Review Article

Effervescent Floating Drug Delivery System

Khairnar vinit S*, Patil ST and Pawar SP.

Department of Quality Assurance, P.S.G.V.P. Mandal's College of Pharmacy,

Shahada, Dist. Nandurbar – 425409, Maharashtra, India.

ABSTRACT

Effervescent floating drug delivery systems release gas CO_2, thus reduce the density of the system and remain buoyant in the stomach 2 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 in detail about effervescent agent and mechanism of effervescent floating drug delivery system.

Keywords: Effervescent system, floating drug delivery system, effervescent agent, floating time.

INTRODUCTION[1, 2]

The floating drug delivery system is a useful approach to avoid variability. Floating drug delivery systems are low-density systems that have able to keep the float over the gastric fluid and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This system faced to a several difficulties in designing control drug delivery system for better absorption and increasing bioavailability. The floating system is allow to float on the gastric fluid, the drug is released slowly from the system for the prolong duration of action.

Classification of floating system

1) Single Unit Floating Dosage Systems
   a) Effervescent system or gas generating system
   b) Non-effervescent Systems
2) Multiple Unit Floating Dosage Systems
   a) Effervescent Systems
   b) Non-effervescent Systems
   c) Hollow microspheres
3) Raft forming system

Effervescent system or gas generating system[3]

This is buoyant delivery system prepared with the help of low density polymer, and effervescent compound, e.g. sodium bicarbonate, tartaric acid, and citric acid. This system utilized effervescent reaction when the drug is coming in contact with the gastric fluid, due to carbon dioxide gas is generated from the system, when the fluid penetrates into the tablet, and tablet gets starts to float. The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix system in which the drug is released without disintegration of the tablet. The Effervescent floating tablets can be used as sustain release dosage form to overcome some problems associated with conventional dosage forms. This also reduces fluctuations of drug concentration and enhances the bioavailability of drug.

Effervescence floating drug delivery system means release of carbon dioxide gas due to reaction of acids and bicarbonates, e.g. of acids are citric acid, tartaric acid, and fumaric acid and e.g. of bicarbonate/carbonate are sodium bicarbonate, calcium carbonate, sodium carbonate and potassium carbonate. This reaction occurs in presence of water, water is act as a catalyzing agent it is used in small amount, which increases the rate of reaction. The development of effervescent floating drug delivery systems is reduced the density of the system and the dosage form is allow to float on gastric content 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.

These effervescent formulations generally include an agent which are capable of releasing

CO_2, and an agent which induces the release of CO_2. Suitable agents capable of releasing CO_2 which are used include alkali metal carbonates or alkali metal bicarbonates, such as sodium carbonate and sodium bicarbonate. Alkaline earth metal carbonate formulations are mainly contained in mineral preparations. Suitable agents for inducing CO_2 release include edible organic acids, or their acidic salts, which are present in solid form and which can be formulated with the active ingredient and the other auxiliaries to provide granules or tablets, without premature evolution of CO_2.

Suitable edible organic acids include, for example, tartaric acid, malic acid, fumaric acid, ascorbic acid, or citric acid. Pharmaceutically acceptable acidic salts include, for example, salts of polybasic acids which are present in solid such as sodium dihydrogen or disodium hydrogen phosphate or the corresponding citrates.

Effervescent drug delivery system for oral administration

The pharmaceutical compositions of the oral solid dosage form in combination with an effervescent as a penetration enhancer for influencing absorption of a drug in the gastrointestinal tract. Effervescence leads to an increase in the rate and/or the extent of absorption of the drugs that are known or suspected of having poor bioavailability. It is believed that such increase can rise from one or all of the following mechanisms:

1. Reducing the thickness and/or the viscosity of the mucus layer which is present adjacent to the gastrointestinal mucosa;
2. Alteration of the tight junctions between cells, thus promoting absorption through the paracellular route;
3. Inducing a change in the cell membrane structure, thus promoting Trans cellular absorption;
4. Increasing the hydrophobic environment within the cellular membrane.

The present dosage forms include an amount of effervescent agent effective to aid in penetration of the drug in the gastrointestinal tract, aid in penetration of the drug across the gastrointestinal mucosa. The formulations may be distinguished from other effervescent formulation that are enteric coated on the basis of the amount of effervescent material that they contain. Prior formulations contain approximately half to a quarter as much bicarbonate as drug on a weight basis.

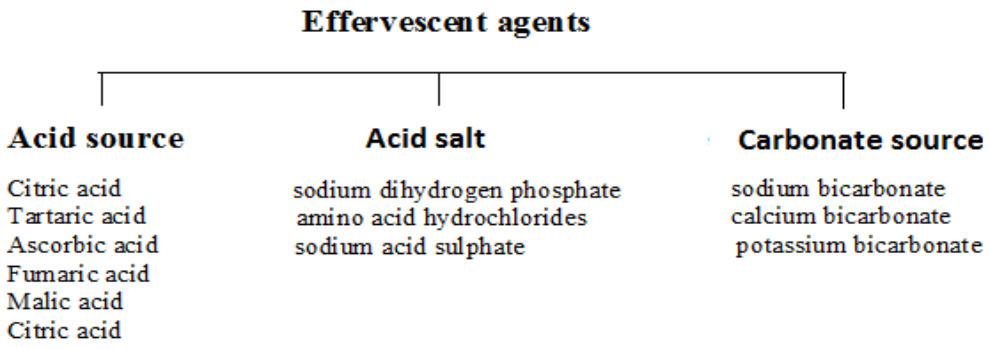

Fig. 1: Examples of effervescent agent

Acid source

1. **Citric acid**

It is available as a monohydrate and as an anhydrate form. It is available in in the form of colorless, translucent, crystals and white crystalline powder. It is very freely soluble in water and alcohol. It produces a solution with citrus- like taste.

2. **Tartaric acid**

Tartaric acid is commonly used in effervescent tablet, as it is readly available commercially. It is more soluble than citric acid, 1 part of acid in less than 1 part of water. It is available as colorless monoclinic crystal or as white crystalline powder.is is also most hygriscopic than citric acid.

3. Ascorbic acid

A comparison of formation of carbon dioxide from effervescent tablet based on anhydrous citric acid, ascorbic acid or tartaric acid and sodium bicarbonate indicated that ascorbic acid and citric acid behave similarly

Carbonate source

1. Sodium bicarbonate

Sodium bicarbonate is one of the most used carbonate because it is very soluble and of low cost. Alternatively, modified sodium bicarbonate can be used, obtained by heating, common sodium bicarbonate in order to convert the surface of its particles to sodium carbonate so increasing its stability. Normal sodium bicarbonates products are highly unstable and react with acid component of an effervescent formulation if any amount of moisture is present, this ingredient are commonly used in effervescent powder and tablet. It is used an acidic agent, such as citric acid and tartaric acid, to cause a reaction that produce carbon dioxide.

2. Calcium carbonate

This is available as fine, white, odorless, and tasteless powder or crystals. It is non-hygroscopic and absorbs less than 1%moisture at 90%RH and 25^{o}c. the calcium carbonate is a high density materials, which is not very compressible. Also is solubility in water is 1 in 50,000. These factors limit usage of calcium carbonate in effervescent tablet.

Other physiologically acceptable alkaline or alkaline earth metal carbonates may be used, such as potassium or calcium carbonate, sodium carbonate or sodium glycine carbonate.

Conventional excipients such as diluents, ligands, buffering agents, sweeteners, flavorings, colorings, solubilizes, disintegrants, wetting agents and other excipients of common use may be added to the formulation.

Limitations of effervescent formulations[4, 5]

1. It cannot be given to the children because of possibility of gas (CO2) toxicity.
2. If packaging is not done properly then there are chances of degradation by environmental moisture.
3. It has shorter shelf life as compared to other solid dosage forms.
4. It requires special machinery requirements for manufacturing.
5. This dosage form is costly than tablets.

Factors affecting to floating drug delivery system:

a) Formulation factors

1. Size of tablets[6]

Retention of floating dosage forms in stomach depends on the size of tablets. Larger dosage form tends to have longer gastric retention time than smaller ones because they are emptied in digestive phase. Diameter of dosage forms more than 7.5mm which is increase in GRT compared with diameter of 9.9mm.

2. Density of tablet[6]

Density is affecting the gastric residence time of floating dosage form. A density of floating dosage form should be less than the gastric fluids. A density of floating dosage form is less than 1.0g/ml.

3. Shape of tablets[6]

The shape of dosage form is one of the factors that affect its gastric residence time. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr. Tetrahedron and ring shape device with a flexural modulus of 48 and 22.5 kilo pounds per square inch have a better GRT.

b) Idiosyncratic factors[6]

4. Gender

Women have slower gastric emptying time than men. Males showed comparatively longest mean ambulatory GRT than Females, and the gastric emptying in women was slower than in men. Mean ambulatory GRT in males (3.4±0.4 hours) is less compared with their age and race-matched female counter parts (4.6±1.2 hours), regardless of the weight, height and body surface.

5. Age

The age of human is also affecting the gastric residence time. Elderly people, especially those over 70 years have a significantly longer GRT.

6. Posture

Posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state.

7. Fed or unfed state[7]

Under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 hours.

8. Biological factors [7]

The biological factors also affected to gastric empting rate. Diseases like diabetes, gastroenteritis, gastric ulcer, and hypothyroidism retards the gastric emptying.

Mechanism of Floating Effervescent Tablets[8, 9]

After administration of effervescent floating dosage form coming in contact with the gastric fluid the dosage form get swells up and the slowly release 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_2 gas. When the fluid penetrates into the tablet, tablet starts to float.

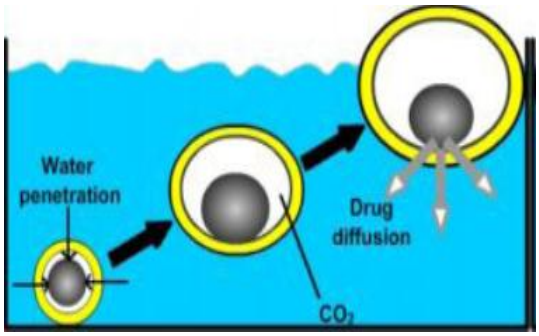

Fig. 2: Mechanism of floatation via CO_2 liberation

Method for preparing floating dosage form

Floating dosage forms prepared by following approaches.

- Using low-density enteric materials such as cellulose acetate phthalate, methacrylic polymer.
- Using gel-forming hydrocolloids such as alginates, gelatin, hydrophilic gums, cellulose derivatives, etc.
- By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
- By reducing particle size and filling it in a capsule.
- By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.

Advantages of FDDS[13, 14]

1. The main advantages of this dosage form are patient compliance; increased rate of absorption, large dose can be given.
2. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT.
3. This technique is generally employed for antacid preparations. In this preparation alkali metal bicarbonates & alkali metal carbonates like Sodium carbonate &Sodium bicarbonates are added which reacts with citric acid or tartaric acid to give effervescence.
4. The FDDS is a site-specific drug delivery system reduces undesirable effects.
5. The effervescent floating dosage form is better for drugs which get absorbed through the stomach.
6. Effervescent formulations are those which are capable of producing CO2 on contact with water.
7. Effervescent floating drug delivery are good for drugs meant for local action in the stomach, e.g.: Antacids
8. EFDDS can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).
9. The slow delivery of drug from a dosage form provides sufficient local action at the disease site, thus minimizing or eliminating systemic exposure of drugs.
10. Minimize the fluctuation of drug concentrations and effects. Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
11. The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.
12. The future of effervescent preparation is very bright. There are many advances in this technology that are: floating or pulsatile drug delivery system based on coated effervescent cores, effervescent micro spheres, effervescent vaginal preparation etc.

Disadvantages of FDDS

1. Plenty of water is required (Glassful of water) for effective effervesces.
2. There are certain limitations too, like it cannot be given to the children because of risk of carbon dioxide toxicity; it's shorter

shelf life; chance of product deterioration if packaging is not done properly and the cost of manufacturing is high, as compared to other tablets.

3. Some drugs causes irritation to gastric mucosa this type of drug not use in floating system.
4. Some drugs not suitable for FDDS as they have solubility or stability problem in GIT and unstable in acidic environment.
5. Size-increasing drug delivery systems potentially present the hazard of permanent retention in the stomach and could lead to life-threatening effects upon multiple administrations.

Evaluation technique[15, 17]

a) Pre-compression parameters

1. Density

The bulk density and tap density were determined by following formula:

Bulk density = weight of powder/ volume of powder in measuring cylinder.

Tap density = weight of powder / Tapped volume of powder in measuring cylinder.

Procedure

The 2gms of powder was introduced into a 10 ml of measuring cylinder. Then for bulk density, firstly note down the initial volume, then tapping was continued for tap density determination until no further change in volume was noted.

2. Angle of Repose

The angle of repose was determined by using fix funnel method. The accurately weighted powder was allowed to flow through the funnel. The funnel is adjusted to a stand at definite height. The radius of powder and height of heap of cone was measured. The angle of repose was then calculated by following formula.

$$\text{Tan } \theta = h / r$$
$$\theta = \tan^{-1} (h/r)$$

Where,
θ = angle of repose
h = height of the heap
r = radius of the heap

3. Compressibility Index

The flow ability of powder can be determine by comparing the bulk density and tapped density of powder. Carr's index was calculated by **=**

Carr's index **=** (tap density – bulk density) ×100 / tap density

4. Hausner ratio

Hausner ratio of each tablet blend was also calculated by using following formula:

Formula= tapped density / bulk density

b) Post-compression parameters

5. Tablet thickness and diameter

Thickness and diameter were measured using a calibrated Vanier caliper. Twenty tablets of each formulation were picked and measure for the thickness and diameter individually.

6. **Hardness**

The hardness of the tablets was determined using Monsanto hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness was expressed in kg/cm^2.

7. Friability test

The friability of tablets was determined by using Roche Friabilator. Twenty tablets were initially weighed and transferred into friabilator. This was given 100 revolutions at 25rpm for 4 minutes. It was expressed in percentage (%). The tablets were reweighed after friability test. The % friability was then calculated by:

$$\%\text{Friability} = W_i - W_o / W_i * 100$$

Where,

W_i = initial weight
W_0 = final weight

% Friability of tablets less than 1% was considered acceptable.

8. Weight Variation Test

Twenty tablets were selected and weighted collectively and individually. From the collective weight, average weight was calculated. Each weight of tablet was compared with average weight to ascertain whether it was within permissible limit or not. The percentage deviation was calculated by following formula:

% deviation = individual weight – average weight / average weight × 100

9. Buoyancy / Floating Test

The tablet was introduce in to beaker containing 100ml of 0.1 N HCL. The time is taken by the

tablet to come up to surface and floated was taken as the buoyancy time. The time taken for dosage form to emerge on surface of medium called Floating Lag Time and total duration of time by which dosage form remain buoyant is called Total Floating Time.

10. Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain as given by the equation.

$$WU = \frac{(W_t - W_0) \times 100}{W_0}$$

W_t= Weight of dosage form at time t.
W_0 = Initial weight of dosage form.

11. Determination of drug content in tablets[17]

Tablets are selected from each batch and transferred into a 0.1N HCL in 100 ml volumetric flask, and kept it for 48hrs, then take 1ml from each of volumetric flask and transferred to the test tubes. Then Samples are diluted and filtered suitably, and analyzed in UV spectrophotometer at a suitable wavelength.

12. Determination of In – Vitro Dissolution Study[17]

Dissolution study is carried out in USP dissolution testing apparatus II (paddle type). Dissolution study was performed using 900ml 0.1N HCL, at 50 rpm. A 5ml of sample was withdrawn from the dissolution apparatus at a predetermined interval and the sink condition is maintained by adding same volume of dissolution medium. The sample diluted to a suitable concentration with 0.1 N HCL. The absorption of withdrawn sample was measured spectrophotometrically, and the corresponding concentration was determined from the respective calibration curve.

Application of FDDS[19].

• Absorption enhancement

The Bioavailability of drugs found to be poor because of drug site specific absorption from the upper part of the gastrointestinal tract, so potential candidates to be formulated as floating drug delivery systems, and enhancing the rate of absorption.

• Sustained drug delivery

FDDS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. In this systems dose large in size and passing from the pyloric opening is prohibited. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems.

• Reduce fluctuations of drug concentration

In case of controlled release dosage form produces blood drug concentrations within a narrow range compared to the immediate release dosage forms. That's why fluctuations in drug effects are minimized.

• Site–specific drug delivery systems

These systems are particularly advantageous for drugs those are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. It reduces the side effects which are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

• Minimize adverse effect at the colon

In floating drug delivery system, a drug is slowly release in stomach so the amount of drug that reaches the colon is get slow down. Retention of the drug is minimizes at the stomach thus, undesirable activities of the drug in colon may be prevented.

REFERENCES

1. S. D. pande floating drug delivery system: a new way for oral drug delivery system international journal of pharmaceutical and clinical science universal research publications. 2013. 1-3p
2. Satinder kakar, Raman deep Singh, a review on floating drug delivery system in himachal institute of pharmacy, national journal of recent advances in pharmaceutical research India 2015. 56-57p.
3. Shukla shruti, patidar Ashish, a review on: recent advancement of stomach specific floating drug delivery system international journal of pharmaceutical & biological archives 2011.1561-1562p.

4. Bharkatiya meenakshi, floating drug delivery system: a review 1b.n. Institute of pharmaceutical sciences, Udaipur. , India, geetanjali institute of pharmacy, Udaipur. India 2014, 132p.
5. Anup amasarawade, M. P. Ratnaparkhi, shilpa Chaudhary floating drug delivery system: an overview department of pharmaceutics, marathwada Metra Mandal College of pharmacy, thergoan, pune2014, 1112-1114p.
6. Chaturvedi shashank, kumara prabha approaches to increase the gastric residence time: floating drug delivery systems- a review department of pharmaceutics, invertis institute of pharmacy, invertis university Bareilly 2013.2p.
7. Abhishek chandel, kapil Chauhan et-al. A review article floating drug delivery systems: a better approach department of pharmacy, manav Bharti University, solan -173229, himachal Pradesh, india2012.114p.
8. Binoy. B., jayachandra N., Nair C. V. floating drug delivery system- a new approach in gastric retention- a review department of pharmaceutics, sree Krishna college of pharmacy and research Centre, Thiruvananthapuram ,Kerala, India 2012. 18-24p.
9. Praveen NASA, sheefali mahant floating systems: a novel approach towards gastro retentive drug delivery systems m. m. college of pharmacy, m. m. university, mullana ambala 2010. 2-4p.
10. Bhavjit Kaur, shivani Sharma, geetika Sharma, a review of floating drug delivery system pharmaceutics division, Chandigarh College of pharmacy, land ran, Mohali 2013. 1-6p.
11. Geetha, J. Rajendra Kumar, Ch. Krishna Mohan, V. sateesh & P. N. Raju 1st a review on floating drug delivery systems. John College of pharmacy, yellapur, hasanparthy, Warangal, India Klr College of pharmacy, paloncha, khammam, India 2012. 1-13p.
12. Kunal. P. Nayak, prati kupadhyay, jayant Deshpande, Arohi R. Gastro retentive drug delivery systems and recent approaches: a review l.j. Institute of pharmacy, ahmedabad-382210, Gujarat, India 2012.1-8p.
13. G. Dakineswara Rao, B. Krishna Moorthy, M. Muthukumaran a typical review on floating drug delivery system Montessori Siva sivani institute of science & technology-college of pharmacy, mylavaram, andhrapradesh, India 2013. 140-141p.
14. Natasha Sharma, dilip Agarwal, m. k. Gupta and mahaveer pr. Khinchi a comprehensive review on floating drug delivery system. Department of pharmaceutics, Kota College of pharmacy, Kota, Rajasthan, India 2011.434-435p.
15. Jaimini Manish, Patel hardik gastro retentive floating drug delivery system: a review dept. Of pharmaceutics Jaipur college of pharmacy, sitapura, Jaipur, Rajasthan 2013.469-481p.
16. Jain Amit k, hatila Uma Shankar A review on floating drug delivery system, head of the department, student department of pharmaceutics, B. R. Nahata college of pharmacy, mandsaur.2229-4619p.
17. Shweta Arora, javed Ali, floating drug delivery systems: a review department of pharmaceutics, faculty of pharmacy, Hamdard University, New Delhi 110062, India 2005.E383-E386P.
18. A review avmaya vanshi and s. s. gajjarar floating drug delivery systems to increase gastric retention of drugs: college of pharmacy and G. H. Patel institute of pharmacy, vallabh vidyanagar, anand, Gujarat India 2008.347-348p.