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A Review on Formulation and Evaluation of Gastroretentive Floating Tablet of Nifedipin

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ABSTRACT

Different mass transport processes may occur during drug release from polymer-based matrix tablets, including water imbibition into the system, polymer swelling, drug dissolution, drug diffusion out of the tablet, and polymer dissolution. Depending on the type of drug, polymer and release medium and on the tablet composition, the respective processes are more or less important. Velasco et al.[24] reported that the rate and mechanism of nifidipine release from HPMC K15M-based matrices were mainly controlled by the drug/ HPMC ratio, and that drug release was independent of the compression force in the range between 3 and 12 kN. The effects of the two formulation variables "HPMC/ lactose ratio" and "HPMC viscosity grade" on the release of adinazolam mesylate from cylindrical tablets was studied by Sung et al. The resulting drug release rate was found to increase with decreasing "HPMC/ lactose ratio" and decreasing "HPMC viscosity grade

Keywords: HPMC, Floating tablet, Gastroretentive, Gastric residence.

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1. INTRODUCTION:

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting good in vitro floating behavior show prolonged gastric residence in vivo [1,2,3,4]. The physical properties of the drug delivery system (e.g., density and size) as well as the presence of food in the stomach have been identified as the two most important parameters determining the in vivo performance of the dosage form[5]. Under fasted conditions the stomach is cleared of undigested material every 1.5 to 2 h by housekeeper waves. To provide good floating behavior in the stomach, the density the density of the device should be less than that of the gastric contents (≅1.004 g/cm^3). However, it has to be pointed out that good in vitro floating behavior alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

2. BASIC PHYSIOLOGY OF THE GASTROINTESTINAL TRACT:

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[12]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.[13] This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.[13]

2.1 Gastric emptying and problems

It is well recognized that the stomach may be used as a depot for Sustained release dosage forms, both in human and veterinary applications, stomach is anatomically divided in to three parts: Fundus, body and pylorus.[15]

The proximal stomach made up of the fundus and body region serves as a reservoir for ingested materials, while the distal region (antrum) is the major site for the mixing motion, acting as a pump to accomplish gastric emptying. The process of the gastric emptying occurs both during fasting and fed stages.

2.2 Approaches to gastric retention

Various approaches have been paused to increase the duration of oral dosage form in the stomach, including

floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems, Super porous – biodegradable hydrogel systems).

Hydrodynamically balanced systems (HBS) –incorporated buoyant materials enable the device to float.[33, 34]

Table 1.1 Drawbacks associated with different types of GRDDS [9]

Formulations	Drawback
Incorporation of passage delaying food excipient such as fatty acids	- Affect the emptying mechanism of the entire content.
Bio adhesive drug delivery systems	- Adhesive is non specific - Efficiency is limited by the possible interaction with food.
Biodegradable and non biodegradable (swelling) formulation in which the size and shape retain in the dosage form.	- Present the hazard of permanent retention and might lead to serious life threatening effects if multiple dosing.

3. APPROACHES TO DESIGN FLOATING DOSAGE FORMS:

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.[18]

3.1 Single-Unit Dosage Forms

In Low-density approach[21] the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells[23] popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells.

4. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Floating drug delivery systems are classified depending on the use of two formulation variables: effervescent and non-effervescent systems.

4.1 Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

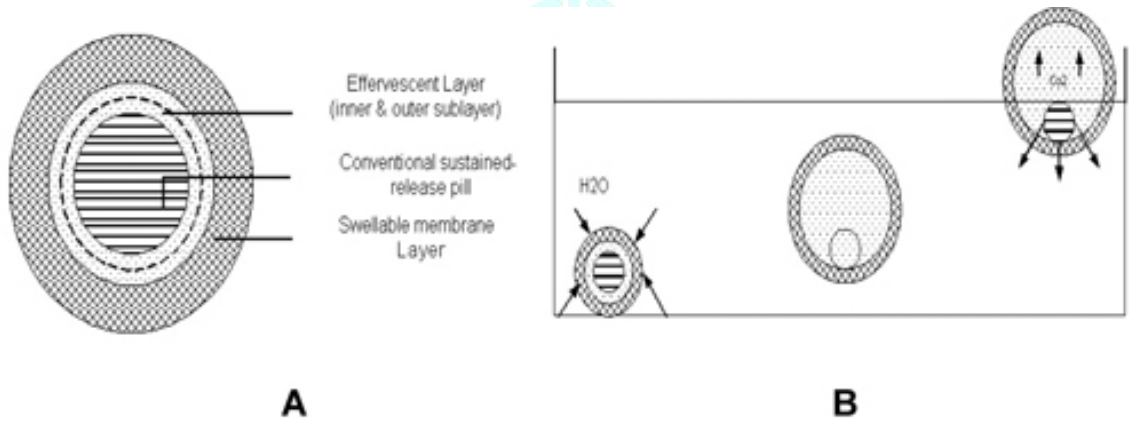

Figure 1.1. (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.

Yang et al[19] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in *Helicobacter pylori*–associated peptic ulcers using HPMC and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. (Figure 1.2).

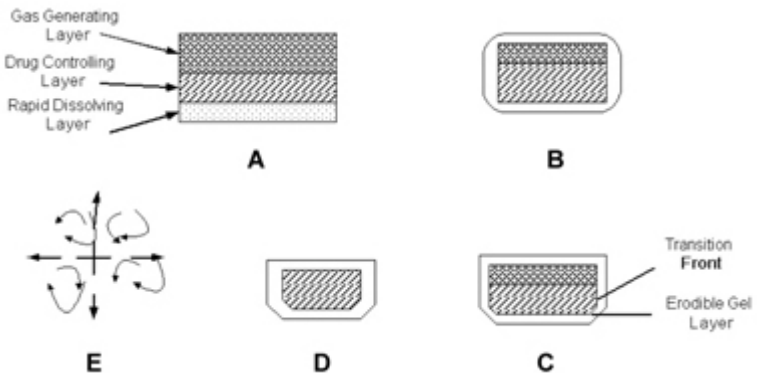

Figure 1.2. Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.

Li et al[25] evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived using taguchi design. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system.

4.2 Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1.

5. FACTORS AFFECTING GASTRIC RETENTION

5.1 Density

The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids (≅ 1.004 gm/ml) floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

5.2 Size and shape

To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm.[26] Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT (≅ 90 to 100 %) retention at 24 hours compared with other shapes.[27,28,29]

5.3 Fasting or fed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of 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.[36] The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.

Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

5.4 Nature of the meal

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time.[35] Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.[35]

5.5 Effect of liquid, digestible solid and indigestible solid type food

It has been demonstrated using radiolabeled technique that there is a difference between gastric emptying times of a liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (>1 mm) indigestible objects from stomach was dependent upon interdigestive migrating myoelectric complex. When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.[26]

5.6 Biological factors

Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females

have slower gastric emptying rates than males. GRT can very between supine and upright ambulatory states of the patients.[77] Stress increases gastric emptying rates while depression slows it down.[36]

5.7 Frequency of feed

The gastroretentive time can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.[32]

5.8 Gender

Mean ambulatory GRT in meals (3.4 ± 0.4 hours) is less compared with their age and race-matched female counterparts (4.6± 1.2 hours), regardless of the weight, height and body surface.

5.9 Posture

Gastroretentive time can vary between supine and upright ambulatory states of the patients [33]

5.10 Volume of liquids

The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

5.11 Effect of size of floating and nonfloating dosage

Timmermans and Andre[34] studied the effect of size of floating and nonfloating dosage forms on gastric emptying and concluded that the floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the nonfloating units, which lie in the antrum region and are propelled by the peristaltic waves.

6. FORMULATION OF FLOATING DOSAGE FORM

Following types of the ingredients can be incorporated in to HBS dosage form in addition to drugs.[31]

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous

6.1 Hydrocolloids

Suitable hydrocolloids are synthetics, anionic or nonionic like hydrophilic gums, modified cellulose derivatives. E.g. acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, methyl cellulose, hydroxyl propyl cellulose, hydroxyl ethyl cellulose, and sodium carboxy methyl cellulose can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when it enters in the gastric fluid system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

6.2 Inert fatty materials

Edible, pharmaceutically inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increase the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and minaral oils can be used. Such materials may be present from about 5 – 75 % by weight.

6.3 Release rate accelerant

The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5 – 60% by weight.

6.4 Release rate retardant

Insoluble substances such as dicalcium phosphate, talc, magnesium stearate decreased the solubility and hence retard the release of medicaments. Such, materials may be present about 5 – 60 % by weight.

6.5 Buoyancy increasing agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be added up to 80 % by weight.

6.6 Miscellaneous

Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporated in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

7. EVALUATION OF FLOATING SYSTEMS

Various parameters[9] that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

7.1 Floating time

The test for buoyancy is usually performed in simulated gastric and intestinal fluid maintained at 37°C. The floating time is determined by using USP dissolution apparatus containing 900 ml of o.1 N HCl as the testing medium maintained at 37°C. The time for which the dosage form floats is termed as the floating or floatation time.[29]

7.2. Swelling index

The swelling index of tablets was determined n 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = \frac{W_t - W_0}{W_0}$$

Where, W_0 is the initial weight of tablet, and W_t is the weight of the tablet at time t.

7.3 In vivo study

In vivo gastric residence time of a floating dosage form is determined by X-ray diffraction studies, gamma scintigraphy,[30] or roentgenography[82]. In X-ray method the formulation is modified to incorporate Barium Sulphate as X-ray opaque substance. The study is carried out by administering the gastroretentive tablets to human volunteer. The tablet was administered in the fasting state. The X Ray opaque formulation is administered along with 250 ml of water. The subjects are allowed to remain in sitting or upright position. A light meal is given to volunteer 2 hour after administration of the tablet to evaluate effect of food of

gastroretentive property. The position of tablet is monitored by X-Ray screening technique X-Ray photographs taken at desired intervals to monitor tablet position in human gastrointestinal tract.

8. ADVANTAGES OF FLOATING DOSAGE FORM [20,31]

- The Principle of HBS may not limited to any particular medicament or class of medicament
- The HBS formulations are not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicament, which absorbed from the intestine.
- Acidic substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- The HBS are advantageous for drugs absorbed through the stomach. e.g. Ferrous salts, antacids.
- The efficacy of the medicaments administered utilizing the sustained release principle of HBS formulation has been found to be independent of the site of particular medicaments.
- The HBS are advantageous for drugs meant for local action in the stomach. e.g.Antacids.
- Administration of prolongs release floating dosage forms, tablet or capsules, will results in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- When there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

9. CONCLUSION:

Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers. The floating concept can also be utilized in the development of various anti-reflux formulations.

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