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Review Article

PROGRESS IN FLOATING DRUG DELIVERY SYSTEMS: A REVIEW

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Abstract

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastro retentive dosage forms that will provide us new and important therapeutic options. This review focus primarily on floating drug delivery systems (FDDS) and to compile the recent literature on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention. FDDS provides local delivery to specific region like stomach and proximal small intestine and it also shows better bioavailability and improved therapeutic activity and substantial benefits to patients.

Keywords: - Gastric emptying time, Floating drug delivery systems, Extended release, Gastrointestinal tract.

Introduction

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the major factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine)

Extended release dosage forms are now used with number of drugs. These products permit reduced dosing frequency leading to improved patient compliance and, in some instances, improved therapeutic response.

Advantages of Extended Release Formulations:

i) Minimize patient noncompliance
ii) Employ less total drug, therefore
  a) Minimize or eliminate local side effects
  b) Minimize or eliminate systemic side effects
  c) Obtain less potentiation or reduction of drug activity with chronic dosing
iii) Minimize loss of valuable drug substances which has high solubility and low permeability or those which utilize carrier mediated transport in gut, in turn improves efficiency in treatment.
iv) Improve control of disease condition by avoiding fluctuations in plasma drug level
v) Improve bioavailability of some drugs

Improve bioavailability of some drugs.

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Disadvantages of Extended Release Formulations:

i) Decrease systemic availability due to incomplete release
ii) Poor in vitro – in vivo correlation
iii) Possibility of dose dumping
iv) Retrieval of drug is difficult in case of toxicity
v) High cost of formulation

Extended release (ER) dosage forms have been extensively used to improve therapy of many important drugs. However, this simple pharmaceutical approach of extended release could not be beneficial for oral (i.e. most preferable route) delivery of certain drugs. For example:

- Drugs that have absorption window in upper gastrointestinal tract
- Drugs that are unstable in lower Gastro Intestinal Tract (GIT), either due to pH variation or enzymes present in intestinal brush border epithelium (P450 isoenzymes) or due to efflux proteins (P-glycoprotein).
- Drugs that have poor solubility at higher pH e.g. Ofloxacin
- Drugs having adverse activity in colon
- Drugs given for local action in gastric region
- Drugs for acute conditions require greater physician adjustment of the dosage form than that provided by extended release products.
- Drugs with cumulative action and low therapeutic indices (E.g. Phenobarbital, Digoxin) are not suitable because of the technologic limitation of precise controls over release rates and the risk of dose dumping.

Thus, the optimal site of absorption and the mechanism of a drug's action often suggest that something other than immediate or extended release formulation is required to develop the best possible product. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to prolong the *Gastric Residence Time* (GRT) by controlling the gastric emptying of the dosage form. Dosage forms with a prolonged GRT are called *Gastro Retentive Dosage Forms* (GRDFs).

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 action.

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 inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.14 This is called the inter digestive mylo-electric cycle or migrating mylo-electric cycle (MMC),which is further divided into following 4 phases as described by Wilson and Washington.

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 occur between phases III and I of 2 consecutive cycles.

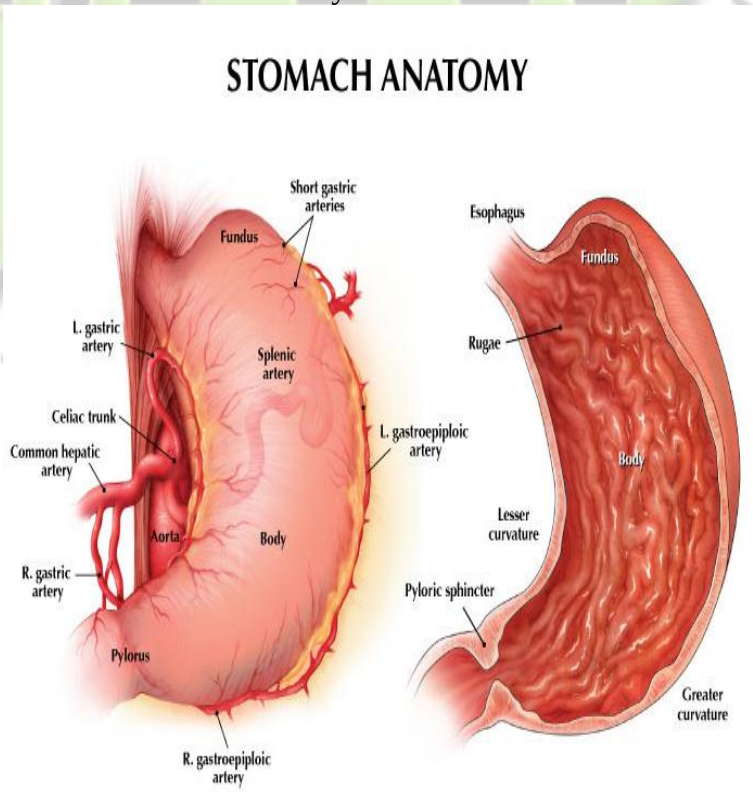

Figure- 1: Anatomical regions of stomach

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), which are propelled toward the pylorus in a suspension form.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Factors affecting gastric retention time

Density – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.

Size – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (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.

Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender – Mean ambulatory GRT in males (3.4±0.6 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).

Age – Elderly people, especially those over 70, have a significantly longer GRT.

Posture – GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.

Biological factors – Diabetes and Crohn's disease, etc.

Floating systems

Floating drug delivery systems (FDDS) have bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided in to non-effervescent and gas-generating system.

Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types:

1. Colloidal gel barrier system

Sheth and Tossounian first designated this 'hydro-dynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on

the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g.,hydroxypropyl cellulose, hydoxy ethyl cellulose, hydroxypropyl methyl cellulose(HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylateand polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

2. Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

3. Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40 ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

4. Hollow microspheres / Microballons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

(b) Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swell able polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach.

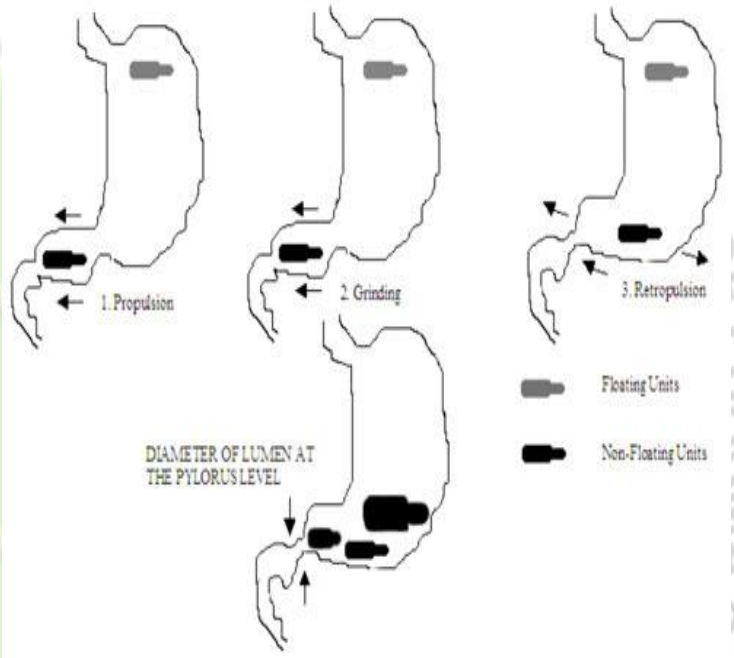

Figure-2: Intragastric residence positions of floating and nonfloating units

Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology.

Applications of floating drug delivery systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and

hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. E.g. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

2. Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide. E.g. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide.

3. Absorption Enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. e.g. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

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