low encapsulation efficiency even after modification of the beads.

In a study conducted by Ma *et al.*, multi-unit floating alginate microspheres were prepared to provide an efficient drug delivery system for a hydrophilic drug, diltiazem hydrochloride, which has a relatively short biological half-life of 3 – 4 h. Chitosan was included in the Ca–Alg microspheres followed by coating with Eudragit RS to enhance the drug encapsulation efficiencies. Such an alginate floating dosage form delayed the release of Diltiazem (DTZ) for 24 h through an extended gastric retention time, which could provide evidence in enhancing bioavailability of some hydrophilic drugs [52]. More recently, in 2010 Singh *et al.* published a paper in which they examined gelation of alginate and sterculia gum by using $CaCl_2$ as crosslinker to form alginate beads. Pantoprazole, an anti-ulcer irreversible proton pump inhibitor drug, was evaluated in the study to improve the bioavailability and therapeutic efficacy of the drug used for the disease associated with the stomach. According to the results, the buoyant nature of the beads was responsible for the longer retention time of drug delivery systems in the stomach and improved therapeutic efficacy of the locally active drugs such as pantoprazole [53]. In the authors' previously published paper, they prepared alginate beads of metronidazole using gas-generating and porous agents followed by physicochemical evaluations. The findings of the study revealed high compatibility of the alginate beads in achieving suitable floating dosage forms that could control drug release from the beads with a definite kinetic of release [9].

2.2.4 *Hollow microspheres/microballoons*

One of the promising drug delivery floating systems is hollow microspheres (microballoons) that are designed to float on gastric juice with a specific density of < 1. Solvent evaporation and also solvent diffusion-evaporation are the practical methods utilized in the preparation of the hollow inner core spherical microspheres [54]. Multi-unit empty particles having the potential to control drug release incorporate the dispersed drug in their outer polymer shelf. The entrapped air in the microspheres lessens the density of the particles, ensuring buoyancy of the hollow microspheres. On account of many factors, such as quantity of polymers, the polymer ratio and the solvent used in the preparation of the microspheres, floating and drug release vary [55,56]. Hence, it seems possible to prepare microspheres of the desired character by adjusting some of these parameters. Frequently used polymers in developing hollow microspheres are polycarbonate, cellulose acetate, calcium alginate, Eudragit, agar and also pectin. In general, hollow microspheres are believed to be one of the prominent buoyant systems as they provide a multi-unit system with an improved floating property [57,58].

This view is supported by Sato *et al.*, who developed the emulsion solvent diffusion method to form hollow microspheres (microballoons) using enteric acrylic polymers with drug in a mixture of dichloromethane and ethanol. The preparation temperature appeared to have a remarkable effect on the formation of cavities inside the microsphere and the surface smoothness, determining the floatability and drug release rate of the microballoon. Also, the drug loading efficiency of microballoons was in close relation with the distribution coefficient of the drug between dichloromethane and water as well as the drug properties. Concisely, microballoons ensure a promising drug delivery system floating in the stomach [59,60].

3. Physicochemical evaluations

In the development phase for floating dosage forms, designing a selection of suitable control principles is of crucial importance. Besides, health authorities worldwide necessitate accurate adjustment of the physicochemical parameters of the formulation for all individually administered dosage forms in advance of the clinical phase [61].

3.1 *In vitro* buoyancy and drug release properties

An important feature to take into account in the physicochemical parameters of a floating drug delivery system is the floating behavior of the dosage form, in view of the fact that different physiological situations affect the results of buoyancy and dissolution as well as the release of a drug from the pharmaceutical dosage form. The test for buoyancy and *in vitro* drug release studies are usually carried out in close proximity to the physiological conditions of the human body to lessen the variation derived from altered dissolution medium. To ascertain a reliable correlation between *in vitro* and *in vivo* results, the apparatus and procedures of United States Pharmacopeia (USP) are preferred as it has been adopted by most countries' pharmacopeias for the floating and drug release tests. The basket and paddle stirring elements containing 900 ml of 0.1 N HCl as a testing medium maintained at 37°C are generally used [62]. The floating behavior is frequently evaluated with the time needed for the dosage form to float and duration of the floating, which are noted as the floating lag time and flotation time, correspondingly. Moreover, a verified method for multi-unit floating particles is to determine the buoyancy of these dosage forms by the number of floating particles and the time during which they remain buoyant on the test solution. Apart from environmental factors, floating is primarily controlled by apparent density of the dosage form, which in turn is concerned with different kinds and quantities of formulation variables, such as polymers, porous carriers and gas-forming agents [63-65].

A large and growing body of papers has been published on challenging improvements of floating drug delivery systems, applying a variety of floating agents to encourage buoyancy of the pharmaceutical dosage forms with a controlled drug

release pattern. In 2008, Sriamornsak *et al.* studied the effects of various types and amounts of wax on floating and drug release behavior of emulsion gel beads of calcium pectinate. They showed that, having included a sufficient amount of pectin–olive oil in the formulations, emulsion gel beads could float immediately with a floating duration > 24 h, signifying the low apparent density of the beads containing oils. Furthermore, drug release was influenced by the solubility of the wax incorporated in the formulations, so that the hydrophilic wax (i.e., polyethylene glycol) increased drug release whereas the hydrophobic waxes (i.e., glyceryl monostearate, stearyl alcohol, carnauba wax, spermaceti wax and white wax) slowed down the drug release meaningfully. Sriamornsak *et al.* concluded that the wax-incorporated emulsion gel beads could be used as a carrier for intragastric floating drug delivery [66]. According to Li, viscosity has the foremost role in management of drug release and floating properties in floating dosage forms. Inhibition in the initial burst effect followed by prolonged calcium release was established, with an increase in viscosity of the polymeric system. Conversely, floating behavior was improved with lower viscosity polymers (HPMC K100LV) than higher viscosity ones (K4 M) [67]. In another study Baumgartner *et al.* provided in-depth analysis of the optimization of floating matrix tablets, determining the effect of tablet hardness on the floating and drug release properties along with tablet composition. Addition of the gas-generating agent sodium bicarbonate with citric acid to the formulations produced a marked reduction in the floating lag time up to < 1min and the duration of floating was extended to > 8 h [68]. Then again, in another study Sriamornsak *et al.* evaluated the effects of some variables on release behavior of metronidazole from floating emulsion gel beads of calcium pectinate. They detected a notably prolonged drug release profile by coating the beads with Eudragit or by hardening with glutaraldehyde, whereas no clear effect on drug release was obtained using PEG 10000, glyceryl monostearate and Eudragit as additives in the formulations [69].

Furthermore, most of the relative papers dealing with the development and optimization of buoyancy lag time and duration of drug release used both swellable polymers with gas-generating systems [31,70]. Badhan *et al.* designed and optimized the sustained release gastroretentive mini matrices of amoxicillin using xanthan gum, rate-controlling polymers (HPMC K100M CR/PEO coagulant (1:1)), carbopol 974P and a gas-generating couple (sodium bicarbonate/citric acid (3:1)). The optimized formulation was said to be optimum because it had minimum buoyancy lag time of 7 min, required maximum time of 9.39 h for 95% drug release and had higher bioadhesive capabilities, indicating its sustained drug release and gastric retention capability [71]. Elsewhere, a new coated multiple-unit floating system was designed for sustained release of levodopa from floating minitablets. The system consisted of a 3 mm drug-containing gas-generating core coated with a flexible polymeric membrane of Eudragit® (Rhöm Pharma, Darmstadt, Germany) RL30D and ATEC as a film former and a plasticizer, respectively. The floating lag time decreased as the proportion of effervescent agents increased. The optimum formulation of coated floating minitablets showed 20 min buoyancy lag time, 13 h duration of floatation and a sustained release of levodopa for > 20 h [72]. In another study conducted by Jagdale *et al.*, a gastroretentive drug delivery system of propranolol hydrochloride was designed, in which they evaluated the ability of various polymers in different concentrations for their gel-forming abilities and prolonging the drug in the stomach. In preliminary trials, tablets formulated with HPC, sodium alginate and HPMC E 15 LV failed to produce a matrix of the required strength, whereas formulations containing xanthan gum showed good drug-retaining abilities but the floating abilities were found to be poor. However, floating was achieved for the formulations with HPMC K4M and HPC, which showed excellent buoyancy for > 24 h with floating lag time < 1 min [73].

Accordingly, different factors influence the buoyancy and drug release from a pharmaceutical dosage form. Solubility of the drug in dissolution medium as well as the formulation variables in the dosage form are the dynamic items, contributing distinctively to drug release differences of the floating dosage forms with similar basic floatation preparation methods. However, it has always been a great challenge to modify the drug release in an expected manner and assess the efficiency of the dosage form in an *in vivo* environment.

3.2 *In vivo* assessments

The *in vitro* assessments are barely full counterparts of the *in vivo* results, as the standard USP methods have not been reliable predictors of *in vivo* performance of the floating pharmaceutical dosage forms. Owing to the fact that interplay of the pharmacokinetic and pharmacodynamic parameters for a particular drug also has a notable effect on the efficiency of the floating dosage form, *in vivo* evaluations appear to be requisite. Sawicki considered pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans for assuring proper drug delivery compared with the conventional tablets in use today. In his *in vivo* examination, floating pellets stayed longer in the maximum solubility conditions, unlike conventional tablets, allowing for an enhanced rate of absorption for verapamil and more promising pharmacokinetics [74]. As follows, tracking the location of the dosage form through the GI tract provided a broad insight for formulating the optimal floating drug delivery system. Radiography, gamma scintigraphy, gastroscopy, ultrasonography and magnetic resonance imaging are some of approaches used in evaluating the *in vivo* behavior of a dosage form in animals or even in healthy volunteers. However, drawbacks and benefits of a certain method provide us with a selection of varied choices in the application of these techniques. Owing to the many *in vivo* reports by gamma scintigraphy methods, it appears to be the most popular approach for evaluating the *in vivo* performance of floating systems. Jain *et al.* studied the gastroretentive performance and

pharmacokinetic parameters of the floating calcium silicate-based microspheres of repaglinide based on gamma scintigraphy of the formulations in albino rabbits [75]. In 2008, Goole *et al.* reported a study in which they determined the formulation buoyancy on gastric fluid for > 4 h with a sustained pharmacokinetic profile of levodopa and carbidopa using gamma scintigraphic and pharmacokinetic studies on 10 healthy human volunteers [76]. In a recent survey, Zhao *et al.* assessed the pharmacokinetics of the phenoprolamine hydrochloride floating sustained release tablets by determining the plasma concentrations of the drug in 116 healthy human volunteers, which showed wide intersubject variability in pharmacokinetic parameters [77]. This shows the relative necessity of evaluating the correlation between *in vivo* and *in vitro* results from case to case. However, Chavanpatil *et al.*, in a parallel study, assessed the buoyant ofloxacin dosage form for the pharmacokinetic parameters in 24 healthy human volunteers compared with the marketed formulation (Zanocin). They stated that all the formulations revealed 97.55% bioavailability bioequivalent to the marketed product [32]. Kakumanu *et al.* determined the bioavailability of floating cefpodoxime dosage forms with *in vitro* and *in vivo* experiments. The *in vivo* results in rats were consistent with the *in vitro* data, indicating the possible increase of oral bioavailability of cefpodoxime in humans donating a better therapeutic plasma level of drug [78].

Following on from extensive surveys and also *in vivo* assessments, some of the floating dosage form products became available on the market, such as: i) Madopar®HBS (Prolopa®HBS), a commercially available product used in Europe and other countries containing 100 mg levodopa and 25 mg benserazide, which consists of a gelatin capsule that is designed to float on the surface of the gastric fluids; ii) Valrelease®, a second example of a floating capsule marketed by Hoffmann-LaRoche, which contains 15 mg diazepam applying a HBS system to maximize the dissolution of the drug by prolonging the gastric residence time [79]; iii) Gaviscon (Reckitt and Colman, UK), a floating liquid alginate preparation consisting of a mixture of alginate and sodium bicarbonate, which becomes buoyant by entrapping the gas bubbles, and the gel floats on the gastric contents as a physical barrier raft on top of the stomach, preventing contact of the acid with the epithelium [80]; and iv) Topalkan® and v) Almagate Flot-Coat® are antacids that have antipeptic and protective effects on the stomach mucous membrane and provide, together with the magnesium salts, a floating layer of the preparation in the stomach [12].

On the whole, there was a relevant correlation in most of the surveys between *in vivo* and *in vitro* assessments. Most of the articles dealing with the evaluation and development of the floating drug delivery systems underline the effectiveness and reliability of these floating systems as an excellent strategy for establishing an efficient controlled drug delivery system. Nevertheless, characterization of the mechanisms implied in the drug release from the floating dosage form is still a matter of interest in this field. Having reviewed the documentation on drug release mechanisms in floating pharmaceutical dosage forms, let us try to provide an overview of the kinetics of drug release.

3.3 Drug release kinetics for the floating drug delivery systems

The merit of kinetic studies in designing a more systematic and intelligent pharmaceutical floating dosage form is closely linked to a better understanding of the drug release mechanism. As the qualitative and quantitative changes in a formulation could alter drug release and *in vivo* performance of a dosage form, it seems indispensible to have a deeper insight into the mechanisms of drug release. A category of approaches used for kinetic investigations is model-dependent methods comprising a variety of kinetic models expressing dissolution profiles and overall release of drug from the dosage forms [81-87]. Zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas, Baker–Lonsdale, Weibull, Hopfenberg, Gompertz and regression models are the commonly used models for clarifying the mechanism of drug release [9,88,89]. Some of the mathematical equations and kinetic models that are commonly used for evaluating the release kinetics are outlined in **Table 1**.

Studying drug release kinetics is often useful in obtaining one or two physically meaningful parameters that are used for comparative purposes and relating the release parameter with important parameters such as bioavailability [90,91]. For example, the n value is generally used in the Korsmeyer–Peppas model to characterize different release mechanisms. This equation has two distinct physical realistic meanings in the two special cases of n = 0.5 and n = 1, indicating diffusion-controlled drug release for the former and erosion-controlled drug release for the latter. More to the point, an n value between 0.5 and 1 could be regarded as an indicator for the superposition of both phenomena (anomalous transport). Likewise, in the case of the Weibull model, according to Papadopulou *et al.* the exponent of time b is linearly related to the exponent n of the power law derived from the analysis of the first 60% of the release curves. The value of the exponent b is an indicator of the mechanism of transport of a drug through the polymer matrix. Estimations for $b \leq 0.75$ indicate Fickian diffusion in either fractal or Euclidian spaces, whereas a combined mechanism (Fickian diffusion and Case II transport) is associated with b values in the range $0.75 < b < 1$. For values of $b > 1$, drug transport follows a complex release mechanism [92]. Hence, a kinetic parameter can be used to study the influence of formulation factors on the drug release for optimization as well as control of release. Developing these kinetic parameters is also valuable in reducing the necessity of *in vivo* studies by using release data in predicting the *in vivo* performance of the dosage form.

Herein, the authors gathered some kinetic data to have an overview on release kinetics and give a rule in relation to drug release kinetics from floating dosage forms (data are summarized in **Table 2**) [9,15,33,41,73,89,93-114]. As is clear from

Table 1. The usual kinetic models with their mathematical equations for analysis of drug release data.

No.	Model name	Model
1	Zero order	$F = k_0 t$
2	First order	$\ln(1-F) = -k_f t$
3	Higuchi	$F = k_H \sqrt{t}$
4	Power law	$\ln F = \ln k_p + p \ln t$
5	Hixson–Crowell	$1 - \sqrt[3]{1-F} = k_{\frac{1}{3}} t$
6	Square root of mass	$1 - \sqrt{1-F} = k_{\frac{1}{2}} t$
7	Three seconds root of mass	$1 - \sqrt[3]{(1-F)^2} = k_{\frac{2}{3}} t$
8	Weibull	$\ln[-\ln(1-F)] = -\beta \ln t_d + \beta \ln t$
9	Linear probability	$Z = Z_0 + qt$
10	Log-probability	$Z = Z_0' + q' \ln t$
11	Reciprocal powered time	$\left(\frac{1}{F} - 1\right) = \frac{m}{t^b}$
12	Gompertz	$F = F_\infty e^{-e^{-jt}}$

the table, there is not a general rule for predicting best fitting of dissolution data to the proposed models based on the kind of floating system as well as the dosage form. For example, in the cases of floating matrix tablet dosage forms using gas-forming agents during the procedures, different models were best fitted for dissolution data. Different ingredients in the relative matrix tablets appeared to be the key factor responsible for the multiplicity of the models fitting the dissolution data and also the differences in drug release patterns. Also, different models in analyzing the drug release data in each study made it difficult to acquire a general rule in proposing a model for the best fit of dissolution data.

4. Expert opinion

Very early on, floating systems were considered to be one of the promising trends in enhancing drug residence in the GI track. In most cases, prepared formulations can be retained on the gastric fluid with a bulk density. Owing to the interplay of the pharmacokinetic and pharmacodynamic parameters for a particular drug and the different conditions in drug delivery as well as the varying nature of the standard *in vitro* USP methods in predicting the *in vivo* performance of the floating pharmaceutical dosage forms, *in vivo* evaluations appear to be requisite for confirming buoyancy behavior. Lag time and duration of floating are the main phenomena when considering characterization of these systems. Floating formulations based on effervescent reactions are able to reduce floatation lag time a great deal, but it should be considered that these systems are not characterized for sustained drug release intentions because of the lowered duration of buoyancy. Taking into consideration the size of the small molecule, CO_2 generated via acid–base reactions able to diffuse outside the system freely accounts for the decreased flotation time and the fast profiles of drug release in most cases. By contrast, formulations with swellable polymers usually have suitable buoyancy duration but no proper floating lag time. Gradual swelling properties of these polymers are the main reason for these phenomena. The colloidal gel barrier created by swollen polymers controls the drug release with a sustained release pattern from these systems. Combination of these two mechanisms, gas-generating systems with swellable polymers, will be beneficial for obtaining an appropriate floating lag time and duration of buoyancy that guarantees optimum efficiency of the pharmaceutical dosage form. Besides, in the case of predicting the drug release mechanism for floating drug delivery systems, no single kinetic model is customary, even if the flotation strategies are the same. It seems the application and evaluation of model-dependent methods for estimating the mechanism behind drug release from floating dosage forms are complicated, and require careful observance of the physicochemical properties of the dosage form. To present an acceptable model for these systems, formulation variables, approaches in establishing formulation buoyancy and the kinetic models in analyzing the drug release data should be chosen in parallel.

Table 2. Summary of some release kinetics with their relative floatation systems and different drugs embedded in the dosage forms.

Article	Medicine	Dosage form	Floating system	Kinetic
Garg and Gupta (2009) [100]	Silymarin	Matrix tablets	Effervescent and non-effervescent	Higuchi and Korsemeyer–Peppas
Rajinikanth and Mishra (2009) [110]	Clarithromycin	Alginate beads	Effervescent	Higuchi
Balasubramaniam and co-workers (2008) [108]	Clarithromycin	Microspheres	Mucoadhesive polymer	Higuchi
Bandari *et al.* (2010) [94]	Fenoverine	Matrix tablets	Effervescent	Zero order
Nagarwal *et al.* (2010) [106]	Cinnarizine	Matrix tablets	Gas formation	Hixson–Crowell equation/Weibull
Tadros (2010) [33]	Ciprofloxacin	Matrix tablets	Gas formation	Korsmeyer–Peppas
Jagdale *et al.* (2009) [73]	Propranolol	Matrix tablets	Gas formation	Hixson–Crowell
Kamila and co-workers (2009) [105]	Rosiglitazone	Microspheres	(Hollow core)	Higuchi
Bomma *et al.* (2009) [96]	Norfloxacin	Matrix tablets	Gas formation	Zero order and first order and Higuchi
Lingam *et al.* (2008) [103]	Ranitidine	Multi-unit minitablets	Gas formation	Higuchi
Elmowafy *et al.* (2008) [99]	Famotidine	Matrix tablets	Low density	Peppas power law
Meka *et al.* (2008) [15]	Captopril	Multi-unit minitablets	Gas formation	Higuchi
Meka *et al.* (2008) [104]	Furosemide	Multi-unit minitablets	Gas formation	Higuchi
Nama *et al.* (2008) [41]	Clarithromycin	Tablets	Gas formation	Zero order and Korsmeyer–Peppas
Rajinikanth and Mishra (2007) [109]	Acetohydroxamic acid	Alginate beads	Gas formation	Higuchi's square root of time
Strübing *et al.* (2008) [112]	Propranolol	Matrix tablets	Low density	Korsmeyer–Peppas
Rajinikanth *et al.* (2008) [107]	Clarithromycin	*In situ* gelling solutions	Gas formation	Higuchi's square root of time
Ali *et al.* (2007) [93]	Metformin	Capsule	Low density	Zero order
Ishak *et al.* (2007) [101]	Metronidazole	Alginate beads	Low density	Zero-order
Chavanpatil *et al.* (2006) [97]	Ofloxacin	Tablets	Swelling and channeling agent	Higuchi
Kerc and Opara (2007) [102]	Amoxicillin/Clavulanate	Capsule	Hollow core	Zero order
Xu *et al.* (2006) [113]	Phenoporlamine	Matrix tablets	Gas formation	Korsmeyer–Peppas
El-Gibaly (2002) [98]	Melatonin	Microcapsules	Hollow core	Zero order
Asnaashari *et al.* (2010) [10]	Metronidazole	Matrix tablets	Gas formation and low density	Power law and Weibull and Higuchi
Javadzadeh *et al.* (2010) [9]	Metronidazole	Alginate beads	Gas formation and low density	Reciprocal powered time and Weibull and log-probability
Barmpalexis *et al.* (2010) [95]	Nimodipine	Tablets	Gas formation	Korsmeyer–Peppas and zero order
Rohith *et al.* (2009) [114]	Ranitidine	Gelling solution	Gas formation	Higuchi's square root of time
Kuchekar and Boldhane (2010) [40]	Metoprolol succinate	Tablet	Swelling and gas formation	First order and Korsmeyer–Peppas
Bani-Jaber *et al.* (2011) [31]	Metronidazole	Matrix tablets	Swelling and gas formation	Zero order

Further investigations may focus on the compatibility of the mentioned concepts to provide a perfect generalized relation between kinetics of drug release among the floating drug delivery systems.

Declaration of interest

The authors declare no conflict of interest. All authors are employed by Tabirz University of Medical Sciences.

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