

## Effervescent Floating Drug Delivery System: A Review

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**Abstract:** Now a days more advancement has been made in development of oral dosage forms because the oral route is widely accepted and most preferred route for administration of drugs. Gastro retentive dosage forms (GRDF) has achieved significant interest in the past few years because some limitations encountered with conventional and oral controlled release drug delivery system can be avoided. Effervescent floating drug delivery systems release gas (CO<sub>2</sub>), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate so it can be used to prolong the gastric residence time in order to improve the bioavailability of drug. In the present article we will discuss mechanism of effervescent floating drug delivery system, some marketed product related to this as well as various patents on this.

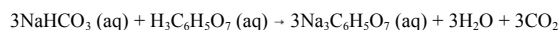
**Key words:** Floating Drug Delivery • Gastro Retentive • Drug Delivery System • Effervescent

### INTRODUCTION

The oral route is most preferable route for administration of the drug but it may have some disadvantages like slow onset of action or slow absorption. This problem can be overcome by using alternative dosage form or administering the drug via other routes. While we are selecting a dosage form or route for administration of drug there are some parameters should be considered like stability and bioavailability of the formulation as well as active pharmaceutical ingredients [1]. The Effervescent floating tablets can be used as alternative dosage form to minimize some problems associated with conventional dosage forms. The Effervescent floating tablets also reduce fluctuations of drug concentration and can be used to increase the bioavailability of drug [2].

Simply, Effervescence means release of CO<sub>2</sub> gas due to reaction of acids and bicarbonates in presence of H<sub>2</sub>O. Some common acids used in this reaction are citric, malic, tartaric, adipic and fumaric acid and bicarbonate used in the effervescent reaction is sodium bicarbonate, potassium bicarbonate, sodium carbonate and potassium carbonate. The most common reaction for pharmaceutical

purpose is the acid base reaction between sodium bicarbonate and citric acid.



This reaction occurs in presence of water, even with small amount as catalyzing agent, which increases the rate of reaction. As water act as a catalyzing agent for the reaction so all the moisture sensitive products or effervescent products is stored in moisture free environment [3].

Due to development of gas in effervescent floating drug delivery systems the density of the system is reduced and the dosage form remains buoyant in the stomach for a prolonged period of time which released the drug slowly at a desired rate. So it is possible to prolong the gastric residence time of drug using effervescent floating drug delivery systems or hydro dynamically balanced system [4].

Effervescent floating drug delivery systems requires matrices prepared with swellable polymers such as methocel polysaccharides, e.g., Chitosan and effervescent components such as sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that

gasify at body temperature [5]. Effervescent floating tablets are prepared by compressing the active ingredients with mixture of sodium bicarbonate and organic acids such as citric and tartaric acid [6]. The main advantages of effervescent floating tablets are quick production of solution. Thus, it is faster and better to absorb [7].

On the other hand floating drug delivery systems (FDSS) is designed in such manner that it has bulk density less than gastric fluids and because of this, these systems remain buoyant for a prolonged period of time (Approx. 3-4 hours) in the stomach without affecting the gastric emptying rate [8, 9]. The underlying principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach. As a result gastric residence time is increased and fluctuations in plasma drug concentration can be better controlled [10].

Floating drug delivery system provides local delivery to specific region like stomach and proximal small intestine and it's also shows better bioavailability, improved therapeutic activity and substantial benefits to patients [11].

Advantages of Effervescent Floating drug delivery system [12, 13].

- Increases the oral bioavailability of drug.
- Enhanced first pass biotransformation.
- Sustained drug delivery/ reduced frequency of dosing.
- Reduced fluctuations of drug concentration.
- Improved receptor activation selectivity.
- Reduced counter-activity of body.
- Extended time over critical (Effective) concentration.
- Minimized adverse activity at the colon.
- Receptor activation selectivity is improved.
- Site specific drug delivery.

#### **Limitation of Effervescent Floating Drug Delivery System [14]:**

- Floating drug delivery requires sufficient high level of fluids in the stomach.
- Not suitable for the drug that have solubility or stability problem in GIT.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

- Drugs which cause irritation to gastric mucosa are not suitable for this.
- The dose should be taken with a full glass of water.

#### **Factors Affecting the Gastric Residence Time of Effervescent Floating Drug Delivery System: [15-17]:**

**Nature of Meal:** Motility pattern of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and because of this the gastric emptying rate is decreased and drug release is prolonged.

**Frequency of Feed:** when successive meals are given, the GRT can increase by over 40 minutes compared with a single meal because of the low frequency of migrating myoelectric complex.

**Gender:** Mean GRT of a male in meals ( $3.4 \pm 0.4$  hours) is less compared to the female of the same age and race ( $4.6 \pm 1.2$  hours), regardless of the height, weight and body surface of the two.

**Age:** Elderly people have a significantly longer GRT, especially those who are over 70 years of age.

**Fed and Unfed State:** under fasting conditions, the GI motility is characterised by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of the administration of the formulation coincides with that of the MMC the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

**Mechanism of Floating Effervescent Tablets:** The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. When the tablet comes in the contact of gastric fluid, it produces effervescence by releasing CO<sub>2</sub> gas. When the fluid penetrates into the tablet, tablet starts floating [18]. Various types of polymer of different grade provide low density system so give better efficiency in gastric fluid. The system is design to float and shows sustain release for better patient compliance and reduce dose frequency and adverse effect of drug [19].

$$F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) g \cdot v$$

Where,

F= total vertical force;

D<sub>f</sub> = fluid density;

D<sub>s</sub> = object density;

v = volume and

g = acceleration due to gravity [20].

#### Method of Preparation of Floating Effervescent Tablet:

- By direct compression
- By wet granulation
- Dry Granulation

**Wet Granulation:** This technique is most widely used and most general method for preparation of tablets. The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (Crystal water of citric acid, liquid water, or water vapour), ethanol (Possibly diluted with water), isopropanol, or other solvents. When granulating either with solvents containing water or pure water, the effervescent reaction will start. Care must be taken to maintain adequate control of the process. Vacuum processing is often beneficial due to the ability to control the effervescent reaction and the drying process [22, 23].

**Dry Granulation:** When ingredients used in tablet formulation is sensitive to moisture then slugging may use. Slugging of the material is done by using heavy-duty tableting equipment or with roller compaction.

**Direct Compression:** In Direct compression vehicles can be used which are having good free-flowing properties, no segregating and are having compressible mixture.

Direct compression technique is mainly used in the formulation of floating effervescent tablet and for all moisture sensitive products [24].

**Natural and Synthetic Polymer Used in Floating Drug Delivery System:** Floating drug delivery system are also called as gastro-retentive drug delivery system that controlled the release of drug and prolong the retention time of drug in compression to the conventional drug by the use of various polymeric substances including natural polymer such as Guar gum, Xanthan gum, Gellan gum or synthetic polymer such as-HPMC (K4M, K 15M,K100M), Carbopol 934 p, Polyvinyl alcohol, Polyamides, Polycarbonates, Polymethacrylic acid.

**Evaluation of Floating Drug Delivery System:** Various parameters used in evaluation of effervescent floating tablet.

Pre-compression parameters: pre-compression parameter include in effervescent floating tablet are-flow properties include, bulk density, tapped density, Hausner ratio and Carr's index [30].

#### Post-Compression Parameter:

- Swelling index
- Measurement of buoyancy capabilities.
- Floating lag time
- *In-vitro* dissolution.
- Drug release

**Buoyancy / Floating Test:** The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time [31].

Table 1: some common effervescent tablets and their brand leaders in India [21]

Name of product	Active ingredient	Manufacturer
Histac	Ranitidine HCl	Ranbaxy
Pepfiz-O and L	Papain, Fungal diastase, Simeicone	Ranbaxy
Effcal	CaCO <sub>3</sub> , Vitamin D <sub>3</sub>	Ranbaxy
Tagame	Cimetidine	Glaxosmithkline
Zantac	Ranitidine	Glaxosmithkline
Vitalmag	Magnesium citrate, Folic acid, Vitamin B <sub>6</sub>	ICN Hungary
Calcium Sandoz	Calcium	ICN Hungary
Ca-C 1000	Calcium, Ascorbic acid	ICN Hungary
Hangoverz	Aspirin, Caffeine	Pious Pharma. Ltd
Solpado	Paracetamol, Codeine phosphate	Sanofi-aventis
Prolyte fizz	Glucose + Potassium Chloride +Sodium Bicarbonate + Sodium Chloride+ Anhydrous Citric Acid	Cipla

Table 2: Marketed products of floating drug delivery system: [25-27]

S.No	Products	Active Ingredients
1.	Madapar	Levodopa and benserzide
2.	Valrelease	Diazepam
3.	Topalkan	Aluminum magnesium Antacid
4.	Almagateflatcoat	Antacid
5.	Liquid gavison	Alginic acid and sodium Bicarbonate
6.	Cytotec	Misoprostol
7.	Conviron	Ferrous sulphate

Table 3: List of some common natural polymers used in floating drug delivery system and their sources [28-29]

Natural polymer	Source
Guar gum	Endosperm of the seed of <i>Cyamopsis tetragonoloba</i>
Pectin	Citrus peel, apple pomace, sugar beet pulp etc.
Chitosan	Shell of marine invertebrate's
Xanthum gum	Fermentation of glucose by xanthomonas campestris
Psyllium husk starch	Seed coat of plant ago ovate storage polysaccharides in plants
Gellan gum	<i>Pseudomonas elodea</i>
Alginates	<i>Laminaria hyperborea</i> , <i>Ascophyllum nodosum</i>

It is determined by using USP dissolution apparatus containing 900 ml of 0.1mole/lit HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time [32].

**Swelling Study:** The floating tablets were weighed individually (Designated as W<sub>0</sub>) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C ± 1°C at a regular 1hr intervals till 24 hrs. The floating tablets are removed from beaker and the excess surface liquid is removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (W<sub>t</sub>) and % swelling index (SI) was calculated using the following formula [33,34].

$$\text{Swelling index \% (SI)} = [(W_t - W_0) / W_0] * 100$$

Where,

S.I. = Swelling index

W<sub>t</sub> = Weight of tablet at time t

W<sub>0</sub> = Weight of tablet before placing in the beaker.

**In vitro Dissolution Studies:** The *In vitro* dissolution study was performing by using a United States Pharmacopeia (USP) type II (Paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl is used as the dissolution medium and the temperature was

maintained at 37°C ± 0.5°C. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 hrs. and the same volume was replaced with pre-warmed fresh dissolution media. The samples were filtered through a Whatman filter paper and diluted to a suitable concentration of 0.1 N HCl [35].

**Drug Release:** dissolution test were performed using dissolution test apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analysed for their drug content after an appropriate dilution [36, 37].

### Various Patents on Floating Drug Delivery System for Different Dosage Forms [38,39]:

- Dudhara *et al.* [40], develop gastric retention control drug delivery system which shows biphasic release of drug in gastrointestinal fluid. A gastric retention control release system comprise a control release core having drug, swellable polymer and gas generating agent thus it may capable of swelling and floating in gastrointestinal fluid for longer period of time and maintain its physical integrity on other hand a rapidly releasing coat having drug and excipients and the core is surrounded with coating composition which shows biphasic release of drug in the gastrointestinal fluids. Thus the drug used in this technique shows better oral absorption and therapeutic effect.
- Lohray *et al.* [41], Work on novel floating dosage form. His invention is based on novel pharmaceutical composition containing active ingredients which may retained in the stomach or upper G.I. tract for controlled release of drug and thus it improve absorption and therapeutic effect of the drug. In his invention he also provide a method for preparation of floating dosage form are in the form of bilayer tablet in which the one layer of tablet is used for spatial control and second one is for temporal control.
- Friedman *et al.* [42], Work on gastro retentive controlled release pharmaceutical dosage forms Pharmaceutical gastro retentive drug delivery systems for the controlled release of an active agent in the gastrointestinal tract are disclosed, which comprise:
- A single-or multi layered matrix comprising a polymer that does not retain in the stomach more than a conventional dosage form selected from

- Degradable polymers that may be hydrophilic polymers not instantly soluble in gastric fluids, enteric polymers substantially insoluble at pH less than 5.5 and/or hydrophobic polymers and mixtures thereof;
- Non degradable polymers; and any mixtures of (1) and (2);
- A continuous or non-continuous membrane comprising at least one polymer having a substantial mechanical strength; and
- a drug; wherein the matrix when affixed or attached to the membrane prevents evacuation from the stomach of the delivery system for a period of time off from about 3 to about 24 hours.
- Nur and Zhang [43], developed floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P. *In vitro* buoyancy studies revealed that tablets of 2 kg/cm<sup>2</sup> hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm<sup>2</sup> sank for 3 to 4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm<sup>2</sup> hardness showed no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.
- Shell *et al.* [44], work on gastric-retentive, oral drug dosage forms for the controlled release of sparingly soluble drugs and insoluble matter. His experiment comprises of tablet or capsule containing a plurality of particles of a solid-state drug dispersed in a swell able/erodible polymer, such as poly (ethylene oxide). The tablet or capsule disintegrates to disperse the particles within the stomach where they imbibe water to cause them to swell and promote retention in fed-mode-induced patients. Thus the drug will release on controlled manner in to the stomach. The drug may contain vesicles, such as liposomes, nanoparticles and enteric coated drug particles.
- Sheth *et al.* [45], works on novel sustain release formulation. In is experiment he work on sustain release formulation and hydro dynamically balanced system to buoyant in gastric juice thereby remaining in the stomach for an extent ended period of time.
- Curatolo *et al.* [46], work on Gastric retention system for controlled drug release. In his experiment he work on drug delivery system having delayed gastrointestinal transit comprising a non-continuous compressible element and an attached controlled release device, which in the expanded form resists gastrointestinal transit; and a modular system for use therein comprising a non-continuous compressible element and an attached receptacle means for receiving and holding a drug-containing orally administrable controlled release device and which in the expanded form resists gastric transit.
- Spickett *et al.* [47] invented an antacid preparation having a prolonged gastric residence time. It comprised 2 phases. The internal phase consisted of a solid antacid and the external phase consisted of hydrophobic organic compounds (Mono di and triglycerides) for floating and a non-ionic emulsifier.<sup>47</sup>
- Dennis *et al.* [48] invented a buoyant controlled release pharmaceutical powder formulation filled into capsules. It released a drug of a basic character at a controlled rate regardless of the pH of the environment. pH-dependent polymer is a salt of a polyuronic acid such as alginic acid and a pH-independent hydrocarbon gelling agent, hydroxypropylmethyl cellulose.
- Baichwal *et al.* [49] invent a controlled release verapamil tablet. In his experiment he develops the controlled release of verapamil and improves its availability and therapeutic effect. In his formulation he made tablet containing excipients having a hydrophilic material and also contain a mixture of natural polymer such as xanthan gum, locust bean gum and also contain inert diluents.
- Bolton *et al.* [50], Work on Floating sustained release therapeutic compositions. His invention is to provide a solid unit dosage form capable of floating on gastric juice and delivering a therapeutic agent incorporated therein over an extended period of time and also provide a therapeutic solid unit dosage form as a non-com pressed tablet which has a bulk density of less than one and sufficient mechanical stability for production and handling be achieved by incorporating into the non-compressed tablet, in addition to at least 75% therapeutic agent, 2.0 to 6.5% gelling agent and water.
- Caldwell *et al.* [51], work on drug delivery device which can be retained in the stomach for a controlled period of time. In his experiment he work on a drug

delivery device which may remain sustain in the stomach for a longer period of time and a device is retained in the stomach comprising a planar figure made up of an erodible polymer which may release a drug associated there with over controlled, predictable and extended period of time.

- Mitra *et al.* [52], developed a sustained release multilayered sheet like medicament device. It was buoyant on the gastric contents and consisted of at least 1 dry, self-supporting carrier film of water-insoluble polymer. The drug was dispersed or dissolved in this layer and a barrier film overlaid the carrier film. The barrier film was composed of 1 water-insoluble layer and another water-soluble and drug-permeable polymer or copolymer layer. The 2 layers were sealed together in such a way that pluralities of small air pockets were entrapped that gave buoyancy to the formulation.

### CONCLUSION

Effervescent floating tablet are an interesting pharmaceutical dosage form offering some unique advantages compared with traditional or conventional tablets. The manufacturing process involves some critical steps that need to be addressed carefully during formulation. FDDS provide to be a potential approach for gastric retention.

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