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Review Article

COMPREHENSIVE OVERVIEW ON RECENT UPDATES OF GASTRORETENTIVE RAFT-FORMING SYSTEMS

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ABSTRACT

A Raft-forming system is an auspicious approach for systematic drug delivery with steady plasma profiles and drug sustained release manner. It has advantages like enhanced bioavailability, better floating capabilities than other floating systems, more patient compliance, and promoting drug efficacy. Although, it has some problems as it can't be used for drugs that possess low acid solubility, drugs that are unstable in gastric media, and drugs used for selective release in the colon along with stability difficulties. This system can be successfully prepared by three methods: the physical approach, chemical approach, and physiologically-stimuli approach. The comparative studies showed that the raft-forming system has more advantage over the other comparatives in the antacid potency and *in vitro* gastric residence time, allowing an intact prolonged delivery of the antacid drug. All the listed applications of the raft system were, fortunately, possessing promising drug delivery with a well-designed drug delivery system. There was a good variety in the active ingredients formulated in a raft, starting from some anti-coughs, anti-spasmodic, anti-inflammatories, and antacids to drugs treating osteoporosis and finally anti-depressants and anti-epileptic drugs. This diversity along with simple *in vitro* and *in vivo* evaluations, gives the potentiality to raft for leading the other gastro retentive drug delivery systems for decades.

Keywords: Raft systems, GRDDS, Applications of raft systems, Oral dosage forms

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INTRODUCTION

This article is designed to comprise all the research trials conducted on the raft system, which is one of the gastroretentive drug delivery systems. Accordingly, most of the recent research papers were cited from PubMed, Research Gate, and Google Scholar. These research papers were selected based on their relevancy, reliability, publication year, published journal, the applicability of the research work, and the ease of accessibility to the paper itself. Besides the research studies, the comparative studies are valuable and so discussed carefully. Patents that have been registered due to the promising application of the raft system are stated. While other gastroretentive drug delivery systems were considered and mentioned briefly.

A long time ago, oral dosage forms were the most convenient and preferable route of administration for all categories of patients. Because of its ease of administration, safety, non-invasive, and low-cost manufacturing process [1, 2]. Although being usually the safest and most commonly used. However, it is never free from problems like low gastric residence time (GRT), small gastrointestinal transit time, unpredictable gastric emptying rate, and the presence of a narrow absorption window in the upper small intestine for some drugs [3]. In addition, Oral conventional dosage forms were showing some limitations such as high risk and incidence of side effects especially those related to GIT and high dose-dumping risk also they were of low use with colon degrading drugs and poorly soluble drugs in alkaline pH [4].

Countless studies have been engrossed to search the ways of potent drug delivery through our stomach so that drugs can have prolonged time in the stomach and exert therapeutically effective treatment with low side effects and dosing frequency and minimizing the fluctuation in plasma drug concentrations [5]. One of these techniques was gastro retentive drug delivery systems (GRDDS).

GRDDS perfectly increases the drugs' gastric retention time so that their bioavailability increases [6]. They can be successfully employed to dump all the difficulties associated with drugs that are rapidly degraded in the intestine or drugs that need particular absorption from the stomach (Albuterol) [7], those that have low solubility and poor absorption due to improper gastrointestinal transit time [8].

GRDDS assigns a lot of advantages and strikes conventional dosage forms for several reasons. First of all, it improves the bioavailability of drugs that can't be properly absorbed from the upper GIT tract. As well, it can boost patient compliance by minimizing dosing frequency [9]. Also, GRDDS can minimize the alteration in drug plasma level concentrations to improve the bioavailability of the drugs [10]. Furthermore, the targeted drug delivery, especially in the upper part of GIT for antacids that treat this part, is successfully prosperous [11]. Last but not least, the controlled release of the drugs gives better safety margins for the highly potent drugs [12].

However, GRDDS are not the ideal delivery systems for some candidates, including acidic drugs that are unable to dissolve in gastric acidic medium, and drugs that can cause irritation or gastric lesions in the mucosa, along with drugs that are selectively absorbed in the colon as corticosteroids, in addition, drugs that can be absorbed from numerous sites in the GIT that may lead to some of the undesired effects and serious side effects [6, 12, 13].

Other concerns regarding GRDDS were related to formula size that will accordingly affect gastric emptying [14]. In addition, the shape of the formula has a remarkable role in achieving gastric retention. Tetrahedron and ring-shaped ones have shown better residence time [15]. Furthermore, the one unit formulations may have some challenges like sticking together or being obstructed in the GIT which may have a powerful chance to produce irritation [15] and will be unreliable and irreproducible in prolonging residence time in the stomach when administered orally. That's why multiple unit formulations have been evolved with a better opportunity to shorten the absorption inter-subject variability and decrease the possibility of dose dumping [16]. A lightly fed stomach proved to be better for enhancing residence time, on the other side fasted stomach is somehow a challenge. It was demonstrated that gastroretentive tablets are physiologically considered as undigested food so they can't pass into the small intestine and show higher retention time with better drug delivery [13, 15]. Eventually, GRDDS should deal with all the present obstacles physically or physiologically and maintain its solidarity to run on [17].

There are multiple current GRDDS applications, including

- **Floating drug delivery systems (low density)**

These systems are characterized by having a density lower than gastric fluids (≈ 1.004 g/cm^3); with this lower density, they kept floating in the stomach without affecting the gastric emptying rate so kept buoyant in the stomach for a prolonged period, through the drug is released slowly and increasing GRT [18–20]. Floating systems are divided into effervescent and non-effervescent systems. Non-effervescent systems are turned out by putting the drug with highly swellable cellulose derivatives or gel-forming polymers are used [21, 22]. While as, in effervescent one's agents such as sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid are used in combination with hydrophilic polymers [23, 24]. So that when they touch the gastric fluid, CO_2 is liberated and entrapped in a hydro-colloid matrix, thus influencing drug release [25, 26].

- **Non-floating systems (high density)**

High-density systems possess a density greater than the density of gastric fluids so that they will be kept in the rugae of the stomach and accordingly oppose its peristaltic movements [27]. When the density is closer to 2.5 g/ml, there will be a noticeable prolongation of GRT, which can be gained by the use of excipients like barium sulfate, zinc oxide, iron powder, titanium dioxide, etc. On varying these system's density, the gastro-intestinal transit time can be extended from an average of 5.8 to 25 h [6].

- **Mucoadhesive/Bio-adhesive systems**

Mucoadhesion is described as the interaction that occurs between the polymer formula and the mucus layer. While bio-adhesion is known as adhesion of dosage form to mucus and/or mucosal surface [28]. There are natural or synthetic bioadhesive agents that enable the formula to attach to the intestinal mucosa and results in an interaction between them [29]. Bioadhesive agents like carbopol, chitosan, lectins, and others are usually incorporated in these systems [30]. These polymers allow a sort of prolongation in the drug resistance time at the application site that will lead to better absorption of the drug [31].

- **Swelling/Expandable systems**

As obvious, after ingestion, these systems enlarges by taking in the gastric fluid so that they block the pyloric sphincter then they could release the drug in a controlled manner with a prolonged presence in the stomach [32]. Some hydrophilic polymers can be used as hydroxypropyl methylcellulose (HPMC), polyethylene oxide, and carbopol; these polymers build physicochemical crosslinks network which will enable extensive swelling of the polymer [33]. Although, expandable systems may tend to cause bowel obstruction, intestinal adhesion, and gastropathy. They also have some restrictions and difficulties in storing easily hydrolyzable and biodegradable polymers that are hard to manufacture and may not be cost-effective with complications in maintaining the structural integrity [32, 34, 35].

- **Magnetic systems**

These systems are characterized by the presence of the drug, excipients, and a minute amount of an intramural magnet, with the availability of an extramural magnet placed on the stomach. This extramural magnet is capable of directing the location of the formula containing the internal magnet [36]. Both the magnetic field strength of the extramural magnet and its position may influence the GRT [37]. If the position of the extramural magnet wasn't accurately specified, the desired outcomes won't be satisfied [6]. Thus, the appropriate use of these systems will be doubtful.

- **Super-porous hydrogel systems**

Super-porous hydrogel systems are described as one category of water-absorbent polymer systems. These systems consist of countless unlocked interconnected pores with an average pore size greater than 100 µm [38]. Consequently, they swell rapidly due to water uptake by capillary wetting and reaching an equilibrium size. Thus, such systems acquire enough mechanical strength to withstand the pressure of gastric contraction and increase GRT [39]. This approach has gained wide approval in the controlled-release formulation due to its high mechanical strength and elastic properties [40].

However, the swelling capability of these systems may be affected by the change in pH and may have low mechanical strength of the structure. Examples of highly swellable polymers are croscarmellose sodium and sodium alginate [41].

- **Ion-exchange resin systems**

These systems consist of a lipid-soluble cross-linked polymer that may be cationic or anionic. They are designed to increase GRT, especially for low bioavailable drugs. They are developed by mixing drug and ion exchange resin in a polymeric matrix in addition to other compatible excipients [42].

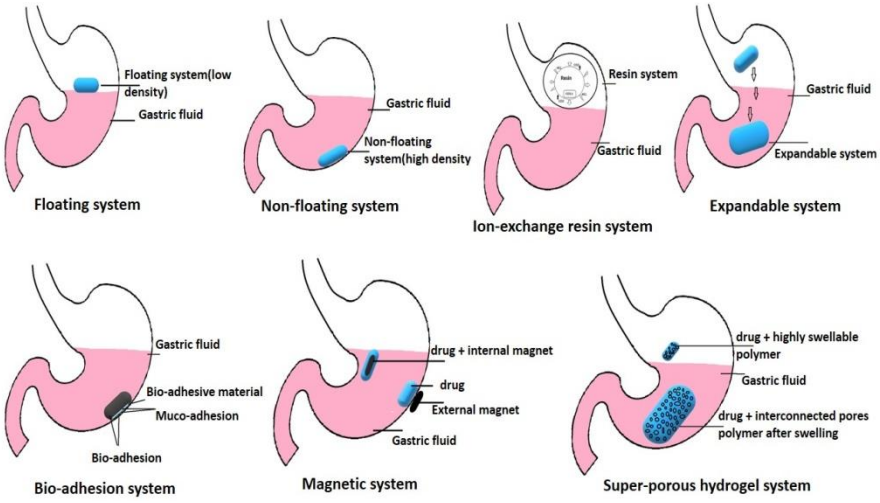

Fig. 1: Illustrates the concept of different GRDDS applications [43] (Panda *et al.* 2019)

- **Raft-forming systems**

Raft-forming systems are mostly made up of in-situ gel-forming polymer (as alginate salts, gellan gum, pectin, chitosan, and others) and a gas-forming agent (carbonates or bicarbonates). They are designed to be hydrogels at 25°C and then are transformed to gelatin when coming in contact with body fluids or with some changes in pH (fig. 2) [44]. The theory is to act as a blockade between the

esophagus and stomach, thus preventing the reflux of gastric contents into the esophagus. They swell and form a viscous cohesive gel leading to the formation of a continuous layer known as a raft [27, 36, 45]. This gel is lighter than stomach fluids, allowing it to stay on the surface and over the stomach contents or even adheres to the gastric mucosa because of the bioadhesive nature of the polymers used [46]. This consequently leads to increasing residence time due to the presence of the gel-forming agent [47]. They have a low bulk density which allows them to release the drug molecule in a sustained way with relatively constant plasma profiles. Besides, the gels formed in situ remained intact for more than 48 h easing the sustained release of drugs [48]. As a result, they remain buoyant in the stomach with no change in the gastric emptying rate for a prolonged period [49].

The design of the system depends on the diseased status, the patient population, and the physicochemical properties of the drug molecule such as molecular weight and lipophilicity. Some anatomical and physiological factor includes membrane transport and pH of tissue fluid. Besides, formulation factors include pH, gelation temperature, viscosity, osmolality, and spreadability [50].

Many obstacles are facing the raft system to accomplish the required retention time of the dosage that is needed to be faced and solved, including:

- The capability of the drug to be slowly released from the formulation.
- The ability of the formulation to resist the force from peristaltic movement in the stomach.
- Systems should maintain specific gravity smaller than gastric contents (1.004–1.01 g/cm^3).
- Prolongation availability of the formulation in the stomach.
- Feasible removal of the system from the stomach.

Ingredients used in the preparation of this system are a gel-forming agent and alkaline bicarbonates or carbonates, which influence the formation of a low dense system that floats on the gastric fluids [51]. Regarding suitable drugs, they should be cautiously selected to be locally active in the stomach [52], have a narrow absorption window [10, 52], drugs that can be absorbed from the upper part of GIT, drugs that degrade in the colon, and drugs that show weak solubility at high pH [52, 53]. The Raft system perfectly fits acid-soluble drugs that are poorly soluble or unstable in intestinal fluids [46].

Numerous polymers are used in the development of raft systems. Different polymers, either natural or synthetic, are available in an important manner [54]. These features comprise firstly being biocompatible, secondly possessing pseudoplastic behavior, and finally should have the ability to increase the viscosity with the increase in shear rate [36]. Natural polymers are such as alginic acid, guar gum, gellan gum, xyloglucan, pectin, chitosan, etc. while synthetic polymers are such as poly(DL lactic acid), poly(DL-lactide-co-glycolide) and poly-caprolactone, HPMC, etc. [55, 56].

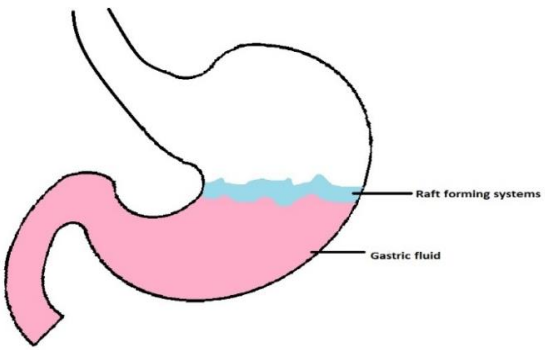

Fig. 2: Raft system approach [57] (Bhavsar 2012)

Raft-systems are the superiors in the controlled release systems due to their favorable traits. They improve the drug release and its' bioavailability; they have a low-density viscous layer on gastric contents and hence provide a more effective surface area. Additionally, they provide uniform drug delivery. Improving both the efficacy and the sustained release manner of the drug. Their floating capabilities are advanced over the other floating systems. Also, patient compliance is strongly ameliorated; as there is a reduction in the dose frequency and ease of administration. As well they possess a simple manufacturing process [36, 44]**.** However, there are also some limitations of the raft systems; they are easily susceptible to microbial or chemical degradation. Careful storage requirements are needed to avoid its' stability problems. Subjection to different radiations like UV, Visible, electromagnetic waves, or others, can cause the formation of the gel within the package and hence render the formula damaged. The mechanical strength is n't strong enough to withhold the migrating motor effect and can be easily disrupted [45, 58]. Finally, raft systems can't be used for drugs that possess low acid solubility, drugs that are unstable in gastric media, and drugs used for selective release in the colon [36]**.**

Strategies used to formulate raft-forming system

i. Physical based raft system

These systems formed on a physical basis are divided into two mechanisms. The first one is swelling, in which the polymer absorbs water and then swells, forming the gel [59]. So, the formation of the gel occurs when the liquid effervescent structure touches the gastric fluid. Also, in situ formation of gel takes place when materials absorb water from the surrounding environment and expand at the desired site of action [55]. Glycerol mono-oleate is a polar lipid that swells to form lyotropic liquid crystalline phase structures. It is a biodegradable lipid that can be degenerated *in vivo* by enzymatic action and has some bioadhesive properties [60]. The second one is diffusion, where the solvent is diffused from the polymer solution to the nearby tissues, resulting in the consolidation of the polymer matrix [36].

ii. Chemical-based raft system

Various polysaccharides undergo a phase transition in the presence of countless ions. This chemical mechanism is known as ionic cross-linking. For instance, polysaccharides that belong to fall into the class of ion-sensitive ones that are most widely used [61]. Ion-sensitive polysaccharides such as gellan gum, pectin, and sodium alginate undergo a phase transition in the presence of various ions such as k+, Ca+, Mg+, and Na+. Other polysaccharides undergo gelation in the presence of various monovalent, divalent cations such as alginic acid and low-methoxy pectin. Also, gellan gum is an anionic polysaccharide that undergoes in situ gelling in the presence of mono-and divalent cations [46, 62].

iii. Physiological stimuli-based raft system

Firstly, there is a pH-sensitive gelling where gel-forming takes place according to the medium ph. There are a lot of pH-dependent polymers that are capable of composing in situ gel in the system. Poly (acrylic acid) (Carbopol®, carbomer) or its derivatives, polyvinyl acetal diethyl amino acetate, mixtures of poly (methacrylic acid) and poly (ethylene glycol), could show change from sol to gel with the change of ph. Polymers sensitive to can be neutral or ionic. The anionic networks contain negatively charged moieties, cationic networks contain positively charged moieties, and neutral networks contain both positive and negatively charged moieties [36].

Secondly, systems exhibited temperature-sensitive gelling. This type utilized hydrogels that are liquid at room temperature (20 °C–25 °C) and undergo gelation when in contact with body fluids (35 °C–37 °C), as the temperature elevates. These hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. Polymers such as Pluronic, polymer networks of poly (acrylic acid), and polyacrylamide or poly(acrylamide-co-butyl methacrylate) are commonly used for temperature-sensitive hydrogels formation [63]. Polymer networks of poly(acrylic acid) and polyacrylamide or poly(acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling [64].

Table 1: Different raft system applications in GRDDS

No.	Drug	Excipients	Raft system principle	Reference
1.	Antacid formulations (ALMAGATE FLOT-COAT)	Pepsin, HCL, magnesium oxide, and aluminum hydroxide	A comparative study between classical antacid products and a new formulation (almagate float-coat). The results obtained showed that the new formulation has a high antacid potency together with a prolonged *in vitro* GRT with safe and extended delivery of the antacid drug.	[65]
2.	Gaviscon Liquid and Gaviscon Double Action Liquid	liquid alginate/antacid products	Another comparison study of gastro esophageal reflux disease treatments that contains alginate as the principal active agent and those containing alginate in combination with a significant amount of antacid. There was a minor increase in raft resilience were observed for the new Gaviscon Double Action Liquid compared with Gaviscon Liquid; these were not large enough to be reflected in increased gastric retention in human volunteers. The *in vitro* studies showed that raft strength and raft resilience are both related to the dose of alginate given and that changes in both calcium carbonate content and sodium bicarbonate content also affect the performance.	[66]
3.	Curcumin	Eudragit® EPO, sodium alginate, calcium carbonate and sodium bicarbonate	The formulations were successfully prepared composed of Eudragit® EPO, sodium alginate, and calcium carbonate with the drug. The solubility of curcumin was increased. All tested formulations had a sustained floatability with a 60-85% release of curcumin within 8 h.	[67]
4.	Glycoside-rich extract powder	Eudragit® EPO, sodium alginate, Sodium bicarbonate calcium carbonate, HPMC, and carboxymethylcellulose sodium	Solid dispersions were prepared using the solvent evaporation technique containing Glycoside-rich extract and Eudragit® EPO. The system was prepared to comprise sodium bicarbonate, sodium alginate, HPMC K100, and insoluble calcium carbonate followed by glycoside-rich extract and Eudragit powder. The aqueous solubility and dissolution rate of the glycosides present in the solid dispersion was improved due to their conversion to the amorphous form. The raft-forming systems floated within 30 sec and gradually released more than 80% of the glycosides content over 8 h.	[68]
5.	Mebeverine HCl	HPMC K100M, HPMC K15M, Compritol® 888, Precirol®, sodium alginate, sodium citrate, sodium bicarbonate, calcium carbonate, talc, and magnesium stearate	The raft formulations were liquid solutions of alginate containing calcium carbonate as an effervescent agent with the incorporation of different concentrations of HPMC K100M, Compritol® 888, and Precirol®. The study has demonstrated the suitability of using hydrophilic polymers with lipid polymer to sustain drug release. The optimum formulations were able to control the drugs with a higher relative bioavailability of the drug than the reference one. Also, the raft floating system showed a higher concentration and extent of drug absorption *in vivo*.	[69]
6.	Pantoprazole sodium sesquihydrate	Sodium alginate, pectin, HPMC K100M, HPMC E5, citric acid, calcium carbonate, and acetonitrile	The wet granulation method was used for the preparation of granules. The raft was allowed to form in the region of an L-shaped wire probe held straight in the beaker right through the entire phase of raft development. Raft strength was anticipated using the modified balance method. Water was added drop wise to the pan and the weight of water necessary to break the raft was recorded. The presence of alginate and pectin affected the entrapment of the acid within the gel and had an impact on the strength and integrity of the raft. The optimum formulation showed the greatest percentage of alginate and pectin within the alginate-pectin raft. With a controlled release of the drug up to 8 h study.	[70]
7.	Metronidazole	Sodium alginate, Compritol® 888, Precirol®, glyceryl monostearate, sodium citrate, and calcium carbonate.	The formulations were liquid solutions of sodium alginate and gellan gum, containing calcium carbonate and metronidazole dispersed in. Floating raft systems using ion-sensitive in situ gelling polymers such as sodium alginate and gellan gum were designed and evaluated, for their buoyancy, in situ gelation, and sustaining capacity for the release of metronidazole. Formulations also could achieve a reliable, sustained pattern for its release.	[58]
8.	Nizatidine	Sodium alginate, tragacanth, aspartame, citrus pectin, guar gum, xanthan gum, and PVP k30, precipitated calcium carbonate, sodium bicarbonate, menthol, mannitol, talc, and magnesium stearate.	Nizatidine raft forming tablet formulation was successfully prepared using sodium alginate as a raft forming polymer and calcium carbonate. Maximum strength, acid neutralization capacity, and drug release were achieved. X-ray for the most stable optimized tablets showed that raft tablet floated immediately after ingestion and remained intact for approximately 3 h preventing reflux disorders associated with peptic ulcers.	[71]
9.	Gaviscon and anti-reflux agents	Alginate, sodium or potassium bicarbonate;	Both *in vitro* and clinical studies show that after ingestion of either tablets or liquid formulations, an alginate gel or raft forms from the reaction of gastric acid with alginate and sodium bicarbonate and floats on the gastric contents. The alginate raft acts as a barrier to acid and food reflux and has been shown to move into the esophagus during reflux.	[72]
10.	Ambroxol	Calcium carbonate, Carrageenans, and sodium alginate.	This complex can be prepared by kneading and co-precipitation methods. The modified drug release is characterized by being biphasic, with an initial burst release followed by a sustained release phase. Consequently, the suspensions can be optimized as a function of these parameters for minimal burst release and slow-release performance.	[73]
11.	Ibandronate	Citrus pectin, PEG 400, carboxymethyl cellulose,	The system was successfully prepared using citrus pectin and showed effective and porous raft formation. These newly prepared tablets rapidly	[74]

No.	Drug	Excipients	Raft system principle	Reference
		acetonitrile, sodium chloride, calcium carbonate, citric acid, sodium bicarbonate, and pectin-esterase.	dispersed in the simulated gastric fluid rapidly released the drug. This dosage form effectively neutralizes the acidity of the stomach and maintains the pH of the stomach above 3.5 to prevent the reflux of the drug into the esophagus. The bioavailability of the newly developed formula was greater than the already marketed formulation.	
12.	Bupropion	Apple pectin, sodium alginate, compritol®, precirol®, sodium Citrate, calcium carbonate, and sucralose	The optimized raft system containing bupropion as a liquid oral controlled drug delivery system with alginate as gel-forming polymer, precirol® as glyceride lipid, and calcium carbonate were successfully prepared. This optimal formulation showed excellent viscosity behavior that will allow sol-gel transformation in the stomach with the minimum floating lag time and could control the BUP release rate for more than 12 h. Also, *In vivo* pharmacokinetic study stated that the optimal floating system and the marketed reference tablets have comparative relative bioavailability of bupropion.	[44]
13.	Gabapentin	Eudragit NE 30D, Kelcogel CG-LA (gellan gum), LM-101 pectin, glyceryl monooleate, calcium chloride, sodium citrate dihydrate, and potassium dihydrogen orthophosphate	Gabapentin was successfully incorporated in an optimized floating raft forming system. The drug was primarily coated by Eudragit NE 30D, then incorporated into the system. The floating system had an optimum viscosity that will allow easy swallowing as a liquid dosage form, which then undergoes a rapid sol-gel transition and floating due to ionic interaction. Enhanced controlled release profiles for more than 12 h were maintained. The pharmacokinetic study revealed a significant increase in C_{max}; the relative bioavailability was found to increase by 1.7-fold when compared to immediate-release Neurontin oral solution.	[45]

Accomplishments of raft system in gastro-retention drug delivery systems

Since 1994, the raft system has been used to increase GRT of an antacid formula where Fabregas *et al.* [65] justified the floating antacid system. The authors used sodium alginate as a polymer forming gel, and sodium bicarbonate and acid neutralizer as gas- generating agents. Consequently, CO_2 gas is liberated, lowering the system bulk density, and the raft floats on the gastric fluid. The results showed that the prepared raft antacid pharmaceutical formulation does indeed possess high antacid potency along with a prolonged *in vitro* GRT with safe and extended delivery of an antacid drug [65].

Another antacid formulation was discussed by Frank C. *et al.* [66]. Alginate/antacid that has been used in the treatment of gastroesophageal reflux disease was the ideal candidate. The formulation chosen for development contained calcium carbonate and sodium bicarbonate with a minimal dose of Gaviscon (low-acid-neutralizing capacity). The system formed showed higher effectiveness regarding the raft gel strength and resilience compared with the other medications tested. However, there was no obvious change in GRT [66].

In 2015, another study was conducted on curcumin using Eudragit for gastric ulcer treatment. The aim of the study conducted by Nattha *et al.* [67] was to prolong the GRT and have a controlled release of curcumin to treat gastric ulcers. The system prepared is composed of Eudragit® EPO, sodium alginate used as a gelling polymer, and calcium carbonate for liberating Ca^{++}ions and CO_2 to stabilize the floating properties. All tested formulations formed a gelled raft in 1 min and sustained floatability with a 60-85% release of curcumin within 8 h. The curcumin prepared systems showed a flawless curative effect on the gastric ulcer regarding the ulcer index and healing index over the basic antisecretory agents [67].

Saowanee *et al.* conducted a second study comprising both Eudragit® EPO and the raft was used to acquire a prolonged sustained delivery of glycosides, asiaticoside, and madecassoside in the stomach, improving gastric ulcer treatment [68]. The optimized formulation was composed of alginate, HPMC K-100, Eudragit® EPO, and calcium carbonate as a calcium source and carbon dioxide producer. The formulation allocated good properties as sufficient strength, rapid floating behavior, and sustained release of both drugs over 8 h. *In vivo* results in rats showed better curative efficacy as well as a reduction in ulcer severity than standard antiulcer drugs [68].

Nabarawi *et al.* developed a controlled release floating raft system of mebeverine hydrochloride and evaluated their floating behavior and *in vitro* controlled-release using different excipients [69]. The formulations prepared contained liquid sols of alginate with calcium carbonate as an effervescent agent. Different concentrations of HPMC K100M, Compritol®, and Precirol® were incorporated into alginate-based formulations to retard the drug release rate. The optimized formula showed excellent floating lag time and a total floating time of more than 12 h, promoting the sustained release of the drug. *In vivo* results showed higher C_{max} with 3 h. T_{max} and higher oral bioavailability compared to the marketed drug [69].

Pantoprazole sodium sesquihydrate is extensively used in the management of gastroesophageal reflux disorders and peptic ulcer diseases. The authors were able to design a successful system using alginate and pectin with the drug and other excipients [70]. The presence of alginate and pectin affects the strength and integrity of the raft and also allows it to entrap antacid within the gel. The hydroxyl groups of sodium alginate and pectin promote the swelling of the system. Also, HPMC K100M forms viscous gel-like properties around the raft and sustained the release of the drug. The *in vitro* release studies of the best formula showed controlled release of the drug up to 8 h with an observable increase in bioavailability of the drug up to 103.5 %. Stability studies showed that the system prepared was stable in accelerated environmental conditions and DSC studies showed the thermal stability of polymers and drugs [70].

Helicobacter pylori infection is one of the common GIT problems. This study was aimed to use metronidazole in the form of raft formulation to treat the above-mentioned infection. The authors [58] proved the applicability of increasing GRT and the release rate of metronidazole using ion-sensitive in situ gel-forming polymers. Prepared formulations containing sodium alginate and gellan gum with sodium citrate and calcium carbonate. In addition to lipids such as glyceryl monostearate, Compritol®, and Precirol®. Buoyancy, gelation capacity, and viscosity parameters were evaluated. Drug release and kinetics were examined [58].

Raft-forming chewable tablet was a further study conducted by Manal *et al.* [71]. Chewable tablets were prepared using Sodium alginate as the raft forming agent, along with calcium carbonate as an antacid and strengthening agent, and sodium bicarbonate as a gas generating agent. X-Ray scanning showed that the entity floated the following ingestion instantly and remained intact for approximately 3 h while a raft is created on stomach content. That results in instant relief of acid-burning symptoms with enhanced bioavailability [71].

Jorgen *et al.* [72] explained an antacid raft forming a floating system. He used a gel-forming agent, which is sodium alginate, along with sodium bicarbonate and acid neutralizer. A foaming sodium alginate gel is formed upon touching the gastric fluids. So that, when floating on the gastric fluids, avoids the reflux of the gastric contents into the esophagus [72].

Different drug class was used in this research. Ahmad Bani-Jaber *et al.* [73] applied raft system formation on ambroxol that is used to treat respiratory disorders The aim was to develop sustained release of the drug through raft-forming formulations. The authors used calcium-alginate ions for the formation of the system. A biphasic release was accomplished with an initial burst release followed by sustained release. The system was formulated as suspensions in the aqueous vehicle of sodium alginate and calcium carbonate. Compared to Gaviscon liquid, the optimum suspensions formed rafts of similar strength and higher resilience [73].

Ibandronate is a drug used to treat osteoporosis with low bioavailability and irritation capability to the esophagus and stomach. By the ability to form a raft in the stomach, oral bioavailability will be improved. Plus, the induced irritation of the esophagus and stomach is stopped by the formed raft. Citrus pectin was used to accomplish the rapid release of the drug. Along with polymers and the drug, the formulations were prepared. The systems have been successfully prepared from citrus pectin and have shown effective porous formation [74].

Neural treating drugs were applied to raft systems with some remarkable results. They may play significant regulatory roles in synaptic transmission, action potential propagation, and membrane signaling to the nucleus that may improve their bioavailability. Teaima *et al.* were able to formulate bupropion, an antidepressant drug, into the floating system using in-situ gelling pectin and alginate [44]. Bupropion shows high water solubility but with frequent dosing, so possess poor patient compliance. The ideal raft-forming system consists of alginate, Pr, and $CaCO_3$. The authors were able to formulate a system with excellent viscosity that will permit a rapid sol-gel transformation in the stomach, excellent floating behavior, and a controlled release profile with a comparable bioavailability. The optimal raft-forming system improved patient compliance and allowed to control bupropion rate release, especially for depression associated with eating disorders or dysphagia [44].

Furthermore, gabapentin, an anti-neuropathic agent, has a short half-life (5–7 h) and has a narrow absorption window, with poor compliance and poor. In this study, conducted by Samar *et al.* [45], raft forming systems were investigated to prolong the GRT of Gabapentin. Firstly, the drug was coated by Eudragit NE. The coated drug was then incorporated into the system. This floating system had an optimum viscosity that will allow easy swallowing as a liquid dosage form, which then undergoes a rapid sol-gel transition and floating due to ionic interaction. The pharmacokinetic study revealed a significant increase in C_{max} and the relative bioavailability was found to increase by 1.7-fold when compared to immediate-release [45].

Patents on raft forming systems

There were some patents registered on raft forming systems. The first one is US 01199941 in 2001, with a gastric composition. This system involves the formation of a floating raft that releases the drug in a controlled and reproducible manner. The second one is US 0063980 in, within situ gel formation of pectin. This system involves in situ formation of the floating raft when the formulation comes in contact with gastric fluids [6].

Future perspectives

There has been enormous advancement in controlled drug delivery systems in the past decades. Nevertheless, there is still scope for advancement to combat the limitations and expand future possibilities. Raft systems exhibit a wide variety of advantages and controlled release properties, which can be used to achieve the desired dosage form characteristics and release rate for different treatment duration and administration routes. Raft systems dosage forms are well-tailored toward therapies where high adherence to a consistent dose over a long duration is inconvenient and hard.

Owing to their ability to increase the efficiency of drugs and keep steadier levels of the drug in the bloodstream, raft systems can be used in corporations with strong sedatives, pain killers, and other critical drugs for the treatment of serious diseases like cancer and provide enhancement in the patient convenience, reducing their pain with a one-dose for 24h. Studies can be conducted to minimize the limitations and search for solutions to have a substantive type of GRDDS with advantages and applicable uses.

Table 2: *In vitro* evaluation parameters of raft system

Test name	Description	References
1. Texture analysis	This test is held to determine the consistency and cohesiveness of the formulation prepared. The test mainly specifies the ability of the formulation sol to be successfully injected using a syringe with an appropriate needle. The adhesiveness of gels is needed to be high to maintain intimate contact with surfaces like tissues.	[75, 76]
2. Sol-gel transition and gelling time	The sol-gel transition temperature is the temperature at which the phase transition of sol meniscus is first noted when kept in a tube at a particular temperature and then heated at a certain rate. While gel formation is denoted by an absence of movement of the meniscus on tipping the tube. And gelling time is the time for the first appearance of gelation.	[64]
3. Floating/buoyancy test	It is tested to measure the time taken by the dosage form to float on the top of the dissolution medium, following it is placed in the medium. Both the time between the introduction of the dosage form and its buoyancy on the simulated gastric fluid (Floating lag Time) and the time during which the dosage form remains buoyant were measured (known as floating time).	[77, 78]
4. Gel strength	This test is used to test the gelling property of the prepared formulation. This property can be evaluated using a rheometer, where a specified amount of gel is prepared in a beaker, from the sol form. A gel containing beaker is raised at a certain rate, then pushing a probe of rheometer slowly through the gel. The changes in the load on the probe can be measured as a function of the depth of immersion of the probe below the gel surface.	[79]
5. Viscosity and rheology	The viscosity and rheological properties of the polymeric formulations, either in solution or in a gel made with artificial tissue fluid, were determined with a different viscometer. The viscosity can be determined with a Brookfield rheometer or some other type of viscometer such as Ostwald's viscometer. The viscosity of formulations should be such that no difficulties are appeared during their administration by the patient.	[79, 80]
6. Drug–excipient interaction study	This test is performed to study the compatibility of ingredients by using Fourier transform infrared spectroscopy. During the gelation process, the nature of interacting forces can be evaluated using this technique. As well, Differential scanning calorimetry can also be used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.	[81]
7. *In vitro* release studies	The *in vitro* drug release of the raft forming system is carried in 0.1 N HCl from 0 to 8 h by USP type-II apparatus at 50 rpm. The dissolution medium used is 900 ml of simulated gastric fluid (0.1N HCl, pH 1.2) and the temperature is maintained at 37±0.2 °C. At each time interval, a precisely measured sample of the dissolution medium is pipette out and replenished with a fresh medium. Drug concentration in the aliquot can be determined by spectrophotometrically.	[36, 44]

Table 3: *In vivo* evaluation parameters of the raft-forming system

Test name	Description	References
1. Radiology and scintigraphy	It includes the use of radio-opaque markers. X-ray/Gamma Scintigraphy helps to locate dosage form in the GIT, thus can predict the gastric emptying time and the passage of dosage form in the GIT. A radio-opaque marker that is widely used is Barium sulfate. The inclusion of it into a solid dosage form enables it to be visualized by X-rays at different intervals to determine gastric retention. Similarly, the inclusion of γ-emission of radionuclide in a formulation allows indirect external observation using a scintiscanner. In which, the γ-rays emitted by the radionuclide are focused on a camera and enable the monitoring of the dosage form located in the GIT. 99Tc is widely used as the emitting material.	[82, 83]
2. Gastroscopy	Gastroscopy is per-oral endoscopy used with fiber optics or video systems. It is used to inspect visually the effect of dosage form for prolongation in the stomach. It can also give a detailed evaluation of the gastroretentive drug delivery system.	[84]
3. Magnetic marker monitoring	The dosage form is magnetically marked with the presence of iron powder inside the dosage form. The image of the dosage form can be taken by very sensitive bio-magnetic measurement equipment. This technique is less hazardous and has no radiation.	[36, 84]
4. ^{13}C octanoic acid breath test.	A system comprising 13C octanoic acid and the gastroretentive drug delivery system is introduced in the stomach where a chemical reaction occurs and octanoic acid liberates CO_2 gas, which comes out in a breath. The important carbon atom which will come in CO_2 is replaced with 13C isotope. So, the time up to which $13CO_2$ gas is observed in breath can be considered as the gastric retention time of the dosage form. As the dosage form moves to the intestine, there is no reaction and no CO_2 release.	[84]

CONCLUSION

With all the previously mentioned, the raft system has approved its applicability and potentiality in designing promising controlled release of various drugs. The ease of preparation, the availability of most of the excipients used in forming the system, the numerous numbers of advantages with minor limitations, and the simplicity and average cost of *in vitro* and *in vi vo* tests. Furthermore, the stated research work and the patents registered proved the suitability and accuracy of the raft in gradual drug release and constant plasma levels. Exceptional improved bioavailability and reduction in side effects provide raft the superiority over the further gastro retentive drug delivery systems. With the impressive depth and scale of recent work is focused on a raft, the future result of this system is rapidly expanding. Although there is perfection in preparation and the drug loading of the system is now well-established, chances still exist to pull such details to maximize dose loading and overcome the few limitations facing it. With the recent signing up of the raft patents, increased uptake of the raft in the industry is predictable, and continuous efforts to introduce it into another available gastroretentive system will allow remarkable achievements.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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