e - ISSN - 2348 - 2168
Print ISSN - 2348 - 215X

Acta Biomedica Scientia

Journal homepage: www.mcmed.us/journal/abs

AN OVERVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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Article Info

Received 29/10/2014
Revised 12/11/2014
Accepted 18/11/2014

Keywords :-
Swelling, Gastro retentive drug delivery system, Gastric residence time

ABSTRACT

Gastro retentive drug delivery system can be retained in the stomach for long time by formulating. The development of Gastro retentive drug delivery system is to control physiological adversities such as short gastric residence times and unpredictable gastric emptying time. Differences in gastric physiology such as gastric pH and motility exhibit both intra and inter subject variability demonstrating significant impact on gastric residence time and drug deliver. Several approaches are done for drug delivery systems such as, swelling and expanding systems, bio-adhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices have been discovered till now.

INTRODUCTION

The commonly used and most convenient method of drug delivery is oral route of drug administration. Despite tremendous advancements in drug delivery the oral route remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration leading to high levels of patient compliance. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies a brief gastrointestinal transit time, poor bioavailability and the existence of an absorption window in the upper small intestine for several drugs [1].

These difficulties have prompted researchers to design a drug delivery system which can remain in the stomach for prolonged and predictable period. Attempts are being made to develop a controlled drug delivery system, which can provide drug release at a pre determined, predictable and controlled rate. The denovo design of an oral CDDS should be primarily aimed at achieving more predictable and increased bioavailability of drugs [2]. For the successful performance of oral CRDDS the drug should have good absorption throughout the GIT, preferably by passive diffusion.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in GIT is to control the Gastric residence time (GRT) using gastro retentive dosage forms (GRDFS) that offer a new and better option for drug therapy [2-4].

Gastro retentive drug delivery system

Dosage forms which retained in the stomach for an extended period of time are called Gastro retentive dosage forms. These systems allow both time control and spatial drug liberation. 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 to its absorption site thus ensuring its optimal bioavailability, prolonged gastric retention improves bioavailability, reduces drug waste and improves the solubility of drugs that are less soluble in acidic pH environment.

Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. GRDFS can be used as carriers for drugs with so called absorption

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windows. These substances for example antiviral, antifungal and antibiotic agents (Cephalosporin's, Quinolones, Penicillin's, Sulphonamides, Amino glycosides, Tetracycline's etc) are taken up only from very specific sites of GIT. GRDFS can also have application in the for local drug delivery to the stomach and small intestine.

The controlled Gastric retention of solid dosage forms may achieved by the mechanism of Mucoadhesion, Floatation, Sedimentation, Expansion, Modified shaped systems or by the simultaneous administration of Pharmacological agents that delay the gastric emptying [5-7].

Potential drug used for gastroretentive drug delivery systems

- Drugs those are locally active in the stomach.

E.g. Misroprostol, Antacids etc.

- Drugs that have narrow absorption window in gastrointestinal tract (GIT).

E.g. L-DOPA, Para aminobenzoic acid, Furosemide, Riboflavin etc.

- Drugs those are unstable in the intestinal or colonic environment.

E.g. Captopril, Ranitidine HCl, Metronidazole, etc.

- Drugs that disturb normal colonic microbes.

E.g. Antibiotics against Helicobacter pylori, etc.

- Drugs that exhibit low solubility at high P^H values.

E.g. Diazepam, Chlordiazepoxide, etc.

Drugs those are unsuitable for gastro-retentive drug delivery system

- Drugs intended for selective release in the colon.

E.g. 5-aminosalicylic acid, Corticosteroids, etc.

- Drugs that have very limited acid solubility.

E.g. Phenytoin, etc [8-9].

Advantages of gastroretentive drug delivery systems

- Enhanced bioavailability
- Better drug utilization
- Improved efficiency in the treatment
- Improved patient compliance
- Site specific drug delivery
- Sustained drug delivery / reduced frequency dosing
- Reduced fluctuations of drug concentration
- Absorption enhancement
- Minimized adverse effects at the colon

Limitations

- The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float.

delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system.

- Drugs having irritant effect on gastric mucosa are not suitable candidates.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable. Eg. Nifedipine.

Basic gastrointestinal tract physiology

Anatomically the stomach is divided into 3 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.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 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.14 this is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases [10-14].

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm) [15-17].

Factors affecting the gastro retentive system

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying

High-density systems

These formulations have a density of 2.4-2.8 g/cm^3greater than the stomach contents. (1.004 g /cm^3). A

density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time [18].

Drawback: these are technically difficult to manufacture, with a large amount of drug (>50%) and to achieve the required density of 2.4-2.8 g/cm^3. Barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

Floating Drug Delivery System

The concept of FDDS was described in the literature as early as 1962. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. These delivery systems are desirable for drugs with an absorption window in the stomach or in the upper small intestine [19].

Super porous hydrogel system

These swellable systems differ sufficiently from the conventional types to warrant separate classification. These are used to improve gastric retention time (GRT) super porous hydrogels have an average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores.

Swellable systems

Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water.

Drawbacks: Storage of much easily hydrolysable, biodegradable polymers relatively short-lived, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

Bio/muco-adhesive systems

These are used to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention.

Magnetic systems

This approach is used to enhance the gastric retention time (GRT), and is based on the simple principle that the dosage form contains a small internal magnet. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [20].

Fig 1. Gastrointestinal motility pattern

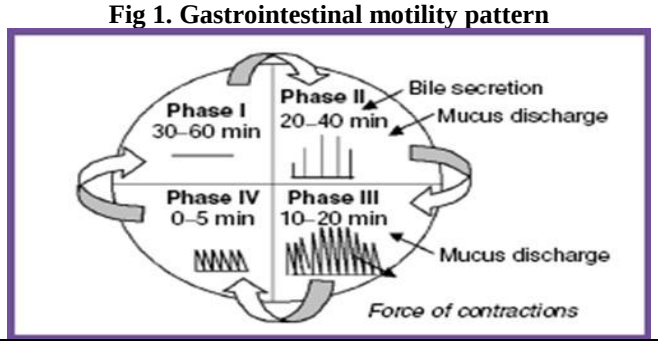


Fig 2. Schematic representation of an intragastric floating system and a high density system in the stomach

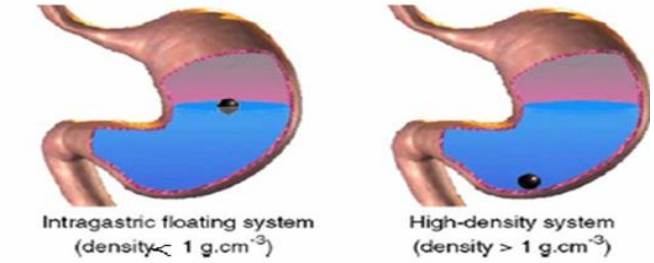
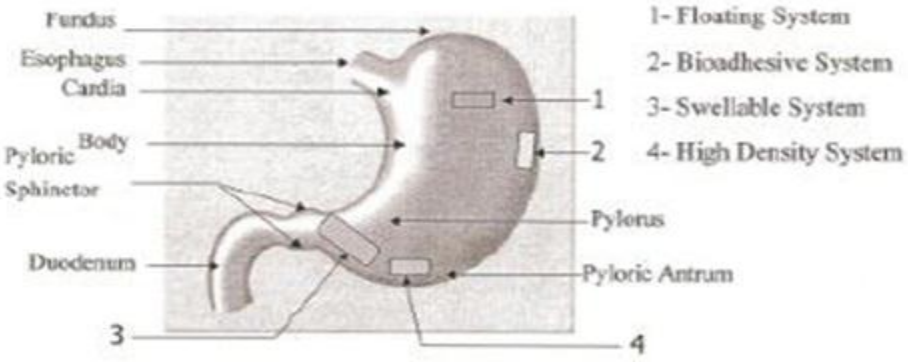


Fig 3. Different techniques of gastric retention



CONCLUSION

The review on FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, advantages, *in vitro* and *in vivo* evaluation parameters, and the future potential of FDDS.

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