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RECENT ADVANCES IN GASTRO RETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Several controlled oral drug delivery systems with prolonged gastric residence time have been reported recently. Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastro intestinal tract improving the oral sustained delivery of drug that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Various approaches for gastric retention are Floating system, Swelling and expanding system, Bioadhesive systems, Modified-shape systems, High density systems etc.

Key words: Gastric retention,Absortion window,Floating dosage form,Polymer.

INTRODUCTION

Oral controlled release dosage forms are being developed for the past 3 decades due to their advantages. The design of oral controlled drug delivery system is primarily aimed at achieving more predictable and increased bioavailability, there by obtaining a maximum therapeutic effect. However, some of these systems do not work as planed due to several physiological difficulties, such as inability to restrain and localize the drug delivery system within desired region of GIT and highly variable nature of gastric emptying process [1].It can be anticipated that, depending upon the physiological state of subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hrs. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in stomach or upper part of small intestine. Thus, placement of drug delivery system in a specific region of the GIT offers a numerous advantages especially to the drug having narrow absorption window, stability problem in intestine, poor solubility in alkaline pH, local activity in stomach and property to degrade in column. Therefore the design of a sustained release preparation requires both prolongation of GI transit of dosage form as well as controlled drug release.

To overcome these limitations, several controlled and drug delivery systems with prolonged gastric residence times have been reported recently. [2] Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastro intestinal tract. The gastro retentive drug delivery system can be retained in the stomach and assist in a improving the oral sustained delivery of drug that have an absorption window in a particular region of the gastrointestinal tract. The systems help is occasionally releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailabilty.

Factors Affecting the Gastric Residence Time

- Density of dosage form – Density of gastric fluid is reported to be 1.004gm/ml. The density of the dosage form should be less than this for buoyancy, so that it is retained in the stomach for a longer time. [3]Dosage forms may have a high density in the beginning but float in the stomach due to reduction in density by swelling.
- Composition of meal: Fats, particularly fatty acids inhibit gastric secretion and have a pronounced reductive effect on the rate of emptying. Proteins and starch are shown to have inhibitory effect on gastric emptying, though to a less extent. As the viscosity of the gastric fluids is increased, there is a corresponding decrease in the rate of emptying.
- Caloric content: Gastric residence time can be increased by 4-10 hrs with a meal that is rich in proteins and fats.
- Frequency of the food :- The gastric residence time can increase by >6 hrs when successive meals are given, compared with a single meal, due to low frequency MMC.
- Size of dosage form :- In general it is known that indigestible solids > 1-2mm are retained in the stomach throughout the postprandial period, after which they are emptied by cyclical recurring brust of interdigestive gastric contractions[4]. Many recent studies have shown that non disintegrating tablets as large as 7.0mm can be emptied from the human stomach during the postprandial period, while 13.0mm tablets are retained until arrival of subsequent sweeping 'housekeeper waves'. This emphasizes the need for size enlargement of dosage forms in the stomach in order to prolong the gastric residence time.
- Sex: - Generally females have a slower gastric emptying rate (4.6 1.2hrs) than males (3.40.6hr) regardless of weight, height and body surface area.
- Body posture: - Gastric emptying is favored while standing and by lying on the right side since the normal curvature of the stomach provides a downhill path whereas lying on the left side or in supine position retards it.
- Emotional state of subject: - The influence of emotional factors on gastric motility depending upon wheather the emotional experience is of an aggressive or a depressive type.
- Effect of drugs: - Drug that retard gastric emptying includes poorly soluble antacids (Aluminum hydroxide), anticholinergics (Atropine, Propantheline), narcotic analgesics (Morphine) and tricyclic antidepressants (Imipramine, amitryptiline), Metoclopramide, domperidom and cisapride (Anti emetics) stimulates gastric emptying.
- Exercise: - Vigorous physical activity retards gastric emptying.
- Disease states:-Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Duodenal ulcer and hyperthyroidism promote gastric emptying rate.
- Gastrointestinal pH: - Gastric emptying is retarded at low stomach pH and promoted at higher or alkaline pH. Chemicals that affect gastrointestinal pH also alter gastric emptying. [5]The inhibitory effect of various acids on gastric emptying decreases with increase in molecular weight and is in the following order HCL>Acetic>lactic>tartaric>citric. With alkaline solutions, a low base concentration (1% $NaHCO_3$) increases

the gastric emptying rate more than the 1 of higher concentration (5%).

Various Approaches for Gastric Retention

- Floating system
- Swelling and expanding system
- Bioadhesive systems
- Modified-shape systems
- High density systems
- Other gastric emptying devices

Floating drug delivery or hydrodynemically balanced system (HBS)

These systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. [6]While the system is floating in the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied form the stomach. This results in an increase in the gastric retention time and a better control of fluctuation in plasma drug concentration.

HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than I thereby being buoyant on the gastric contents of stomach until the entire drug was released.

Hydrodynemically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids.

Hydrodynemically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption[7]. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug continuously from the dosage form. The success of floating capsule, as better system is best exemplified with chloridzepoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000 – fold difference in solubility going from pH 3-6 (the solubility of chlordizepoxide hydrochloride is 150mg/ml at neutral pH.)

Swelling and expanding system

One way to retain a dosage form in the stomach is by increasing its size. The stomach discharges its contents through the pylorus in to the intestine. If the dosage form can attain a size larger than that of the pylorus it can be retained in the stomach for a long time.

[8]Swelling type dosage forms are such that after swallowing these products swell to a extent that prevents their exit from the stomach through the pylorus as a result the dosage form is retained in the stomach for a long period of time. These systems may be referred to as " plug type system" since they exhibit a tendency to remain lodged at the pyloric sphincter.

Bioadhesive Systems

These systems are essentially based on bioadhesive polymers, which adhere to the mucin and / or eptithelial surface. Bioadhesive polymers can bind mucus as well as non-mucus membranes. If bioadhesiion is restricted to mucosal surface it is called mucoadhesion. Non-specific bioadhesive systems bind to mucin and epithelial surface by non-specific interaction between polymer particle and intestinal surfaces. Specific bioadhesive systems are designed by attaching a ligand to polymer particles, the ligand then recognizes and attaches to a specific area of the mucosal surface. Mucoadhesive controlled release systems increase the effectiveness of the drug by maintaining the drug concentration in therapeutic level, inhibiting the dilution of drugs in body fluids, and allowing targeting and localization of drugs at specific site. The duration of contract and intimacy between polymer-drug particles and mucosal surface is increased by mucoadhesion.

Lecithin is the most commonly used ligand for specific bioadhesion. Nonspecific bioadhesion mainly depends on the nature of polymer used for the system. Various polymers such as poly (acrylates), poly (lactic acid) chitosan, alginates, polystyrenes and sodium hyaluronate are reportedly bioadhesive in nature.

Modified Shape Systems (MSS)

MSS are non-disintegrating geometric shapes molded from elastomer or extruded from polyethylene blends, which extend the gastric retention time depending on size, shape and flexural modulus of the drug delivery device.

High Density Systems

The density of the pellets must exceed that of normal stomach content (1.004 gm/cm^2). For preparing such formulations, drug can be coated on a heavy core or mixes with heavy inert materials such as barium sulfate, titanium dioxide, iron power and oxide. The weighed pellets can then be covered with a diffusion-controlled membrane. Other delayed emptying approaches of interest include same feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

Approaches to Design Floating Dosage Form (FDF)

The following approaches have been used for the design of FDF of single and multiple-unit systems:

Single-Unit Dosage Forms

In Low-density approach 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 popcorn, pop rice and polystyrol have been exploited as drug carriers. [9] Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxyl propyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

The three-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion towards the completion of the release process. [10] The system was designed in such a manner that it floated to prolong gastric residence time in vivo, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH dependant solubility, a narrow window of absorption, and are absorbed by active transport form either the proximal or distal portion of the small intestine.

Single – formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.

Multiple-Unit Dosage Forms (MUDF)

The purpose of designing MUDF is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed.

Fluid-filled floating chamber type of dosage forms includes incorporation of a gas filled floatation chamber into a micro porous

component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remain afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

Various types of tablets (bilayer and matrix) have been shown to have floatable characteristics. Some of the polymers used are hyroxypropyl cellulose, hydroxy propyl methylcellulose, crosspovidone, sodium carboxy methylcellulose, and ethyl loading capacity and many polymers used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polylkylcyanoacrylate. Spherical polymeric micro sponges, also referred to as “micro ballons”, have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In carbon dioxide generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the device after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of 12 to 18 mm in their expended state is expected.

Classificatiion of floating drug delivery systems (fdds) [11]

Floating drug delivery systems are classified depending on the use of 2 formulation variables, effervescent and non-effervescent systems.

1. Effervescent Floating Dosage Forms (EFDF)

These are matrix type of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., 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.

2.Non-Effervescent Floating Dosage Forms (NEFDF)

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 or thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluid and attains a bulk density of <1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

CONCLUSION

In the recent scenario of controlled drug delivery, hydrophilic natural polymers, especially gums and natural products have been extremely popular in developing oral controlled release formulations as they have been found to be effective. Their success is linked to many factors like economy, availability, ease of manufacture, less toxic, low incidence of uncontrolled release, etc. With proper control of the manufacturing process of hydrophilic matrices, reproducible release profiles are possible. There is an immediate release of a small amount of active principal from these matrices but there is risk of dumping a large part of the dose. Their safe form and inherent advantages over other systems justify the well-deserved attention of hydrophilic matrices.

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