AN OVERVIEW ON VARIOUS APPROACHES TO ORAL CONTROLLED DRUG DELIVERY SYSTEM VIA GASTRORETENTION

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of oral drug delivery system. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract includes floating drug dosage systems (FDDS), swelling or expanding systems , mucoadhesive systems , magnetic systems, modified-shape systems, high-density system and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used.

Keywords: Gastroretentive systems; Floating systems; Buoyant delivery Systems; Swelling System

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration.[1] Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine[2, 3]. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract includes floating drug dosage systems (FDDS) [4, 5, 6, 7, 8] swelling or expanding systems [9], mucoadhesive systems [10, 11], modified-shape systems [12], high-density system [13], and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used.

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS)[14]. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site (Fig. 1)[15], thus ensuring its optimal bioavailability [16, 17]

Current Approaches to GRDDS

1. Floating drug delivery systems (FDDS)

Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period [18, 19]. While the system floats over the gastric contents (as shown in Fig. 2), the drug is released slowly at the desired rate [20, 21], which results in increased GRT and reduces fluctuation in plasma drug concentration[22].

Floating systems can be classified as *effervescent* and *noneffervescent* systems**.**

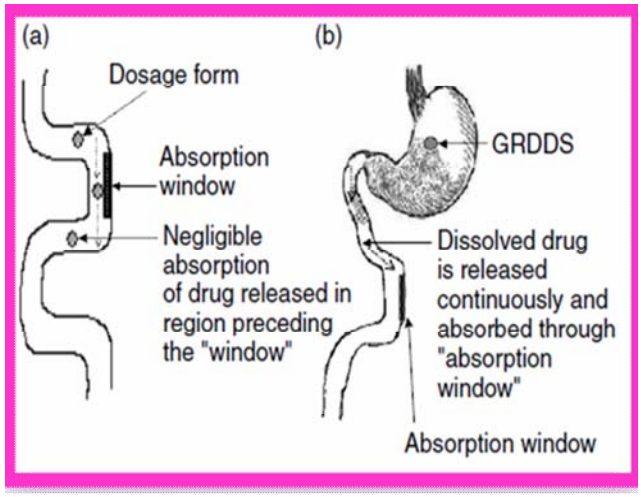

Figure 1: Drug absorption in the case of (a) Conventional dosage forms (b) Gastroretentive drug delivery systems [44].

i) Effervescent systems

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 [23] or matrices containing chambers of liquid that gasify at body temperature[24-26]. Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas[27]. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO2 produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts[28]. The matrices are fabricated

so that upon arrival in the stomach, carbon dioxide 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. A decrease in specific gravity causes the dosage form to float on the chyme [23].

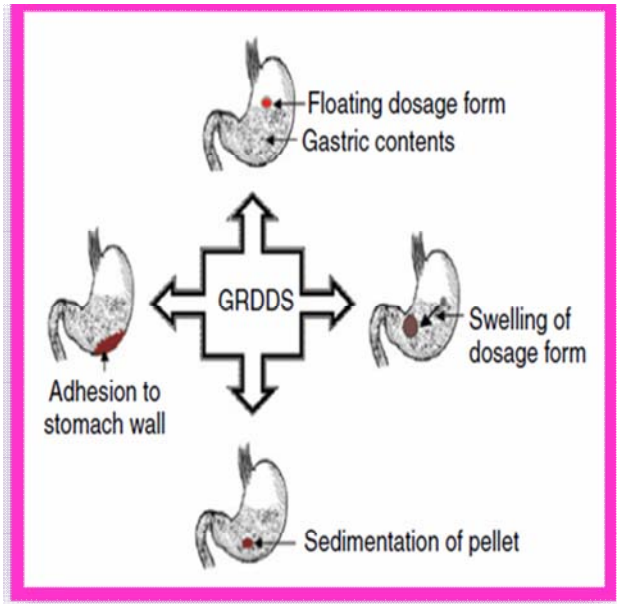

Figure 2: Classification of Gastroretentive Drug Delivery Systems[44].

Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed[19]. The system consisted of sustained- release 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 containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sublayers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sublayer and tartaric acid was 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, with a density much lower than 1 g/ ml. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layers with the diffusion of water through the outer swellable membrane layers. The system was found to float completely within 10 min and approximately 80% remained floating over a period of 5 hr irrespective of pH and viscosity of the test medium. While the system was floating, a drug (p-amino benzoic acid) was released. A variant of this approach utilizing citric acid (anhydrous) and sodium bicarbonate as effervescing agents and HPC-H grade as a release controlling agent has also been reported[29]. In vitro results indicated a linear decrease in the FT of the tablets with an increase in the amount of effervescing agents in the range of 10–20%. Attempts have also been made to develop SR floating tablets using a mixture of sodium bicarbonate, citric acid and chitosan.

ii) Noneffervescent systems

Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose [HPMC], and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules[30]. Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier[31] that controls the rate of fluid penetration into the device and consequent drug release[32]. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form**.**

2. Bio / Mucoadhesive systems

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The concept is based on the self-protecting mechanism of the GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a viscoelastic, gel-like, stringy slime comprised mainly of glycoproteins. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases. In addition, it serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses [33]. The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers [34]. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailibility[35]. A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and nonabsorbable, form noncovalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug and offer no hindrance to drug release, have a specific site of attachment, and be economical.

The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories [36]

1. Hydration-mediated adhesion
2. Bonding-mediated adhesion
3. Receptor-mediated adhesion

1. Hydration-mediated adhesion:

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

2. Bonding-mediated adhesion:

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of

the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

3. Receptor-mediated adhesion:

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

3. Swelling/ Expanding Systems

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus[37]. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as *plugtype systems* because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslinks in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of crosslinking between the polymeric chains. A high degree of crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer [38]. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion [39]. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration[37].

4. High-density systems

Gastric contents have a density close to water (¨1.004 g/cm^3). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall [40, 41]. Sedimentation has been employed as a retention mechanism for high density systems. A density ~3 g/cm^3 seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide, iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. The only major drawbacks with this systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3.

5. Magnetic systems

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe2O3). They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h[42]. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. [43]

CONCLUSION

Gastroretentive drug delivery system comprised mainly of floating, bioadhesive, swelling, high density and magnetic systems have emerged as a current approaches of enhancing the bioavailability and controlled delivery of drugs that exhibit an absorption window. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of the drug for a prolonged period but also present the drug in an absorbable form at regions of optimal absorption. All these drug delivery systems are interesting and present their own advantages and drawbacks. Designing GRDDS requires a thorough understanding of the physicochemical properties of the drug, the physiological events of the GIT and formulation strategies. A careful consideration of the interplay of these parameters can help in designing a successful GRDDS.

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