Trends in floating drug delivery systems

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Among novel drug delivery systems, rate controlled oral drug delivery system forms an important area. Research is directed towards overcoming physiological problems, such as short gastric residence times (GRT) and unpredictable gastric emptying times. Prolonged GRT may widen the stomach potential as a drug-absorbing organ. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. Narrow absorption window drugs compounded in such systems have improved \textit{in vivo} absorption properties. These findings are an important step towards the implementation of FDDS in the clinical setting. In this review, the current technological developments of FDDS including patented delivery systems and marketed products have been discussed. In addition, the pharmaceutical basis of their design, their advantages and future potential for oral controlled drug delivery are discussed.

\textbf{Keywords}: Drug delivery systems, Gastric residence times (GRT), Floating drug delivery system (FDDS)

\textbf{IPC Code}: F16K17/26

\section*{Introduction}

One requisite for successful performance of oral controlled release drug delivery system is that drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion. Oral controlled release dosage forms are not suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT (stomach and small intestine). This is due to the relatively short transit time of the DF (dosage form) in these anatomical segments. Thus after only a short period of less than 6 h, the CR-DF (controlled release DF) has already left the upper GIT and the drug is released in short, non absorbing distal segment of the GIT. This results in a short absorption phase, which is then accompanied by lesser bioavailability.

Pharmaceutical DF with gastro retentive properties would enable an extended absorption phase of these drugs with narrow absorption window. After oral administration, DF would be retained in stomach and release drug there, in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in upper GIT. Another interesting importance for the DF with prolonged residence time in the stomach is: 1) Drugs are locally active in the stomach e.g. drugs used in the eradication of \textit{Helicobacter pylori}, which is now believed to be the causative bacterium for chronic gastritis and peptic ulcer e.g. tetracycline\textsuperscript{2}; 2) Drugs are unstable in the intestinal or colonic environment e.g. ranitidine\textsuperscript{3}; and 3) Drugs have a low solubility at high pH values e.g. verapamil\textsuperscript{4}. Approaches to increase the gastric residence time of drug formulation includes\textsuperscript{5}: i) Floating drug delivery systems (FDDS); ii) High density drug formulation that retained in the bottom of the stomach; iii) Bioadhesive devices; iv) System that rapidly increase in size upon swallowing either by expansion or by unfolding; and v) Slowed mobility of the gastro intestinal tract by concomitant administration of drugs (propantheline).

The current review deals with the FDDS (Tables 1&2) that is one of the most leading methodologies in gastroretentive drug formulations.

\section*{Noneffervescent FDDS}

The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the floating formulations is a gel-forming hydrocolloid in a capsule, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity.

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within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. When such DF comes in contact with an aqueous medium, the hydrocolloid starts to hydrate by forming a gel, which controls the rate of diffusion of solvent-in and drug-out of the DF. As the exterior surface of the DF goes into solution, the immediate adjacent hydrocolloid layer becoming hydrated maintains the gel layer. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a receding boundary within a gel structure. When capsule containing a mixture of a drug and hydrocolloids come in contact with gastric fluid, the capsule shell dissolves; the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time (Fig. 1).

G D Searle and Co. described a bilayer buoyant dosage form consisting of bilayer formulation. One layer was a drug release layer containing misoprostol and other was a buoyant or floating layer. Each layer included a hydrocolloid gelling agent such as hydroxypropylmethylcellulose (HPMC), gums, polysaccharides and gelatin, which upon contact with gastric fluid formed a gelatinous mass, sufficient for cohesively binding the drug release layer and floating layer. DF shown to be buoyant in gastric fluid for a period up to about 13 h, whereby a substantial amount of drug is released in the stomach.

Desai & Bolton developed CR floating tablets of theophylline using agar and light mineral oil. Tablets were made by dispersing a drug/oil mixture in a warm agar gel solution and pouring resultant mixture into tablet molds, which on cooling and air drying formed floatable CR tablets. The amount of agar needed to form floating tablet was remarkably low (2% per tablet). Light mineral oil was essential for the floating property of tablet since relatively high amounts of drug (75%) were used. Secondly, light

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**Table 1**—Potential drug candidates for FDDS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Amoxycillin trihydrate</td>
</tr>
<tr>
<td>Atenolol</td>
<td>p-nitroaniline</td>
</tr>
<tr>
<td>Captopril</td>
<td>Tramulast</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Chlorpheniramine maleate</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Piretanide</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Verapamil HCl</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Chloridiazepoxide HCl</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Metformin</td>
<td>Riseroton</td>
</tr>
<tr>
<td>Minocyclina</td>
<td>Tetracycline²</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Ranitidine Hydrochloride³</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Verapamil⁴</td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2**—Marketed products of FDDS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug (dose)</th>
<th>Company, Country</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar</td>
<td>Levodopa (100 mg), Benserazide (25 mg)</td>
<td>Roche Products, USA</td>
<td>Floating, CR capsule</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann-LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>Liquid Gaviscon</td>
<td>Al-hydroxide (95 mg), Mg carbonate (385 mg)</td>
<td>Glaxo Smith Kline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid alginate</td>
</tr>
<tr>
<td>Almagate FloatCoat</td>
<td>Al-Mg antacid</td>
<td>Ranbaxy, India</td>
<td>Floating liquid form</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulfate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>Cifran OD</td>
<td>Ciprofloxacin (1 g)</td>
<td>Pharmaacia, USA</td>
<td>Gas-generating floating form</td>
</tr>
<tr>
<td>Cytotec</td>
<td>Misoprostal (100 mcg/200 mcg)</td>
<td>Ranbaxy, India</td>
<td>Bilayer floating capsule</td>
</tr>
</tbody>
</table>
mineral in formulation prevents the escape of entrapped air due to its inherent hydrophobicity.

Dennis et al\textsuperscript{12} described a buoyant CR powder formulation, which may be either filled into capsules or compressed into tablets. The formulation consisted of a drug, a pH-dependent polymer, which was a water-soluble salt of alginic acid (such as sodium or potassium alginate), and a pH-independent hydrocolloid gelling agent (such as HPMC, methyl cellulose, HPC, or a mixture of two or more), and binder. The formulation was considered unique in the sense that it released the drug at a rate regardless of pH of the environment, being free of calcium ion and CO\textsubscript{2} producing material, and had drug release properties similar to a tablet of identical composition.

Mitra\textsuperscript{13} described a multilayered, flexible sheet-like medicament device that was buoyant in the gastric juice of the stomach and had SR characteristics. The device consisted of at least one dry, self-supporting carrier film made up of a water-insoluble polymer matrix having a drug dispersed or dissolved therein, and a barrier film overlaying the carrier film. The barrier film consisted of one water-insoluble and the other water- and drug-permeable polymer or copolymer. Both barrier and carrier films were sealed together along their periphery and in such a way as to entrap a plurality of small air pockets, which brought about the buoyancy of laminated films.

Thanoo et al\textsuperscript{14} developed drug-loaded polycarbonate microspheres using a solvent evaporation technique. A high drug loading (50\%) was achieved by this process. Kawashima et al\textsuperscript{15,16} prepared hollow microspheres (‘microballoons’) with a drug loaded in their outer shells by an emulsion-solvent diffusion method (Fig. 2). The ethanol/dichloromethane solution of a drug and an enteric acrylic polymer was poured into an aqueous solution of polyvinyl alcohol that was maintained at 40°C. The latter solution was constantly stirred while adding the former solution to form emulsion droplets. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug.

Harrigan\textsuperscript{17} described the intragastric floating drug delivery device, which comprised of a drug reservoir encapsulated in microporous compartment having pores along its top and bottom surfaces. Peripheral walls of drug reservoir compartment were completely sealed to prevent any physical contact of undissolved drug with the stomach walls. Floatation chamber caused the system to float in gastric fluid. Whitehead et al\textsuperscript{18} developed a multiple-unit floating dosage form from freeze-dried calcium alginate. Spherical beads (approx diam, ≈ 2.5 mm) were prepared by dropping a sodium alginate solution into aqueous calcium chloride. After internal gelation was complete, beads were separated from the solution and snap-frozen in liquid nitrogen before being freeze-dried at -40°C for 24 h. The results of resultant-weight measurements suggested that these beads maintained a positive floating force for over 12 h.

Krogel & Bodemeier\textsuperscript{19} developed a floating device consisting of two drug loaded HPMC matrix tablets, which were placed within an impermeable, hollow polypropylene cylinder (open at both ends). Each matrix tablet closed one of the cylinder’s ends so that an air filled space was created in between, providing a low total system density. The device remained floating until at least one of the tablets was dissolved.

Recent approach in FDDS is based on low-density foam powder based micro particles. This system is advantageous because of its zero to negligible lag time before starting of floatation. These floating microcapsules, prepared by emulsion solvent evaporation technique, contain polypropylene foam powder, polymers (Eudragit RS /ethyl cellulose / methacrylate polymer) and model drug (verapamil HCL). Drug release rate increases significantly with different type of polymers in following order: PMMA> EC > Eudragit RS.20. Another study on foam powder based microcapsules includes the effect of formulation and processing parameters on drug release using different matrix forming polymers e.g. HPMC; polyacrylates, Na-alginate, corn starch, carageenan, gum guar and gum arabic. The study indicated that the release rate can be modified by varying the matrix forming polymer /foam powder ratio, initial drug loading, tablet geometry (radius and height), type of matrix forming polymer, use of polymer blends, water soluble /insoluble fillers (lactose/MCC)\textsuperscript{20}.

The floating flap of albendazole, prepared with concentrations of 8.8, 10.0 and 8.5 % w/v of Eudragit
RL 100, Eudragit RS 100 and Poly lactic-co-glycolide respectively by mercury casting technique, was found to be of good floating behavior and was selected for release rate studies. Chitosan granules having internal cavity were prepared by de-acidification. When added to acidic (pH 1.2) and neutral (deionized distilled water) media, these granules were immediately buoyant and provided a controlled release of the candidate drug prednisolone. Laminated preparations prepared by coating with chitosan granules layer with chitosan membranes were also buoyant and provided controlled release of the drug. Floating chitosan microcapsules can be prepared by ionic interaction of chitosan and negatively charged surfactant sodium dioctyl sulfosuccinate.

Many lipid-based sustained release matrix systems are reported. Kiran Kumar et al. reported floating glycerol monooleate (GMO) single-unit lipid matrix containing high drug: excipient ratio (1:30) to achieve sustained drug release. Hydrophobic lipid, Gelucire 43/01, can be considered as an effective carrier for design of a multi-unit FDDS of highly water-soluble drugs such as diltiazem HCl.

Tablet with Spray dried PVA –PVP shows immediate floating with almost no lag time, floating for 24 h and do not sink. No swelling and erosion takes place in the GIT, so the release does not depend upon osmolarity of the medium. Buoyancy in such system is due to high porosity in the tablet. The exceptionally good compressibility of spray dried PVA-PVP combination makes it possible to produce mechanically stable oral DF, even with extremely low pressures.

In addition to the approaches outlined above, gastroretentive drug delivery systems have been made from a new category of synthetic acrylamide/sulfopropyl acrylates, acrylic acid polymers containing crosscarmelose sodium, also known as “superporous hydrogel composites”.

**Effervescent FDDS**

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid. Another system consists of a liquid that gasify at body temperature. The matrices are so fabricated that on arrival in the stomach, CO$_2$ is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. The CO$_2$ generating components may be intimately mixed within the tablet matrix, to produce a single-layered tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a SR (sustained release) effect.

A multiple-unit type of floating pill, which generates CO$_2$ gas, has been developed (Fig. 3). The system consists of SR pills as seeds surrounded by double layers. The inner layer was an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer. Moreover, the effervescent layer was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sub layer and tartaric acid in the outer layer. When the system was immersed in a buffer solution at 37°C, it sank at once in the solution and formed swollen pills, like balloons (density < 1 g/ml). Attempts have also been made to develop SR floating tablets using a mixture of sodium bicarbonate, citric acid and chitosan. Inouye et al. used two types of chitosan with different degrees of deacetylation (chitosan H and L) and prednisolone as a model drug. Although both chitosans provided SR of drug in acidic dissolution medium, and imparted buoyancy to the preparations, the drug release from the preparation using chitosan L was slower than that from the preparation of chitosan H.
Ichikawa et al\textsuperscript{19} described a capsule, which contained plurality of granules having different residence times in the stomach. The released granules were comprised of a core containing the drug coated by double layers. Inner coat was as foamable layer, and the outer layer was an expansive film layer comprising a polymer, which allowed gastric juice to pass there through and expand by foam produced by the reaction between the gastric juice and the foamable layer. Moreover, foamable layer was divided into two sub layers: an inner layer containing bicarbonate and an outer layer containing an organic acid.

Another approach includes use of ion exchange resin (cholestyramine) loaded with bicarbonate and acetoxyhydroxamic acid (model drug used for treatment of \textit{H. pylori} infection), which was coated with cellulose acetate butyrate (CAB) by emulsion solvent evaporation method\textsuperscript{20}. Ratios of CAB: Drug-Resin (2:1; 4:1; 6:1 w/w) were found to be successful formulations. The buoyancy time of CAB coated formulation was better than uncoated resin particles. With increasing CAB: Drug-Resin ratio to 6:1, better buoyancy was obtained but this resulted in decreased drug release rate due to thick CAB coating.

Atyabi et al\textsuperscript{41} developed floating system utilizing ion exchange resins. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that bound to the resin. The resultant beads were then encapsulated in a semi permeable membrane to overcome rapid loss of CO\textsubscript{2}. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions took place. As a result of this reaction, CO\textsubscript{2} was released and trapped in the membrane, thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. Floating alginate beads of metronidazole were prepared by dropping solution of calcium carbonate/ sodium bi-carbonate containing sodium alginate in 1% CaCl\textsubscript{2} solution containing acetic acid (10 %). Sodium alginate gets gellified in presence of calcium ions and gas entrapped in this gelled structure\textsuperscript{22}.

Floating rafts are used in the treatment of gastric oesophageal reflux. Gaviscon liquid (Reckitt and Colman) is an established floating raft formulation based on an alginate biopolymer. On ingestion, this formulation reacts with gastric acid to form a floating raft structure, which impedes the reflux of acid and food by acting as a physical barrier. The raft has a pH value higher than that of the stomach contents so that in the event of gastric reflux, the wall of the esophagus is not subjected to irritation by HCl. Such formulation on entering the stomach forms a colloidal gel. Sodium alginate solution reacting with gastric acid and this gel floats on the surface of the gastric contents due to CO\textsubscript{2} generation by gas generating excipients impeding reflux of acid into the esophagus\textsuperscript{43}.

An osmotically controlled floating system (Fig. 4) comprised of a hollow deformable unit that was convertible from a collapsed to an expanded position and returnable to a collapsed position after an extended period of time. A housing was attached to the deformable unit and it was internally divided into a first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contained an active drug, while the second contained a volatile liquid, such as cyclopentane or ether that vaporizes at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit from stomach, the device contained a bioerodible plug that allowed the vapor to escape\textsuperscript{33,34}.

Effects of Formulations Variables on the Floating Properties

Moes et al\textsuperscript{44}, have continuously monitored the floating kinetics to see the effect of different types of HPMC, varying HPMC/ carbopol ratio and addition of magnesium stearate on floating behavior. HBS capsules of different density were used for study. Addition of magnesium stearate was observed to improve floating property significantly. HPMC of higher grade generally exhibits a greater floating capacity; but the effect was not statistically significant. For the polymers within the same viscosity (K4M and E4M), the degree of substitution of the functional group did not show any significant contribution. A better floating behavior was achieved at higher HPMC: Carbopol ratio. Carbopol appeared to have negative effect on the floating behavior of FDDS\textsuperscript{46}.

Floating formulations using swelling polymers such as HPMC and HPC do not show reproducibility in release and residence time because the swelling depends greatly on the contents of the stomach and the osmolarity of the medium and such formulations are observed to sink in the dissolution medium after a certain time. Floating lag time with such formulation is 9-30 min. Gel-forming capacity and the gel strength...
of polysaccharides varies from batch to batch because of the variation in the chain length and the degree of substitution, and the situation is exacerbated in the effervescent formulation by the disturbance of the gel structure through evolution of CO$_2$. In addition, gel formers react very sensitively to differences in the osmolarity of the release media, with alterations in the release.

Another study reveals the influence of three basic fillers [microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP) and lactose] on the floating behavior of coated tablets. Tablets containing lactose floated earlier than tablets prepared with inorganic filler, DCP. Different densities could explain this; lactose-containing tablets had the lowest density (1 g/cm$^3$ at hardness of 30 N), whereas DCP tablets had a higher density (1.9 g/cm$^3$ at hardness of 30 N). In addition, lactose has higher water solubility and thus shows osmotic activity and faster uptake of the medium in the core of the tablet through coating. MCC, insoluble filler with a high water uptake and disintegration capability, resulted in the rupturing of the coating and disintegration of the tablet, CO$_2$ did not accumulate under the coating and escaped through the ruptured films, floating was therefore not achieved.

Doelkar et al have showed the effect of film forming polymers on floating behavior of coated floating formulations. Films plasticised with water-insoluble plasticizers are more permeable for aqueous medium but should rupture earlier than films prepared with water insoluble plasticizers. Cellulose acetate, mechanically strong polymer, is too rigid and do not expand to large extent when comes in contact with dissolution medium. Ethyl polymer is mechanically weak polymer, it is not flexible and easily ruptures upon CO$_2$ formation; acrylic polymers are more suitable for the FDDS.

The floatation time decreases with increasing Eudragit RL content in Eudragit RS/RL coating and was longer with coatings containing acetyl tributyl citrate (ATBC) as plasticizer than with coating containing triethyl citrate (TEC).

**Pharmaceutical Aspects**

In designing of FDDS, following characteristics should be sought: i) Retention in the stomach according to the clinical demand; ii) Convenient intake; iii) Ability to load substantial amount of drug with different physicochemical properties and release them in a controlled manners; and iv) Complete matrix integrity of the SR formulation in the stomach, inexpensive industrial manufacture, optimization between the buoyancy time and release rate (Buoyancy time increases by increasing drug: polymer ratio but release retards by increasing polymer level), lag time i.e. the time taken by the dosage form to float should be low. Most of the floating systems reported in literature are single-unit systems; these systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered, owing to their

![Diagram of Intra-Gastric Osmotic Controlled Drug Delivery System](image-url)
fortuitous (‘all-or-nothing’) emptying process. On the other hand, multiple-unit dosage forms appear to be better option since they reduce the inter subject variability in absorption and lower the probability of dose dumping.\textsuperscript{48}

**Evaluation of FDDS**

The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP disintegration apparatus containing 900 ml of 0.1 N HCl as a testing medium maintained at 37°C. The time required to float the DF is noted as floatation time.\textsuperscript{74} Burns \textit{et al.}\textsuperscript{75} developed and validated an *in vitro* dissolution method for a floating dosage form, which had both rapid release and S R properties. The method, although based on the standard BP (1993)/USP (1990) apparatus 2 methods, was modified such that paddle blades were positioned at the surface of the dissolution medium. The results obtained with this modified paddle method showed reproducible biphasic release dissolution profiles when paddle speeds were increased from 70 to 100 rpm and the dissolution medium pH was varied (6.0-8.0). The dissolution profile was also unaltered when the bile acid concentration in the dissolution medium was increased from 7 to 14 m $M$. The specific gravity of FDDS can be determined by the displacement method using analytical grade benzene as a displacing medium.\textsuperscript{74}

The system to check continuous floating behavior (Fig. 5) contains a stainless steel basket connected to a metal string and suspended from asartorius electronic balance. The floating object is immersed at affixed depth into a water bath, which is covered to prevent water evaporation. The upward floating force could be measured by the balance and the data transmitted to an online PC through RS232C.
inter spread sheet could automatically pick up the reading on the balances. Test medium used in floating kinetics measurements was 900 ml simulated gastric fluid (pH 1.2) maintained at 37°C, data was collected at 30 sec interval; baseline was recorded and subtracted from each measurement. Dissolution basket had a holder at the bottom to measure the downward force.44

\[ \gamma \text{-Scintigraphy} \]
\[ \gamma \text{-Emitting radioisotopes compounded into CR-DFs} \]
\[ \gamma \text{-Scintigraphy are the state-of-art for evaluation of gastroretentivity. A small amount of a stable isotope e.g.}^{152} \text{Sm, is compounded into DF during its preparation. The main drawbacks of } \gamma \text{-scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals.76} \]

Radiology
This method is the state of art in preclinical evaluation of gastroretentivity. Its major advantages as compared to \( \gamma \)-scintigraphy are simplicity and cost. However, use of X-ray is declined due to strict limitations, regarding the amount of exposure and it’s often requirement in high quantity. A commonly used contrast agent is barium sulphate77.

Gastroscopy
It comprises of peroral endoscopy, used with a fiberoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation59.

Ultrasonography
Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs78. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

Magnetic Resonance Imaging (MRI)
In the last couple of years, MRI was shown to be valuable tool in gastrointestinal research for the analysis of gastric emptying, motility and intragastric distribution of macronutrients and drug models. The advantages of MRI include high soft tissue contrast, high temporal and spatial resolution, as well as the lack of ionizing irradiation. Also, harmless paramagnetic and supra magnetic MR imaging contrast agents can be applied to specifically enhance or suppress signal of fluids and tissues of interest and thus permit better delineation and study of organs79.

Conclusions and Future Perspectives
Among the drugs currently in clinical use are several narrow absorption window drugs that may benefit from compounding into a FDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment. It is anticipated that FDDS may enhance this possibility. Moreover, it is expected that the FDDS approach may be used for many potential active agents with a narrow absorption window, whose development has been halted due to the lack of appropriate pharmaceutical FDDS technologies. Combination therapy to treat \( H. \) pylori infection in a single FDDS needs to be developed.

- Further investigations may concentrate on the following concepts:
- Identification of a minimal cut-off size above that DFs retained in the human stomach for prolonged periods of time. This would permit a more specific control to be achieved in gastroretentivity.
- Design of an array of FDDS, each having a narrow GRT for use according to the clinical need e.g. dosage and state of disease. This may be achieved by compounding polymeric matrices with various biodegradation properties.
- Study of the effect of various geometric shapes, in a more excessive manner than previous studies, extended dimensions with high rigidity, on gastroretentivity.
- Design of novel polymers according to clinical and pharmaceutical need.

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