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A Review on Buoyant Pharmaceutical Delivery System and Utilisation of Modern Polymeric Excipient

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Abstract: The primary objective of drug delivery systems is to attain a therapeutically effective and non-toxic concentration of the drug in the bloodstream or tissues over an extended period. Numerous endeavors have been undertaken to develop gastroretentive delivery systems, encompassing high-density formulations, swelling systems, and floating systems. This comprehensive review delves into recent advancements in Floating Drug Delivery Systems (FDDS), elucidating the physiological and formulation variables influencing gastric retention. It expounds upon methodologies for designing both single-unit and multiple-unit floating systems, providing a detailed classification and examination of formulation aspects. Furthermore, the review synthesizes findings from studies evaluating the performance and applications of floating systems, shedding light on their various uses. Given the intricacies of gastric emptying, a process introducing uncertainty to the in vivo performance of drug delivery systems, concerted efforts have been directed towards extending the retention time of these systems beyond 12 hours. In this context, hydrodynamically controlled drug delivery systems, particularly those employing floating mechanisms, prove advantageous.

Index Terms **- Floating, gastrointestinal, gastro retentive system, evaluation.**

1. Introduction

The oral route of administration offers a myriad of benefits, encompassing ease of application, strong patient adherence, formulation flexibility for dosages, convenient storage and transportation, and the elimination of the need for specialized personnel. According to analyses within this realm, over 50% of pharmaceuticals accessible in the market are intended for oral consumption. Nonetheless, the majority of oral drug delivery systems are susceptible to physiological variables that can unfavourably influence the active pharmaceutical ingredient's (API) bioavailability and the drug's clinical effectiveness. These factors encompass the pH level of the medium, the non-uniformity of absorption throughout the gastrointestinal tract (GIT), variations in surface area and enzymatic activity along different sections of the GIT, the duration of time spent in sections where absorption takes place, and the pace of metabolic and excretory processes. Due to the substantial impact of these effects on the performance of numerous drugs, two primary strategic avenues have been proposed for enhancing oral dosage forms: targeted delivery and modified release of the API. [1]

An exemplification of the aforementioned paradigm consists of gastroretentive delivery systems that facilitate controlled and prolonged drug release within the upper gastrointestinal tract. This amalgamation of attributes offers the potential to enhance the bioavailability of drugs prone to absorption primarily in an acidic milieu or featuring a limited "absorption window." Furthermore, it ensures the mitigation of fluctuations in blood plasma API concentrations and augments the efficacy of drugs with localized gastric action. Clinical benefits stemming from gastroretentive systems encompass the reduction of concentration-dependent therapeutic effect fluctuations, prevention of concentration-dependent adverse effects, extension of the therapeutic concentration maintenance period for drugs with time-dependent pharmacodynamics, averting undesirable

counterregulatory mechanism activation, rebound effects, and tolerance development. These systems also curtail undesirable effects by limiting API entry into other segments of the gastrointestinal tract [2].

As of current knowledge, several principal categories of gastroretentive systems have been identified, including magnetic, mucoadhesive, high-density, raft-forming, floating, size-increasing, and superporous hydrogels. Among these delineated variations, considerable attention has been directed towards floating drug delivery (FDF) systems within research literature. Notably, FDF systems exhibit an advantageous autonomy from intraspecies anatomical discrepancies (e.g., pyloric sphincter size) and the condition of gastrointestinal mucous membranes. Additionally, they offer relative ease of fabrication through standard technological processes. In the production of all aforementioned gastroretentive delivery systems, particularly the floating variants, diverse polymeric entities are commonly employed to facilitate retention within the stomach. Consequently, meticulous selection of suitable constituents within the pharmaceutical composition becomes imperative to govern the technological, pharmaceutical, and pharmacokinetic attributes of the drug formulation.

2. Floating Drug Delivery Systems

Davis first described the floating drug delivery system (FDDS) in 1968. FDDS is a useful technique for extending the gastric residence period to increase the drug's bioavailability. FDDS, which bulk density initially is less than that of gastric juice (1.004 g/cm^3) or falls to the appropriate value after being consumed for a predetermined amount of time. Due to this ability, the medicine can stay on the surface of the stomach's contents rather than being evacuated to the stomach's deeper portions, preventing damage to the mucous membranes and the rate of emptying. Flotation gives the system the ability to deliver drugs specifically to the right places at the right times for the right therapeutic needs. When it comes to drugs with low intestinal fluid solubility and stability, these devices are helpful. The idea of FDDS is to make the dosage form less dense than the stomach juices so that it can float on them. With enough buoyancy to float over the contents of the stomach and remain buoyant there without noticeably slowing down the process of gastric emptying, FDDS are hydrodynamically regulated low-density devices. The residual system in the stomach is emptied with the drug's release. This results in an extended period of stomach occupancy and more effective management of variations in plasma drug concentration. The idea of buoyant preparation provides a simple and practical way to increase stomach capacity. In some cases, it makes sense to extend a delivery system's stomach retention in order to boost the pharmacological component's therapeutic efficacy. For example, drugs that are poorly soluble or that break down at an alkaline pH are good at prolonging stomach retention. Additionally, there is increased absorption of these medications at the proximal portion of the gastrointestinal tract. Furthermore, in the treatment of certain ulcerative disorders, prolonged gastric retention of the therapeutic moiety permits sustained drug administration to the stomach and proximal small intestine. Numerous advantages result from this, such as increased bioavailability and therapeutic efficacy with fewer dose requirements [3].

2.2 Classification of Floating DDS

2.2.1 Effervescent floating system

The employed administration modality proves optimal for medications characterized by an absorption window within the stomach or upper small intestine. Owing to the lower bulk density of Floating Drug Delivery Systems (FDDS) compared to gastric fluids, these systems exhibit buoyancy within the stomach for an extended duration without impeding gastric emptying kinetics. Simultaneously, they facilitate the controlled release of medication at the appropriate rate. Following oral administration in the GIT, these drug delivery devices release CO_2, which lowers their density and causes them to float in the gastric fluid FDDS should own following properties.

- A cohesive gel barrier is required.
- It should gradually discharge its contents to act as a reservoir.
- It must keep its specific gravity (1.004–1.01 gm/cm^3) below that of stomach contents.

Effervescence Agents: Calcium carbonate, Sodium bicarbonate, Sodium carbonate, Di-SGC (Di-Sodium Glycine Carbonate), Citric acid, Tartaric acid, CG (Citroglycine) and more. [3]

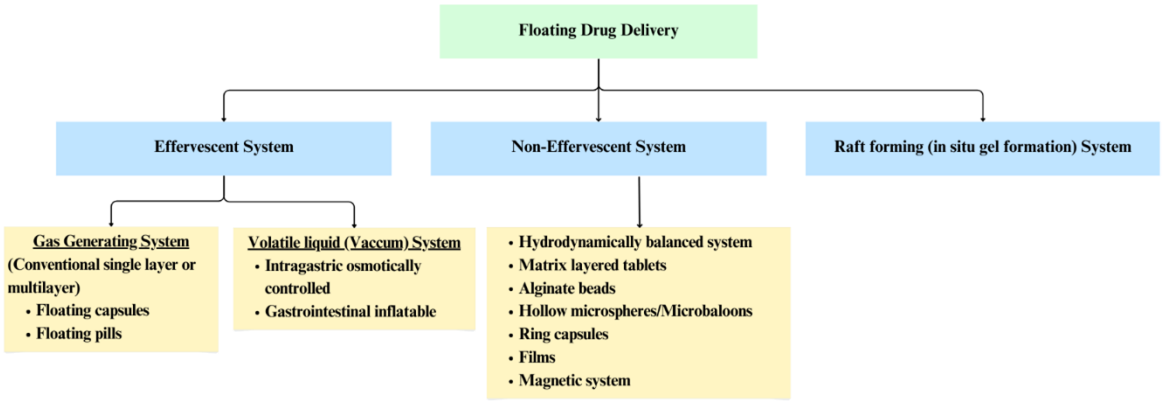

Fig 1: Classification for FDDS

2.2.2 Non-Effervescent floating system

Non-effervescent formulations encompass a substantial proportion (20–75% w/w) of tablets or capsules composed of matrix-forming polymers, gel-forming polysaccharides, and highly swellable cellulosic hydrocolloids, such as hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose. Upon contact with gastric fluid, these polymers and polysaccharides undergo hydration and gel formation, establishing a colloidal gel barrier. This barrier effectively modulates the rate of fluid penetration into the device, thereby regulating the subsequent release of medication. The hydration of the adjacent hydrocolloid layer serves to maintain the integrity of the gel layer as the external surface of the dosage form dissolves. The air captured by the expanded polymer reduces the dosage form's density and gives it buoyancy. [4]

A. Single Layer Floating Tablets

These entities are generated through a meticulous amalgamation of the pharmaceutical agent with a hydrocolloid capable of gel formation upon interaction with gastric fluid, thereby sustaining a bulk density below unity. The buoyancy exhibited by these dosage forms stems from the entrapment of air within the inflated polymer. [5]

B. Bilayer Floating Tablets

The sustained release stratum undergoes absorption of gastric fluid, leading to the creation of an impermeable colloidal gel barrier on its surface. This barrier preserves a bulk density below unity, thereby facilitating buoyancy of the bilayer tablet within the stomach. Simultaneously, the immediate release layer initiates the release of the initial dosage from the system. [6]

C. Alginate Beads

Freeze-dried calcium alginate was employed in the fabrication of multi-unit floating dosage forms. Through the introduction of a sodium alginate solution into an aqueous solution of calcium chloride, calcium alginate precipitates, giving rise to a porous system capable of maintaining buoyancy for over 12 hours. The resultant spherical beads, approximately 2.5 mm in diameter, exhibited an extended residence period exceeding 5.5 hours in contrast to solid beads, which only retained a residence time of 1 hour. [7]

D. Hollow Microspheres

Hollow microspheres, also known as micro balloons, incorporating drug payloads and encapsulated within a polymer matrix, were synthesized employing an innovative emulsion-solvent diffusion methodology. The process involved introducing a solution of the drug in ethanol and dichloromethane to an agitated aqueous polyvinyl alcohol (PVA) solution, maintained at a controlled temperature of 40°C, in the presence of an enteric acrylic polymer. The vaporization of dichloromethane occurred within the dispersed polymer droplets, giving rise to the inner cavity of the polymer-drug microsphere. Over a duration exceeding 12 hours in an in-vitro setting, these diminutive balloons consistently exhibited buoyancy atop the outermost layer of the acidic dissolving media. [8]

E. High-density Systems

To retain pellets of sufficiently diminutive size within the rugae or folds of the gastrointestinal tract, particularly in proximity to the pyloric region—the anatomical region characterized by the lowest position when the body is in an upright posture—sedimentation has been employed as a retention mechanism. Pellets possessing high density (approximately 3g/cm^3), ensnared within rugae, demonstrate resilience against peristaltic contractions of the gastrointestinal wall. Consequently, the passage time of pellets through the gastrointestinal tract can be extended from an average of 5.8 to 25 hours; however, there are many contradictory claims in the literature that claim this is not the case. Excipients including, iron powder, titanium dioxide, barium sulphate, and zinc oxide are frequently utilised. These substances can raise density by 1.5–2.4 g/cm^3 or more. No effective high-density system, though, till now reached the market. Here, a gel-forming solution (for instance, a sodium alginate solution containing carbonates or bicarbonates) expands and creates a thick, cohesive gel that comes into touch with gastric fluid and contains trapped CO_2 bubbles. To lessen gastric acidity, formulations frequently include antacids like aluminium hydroxide or calcium carbonate. Raft producing systems, including liquid Gaviscon (GlaxoSmithKline), are frequently used to treat gastroesophageal reflux because they create a layer on top of stomach contents. [9]

F. Bio/Muco-adhesive Systems

Through augmentation of proximity and duration of interaction between the medication and the biological membrane, bio/muco-adhesive systems harbour the capacity to extend the gastric receptive time (GRT) of drug delivery systems (DDS) within the stomach. The establishment of GRDDS based on bio/muco-adhesive polymers has made use of the mucin's surface epithelial adhesive capabilities. A drug's (or a delivery system's) capacity to adhere to the GI wall allows it to stay at one particular organ site for a longer period of time, improving its local or systemic activity. [10]

G. *In-situ* oral floating gels

Oral drug delivery has undergone a revolution thanks to in situ gel-forming drug delivery methods. Under ambient conditions, these hydrogels exist in a liquid state; however, upon contact with bodily fluids or exposure to a pH alteration, they undergo a gelation process. This phenomenon is characterized by cation-induced and temperature-dependent gelation. The initial phase involves the formation of double helical junction zones, followed by the aggregation of double helical segments to establish a three-dimensional network through interactions involving hydrogen bonding and cations. [11]

3. Floating DDS Advantages

Floating dosage systems exhibit gastric retentive properties and offer numerous benefits in the realm of drug delivery, including:

1. **Simplicity in Formulation:** These systems can be formulated using straightforward and conventional techniques.
2. **Precision in Drug Delivery:** They enable targeted delivery of drugs to specific sites within the body.
3. **Controlled Drug Release:** These systems facilitate controlled and gradual release of drugs over time.
4. **Localized Residual Action:** Drugs can be delivered to and maintained at specific locations within the stomach, allowing for sustained effects.
5. **Enhanced Drug Absorption:** Prolonged gastric retention time (GRT) ensures extended contact between the dosage form and its target site, leading to improved drug absorption.
6. **Mitigation of Irritation:** Drugs with slow-release rates can minimize irritation of the gastrointestinal mucosa. For instance, acidic substances like aspirin can irritate the stomach lining upon contact. Formulating such drugs as hydrodynamically balanced systems (HBS) can reduce this irritation, making them suitable for administration.
7. **Effective Prolonged Release:** Tablets or capsules of prolonged-release floating dosage forms dissolve in gastric fluid, ensuring complete dissolution before reaching the small intestine. This promotes full drug absorption even within the alkaline environment of the intestine.
8. **Diarrhoea Prevention:** In situations where rapid intestinal movement and short transit times could lead to diarrhoea and poor absorption, maintaining the drug in a floating state in the stomach proves beneficial for improved efficacy.
9. **Gastroesophageal Reflux Disorder (GERD) Treatment:** These systems can be employed in the treatment of GERD, a condition involving stomach acid flowing back into the oesophagus.
10. **Enhanced Patient Compliance:** Due to their ease of administration and patient-friendly characteristics, these systems lead to higher patient compliance with prescribed regimens. [12]

4. Floating DDS Disadvantages

1. The principal drawback of a floating drug delivery system stems from its requirement for an adequate volume of gastric fluids to facilitate buoyancy and prevent sinking. Nevertheless, this constraint can be addressed through the application of bio adhesive polymers that readily adhere to the gastric mucosa, ensuring sustained retention.
2. These systems are particularly advantageous for drugs that undergo considerable absorption along the entire length of the gastrointestinal tract and undergo substantial first-pass metabolism.
3. It's worth noting that certain drugs present within a floating system might trigger irritation within the gastric mucosa.
4. Gastric emptying of floating drug delivery systems can occur in an unpredictable manner, heavily contingent upon the dimensions of the dosage form. Consequently, it is advisable for patients not to administer such dosage forms prior to bedtime. [13]

5. Sustained drug delivery

Gastric residence time can be significantly prolonged with Hydrodynamically Balanced Systems (HBS), enabling a gradual release of medication. These strategies offer a resolution to the limited gastric residence period associated with oral Controlled Release (CR) formulations. Due to their bulk density of 1, HBS can float on gastric contents. Their substantial size prevents passage through the pyloric aperture. For instance, sustained release floating capsules containing nicardipine hydrochloride were formulated and evaluated in vivo using rabbits. The performance of these capsules was compared to commercially available MICARD capsules. Notably, the sustained release floating capsules exhibited an extended administration time of 16 hours on plasma concentration-time curves, contrasting with the conventional MICARD capsules with an administration time of 8 hours. [14]

6. The Role of Polymers in Advancing Floating Drug Delivery System Technology

Targeted distribution and the adjusted release of the API are the key benefits of floating Gastroretentive systems, as was already mentioned. These distinctive attributes are commonly attained through the utilization of specific excipients, predominantly of polymeric nature. In this context, the targeted delivery of medication manifests as a buoyant characteristic, achievable through various technological approaches aligned with the conventional Floating Dosage Form (FDF) classification. Presently, such buoyancy can be realized through one of two methodologies: either by incorporating constituents such as air or low-density explosives, or by employing systems whose density diminishes post-ingestion due to swelling or gas generation.

As previously indicated, there are two ways to obtain the originally low density of DF: either by creating air pores or cavities, or by adding specific Es. Freeze drying, sublimation of previously introduced volatile components (such as camphor or menthol), extrusion, sonication of liquid intermediates, production of hollow microspheres, or 3D printing of delivery systems with pre-designed cavities are all methods for incorporating air. This method offers 0% ascent delay time, lowering the chance of MP being prematurely evacuated from the stomach. The stated processes are typically complex or call for adding more steps to the technology to produce DF in the form of tablets, granules, pellets, etc. In this method of flotation, polymers are utilised to build a matrix or shell that will contain the system's gases. However, it permits the employment of conventional technological procedures. The second approach, based on the inclusion of low-density Es, also makes it feasible to secure the instantaneous ascent of the DF. Oils or lipophilic materials are frequently used for these objectives, along with water-insoluble fillers with low bulk densities such ethyl cellulose (EC) and foamed polypropylene, according to the sources [15].

7. Evaluation of FDDS formulation [16]

A. For Single Unit Dosage Forms (ex: tablets) :

(i) Floating lag time: It represents the duration required for the tablet to surface within the dissolution medium, quantified in seconds or minutes.

(ii) Invitro drug release and duration of floating: This is ascertained utilizing the USP II apparatus with a paddle, stirring at either 50 or 100 rpm at a temperature of 37 ± 0.2 °C in Simulated Gastric Fluid (pH 1.2, devoid of pepsin). Subsequent to sample collection, drug content analysis is performed on the aliquots. The duration of floating, denoted in hours, corresponds to the period during which the tablets persist buoyant on the surface of the dissolution medium and is observed visually.

(iii) In vivo evaluation for gastro-retention: This is accomplished through X-ray or Gamma scintigraphic surveillance of the transition of the dosage form within the Gastrointestinal Tract (GIT). Additionally, assessments are conducted on the tablets for parameters such as hardness, weight variation, and others.

B. For Multiple Unit Dosage Forms (ex: floating beads):

In addition to in vitro release, the duration of floating, and in vivo gastro-retention assessments, multiple-unit dosage forms are subjected to further evaluations for:

(i) Morphological and dimensional analyses are conducted utilizing scanning electron microscopy (SEM), while the size can be quantified through the application of an optical microscope.

(ii) % yield of beads: This is calculated from the following formula:

$$\%yield\ of\ beads = \frac{Weight\ of\ beads\ obtained}{Total\ weight\ of\ drug\ and\ polymer}\ x\ 100$$

(iii) Entrapment efficiency: A suitable method is employed to extract the drug, analyzed and is calculated from the following formula

$$\%yield\ of\ beads = \frac{Practical\ amount\ of\ drug\ present}{Theoretical\ drug\ content}\ x\ 100$$

(iv) In vitro floating ability (Buoyancy %): A predetermined quantity of microspheres is evenly distributed across the surface of a USP (Type II) dissolution apparatus, which is then filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80, and subjected to agitation at 100 rpm for a duration of 12 hours. Following this period, the layers corresponding to floating and settled microspheres are segregated, subjected to desiccation, and subsequently weighed. The buoyancy is computed utilizing the ensuing formula:

Buoyancy (%) = Wf/(Wf + Ws) x 100

Where Wf and Ws are the weights of floating and settled microspheres respectively.

v) Drug-excipient (DE) interactions: This is accomplished through Fourier-transform infrared spectroscopy (FTIR). The emergence of a new peak and/or the disappearance of the initial drug or excipient peak serves as an indicator of drug-excipient interaction.

In addition to the aforementioned evaluation parameters, granules (e.g., Gelucire 43/01) undergo assessment for the impact of aging, employing techniques such as Differential Scanning Calorimeter (DSC) or hot stage polarizing microscopy.

Conclusion

It may be inferred from the reviewed literature that there are a number of possible benefits to medication delivery by gastroretentive methods. An increasing variety of GRDDs will be developed to optimise drug delivery of compounds demonstrating regional heterogeneity in drug absorption, thanks to advances in drug delivery technology and growing understanding of the impact of GIT physiology on drug delivery. The therapeutic effectiveness of medications is greatly increased by sustained drug delivery systems. In GRDDs, polymers—natural and synthetic—have potential benefits. A number of plant-derived polymers have been effectively employed in dosage forms for efficient sustained release drug delivery, and more are being researched as potential excipients. The utilisation of natural gums in pharmaceutical applications is appealing due to its affordability, accessibility, non-toxicity, and ability to chemical modifications.

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