FLOATING DRUG DELIVERY SYSTEM ITS IMPORTANCE

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ABSTRACT

Recent technological and scientific research has been devoted to the development of rate controlled drug delivery systems to overcome physiological adversities such as short gastric residence times and unpredictable gastric emptying times. The concept behind the development of novel delivery system in certain drawback of conventional dosages form and to overcome the certain aspect related to physicochemical properties of drug molecule and related the formulation development. Controlled release floating drug delivery system is a promising delivery system for a drug candidate having limited absorption window sparingly soluble and insoluble drugs, drugs those locally release in stomach and shows degradability in colon or poor colonic absorption. Floating drug delivery system comes under a gastro retentive drug delivery system that provides continuous controlled administration of sparingly soluble drugs at the absorption site. This review entitled the detailed scenario related to floating drug delivery system with their advantages over the conventional drug delivery system and also limitation, which are helpful in development of dosages form.

INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of th e therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available i n the market are oral drug delivery systems. Controlled-release drug delivery systems (C RDDS) provide drug release at a predetermi ned, predictable, and controlled rate. Control led-release drug delivery system is capable o f achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproduciblerelease rates for extended ti me period; f activity of enhancement duratio n for short half-life drugs; elimination of sid e effects; reducing frequency of dosing and wastage of drugs; optimized therapy and bett er patient compliances.

Oral route is the most popular and convenient route for various drugs. Oral route generally consider an ideal drug delivery system that will possess two main properties:

a) It should be in a single dose for prolonging action.

b) It should be deliver the active drug directly to the target site.

These considerations have led to the development of a controlled or sustained

delivery system. Sustained delivery describes a drug delivery system with delayed and/or prolonged release of drug. The main purpose for developing these systems is to enhance the safety of a product to extend its duration of action. There are many disadvantages of these systems such as longer time to achieve therapeutic blood levels, more variation in bioavailability, enhanced first pass effect, and dose dumping. These systems are usually more expensive than the conventional systems. Since these products are made for the population at large, and not for an individual, they may result in higher or lower steady state drug level in different individuals. If the therapeutic range of drug is broad enough, it may not cause any problem4. In spite of their disadvantages, research is continued in this area, as there is much scope to further improve currently available systems.

OCRDDS: Advantages

- Reduced dosing frequency
- Better patient convenience and compliance
- Reduced gastro intestinal (GI) side effects
- Less fluctuating plasma drug levels
- Improved efficacy/safety ratio
- More uniform drug effect
- Lesser total dose

Development of controlled release oral drug delivery system (CRDDS) by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. controlled release gastro retentive dosage form (CRGRDFS or GRDDS)

Need for controlled release Gastroretentive Drug Delivery

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as6 – This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

- GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).
- GRDFs can be used as carriers for drugs¬ with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones,

penicillins, cephalosporins, aminoglycosides, tetracyclines etc.), are taken up only from very specific sites of the GI mucosa.

- In general, appropriate candidates for¬ controlled release gastroretentive dosages form (CRGRDF) are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrat.

BIOLOGICAL ASPECTS OF CRGRDFs

Stomach Physiology: The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae.

Gastric motility: Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility- for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach.

Gastric empty rate: 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.9This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.

FACTORS AFFECTING GASTRIC RETENTION

The gastric retention time (GRT) of dosage form is controlled by several factors, which affect their efficacy as a gastroretentive system.

Density: GRT is a function of dosage form buoyancy that is dependent on the density.

Size: Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT. **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilopounds 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 0.6 hours) is less compared with their ±(3.4 age and race-matched female counterparts 1.2 hours), regardless of the weight,±(4.6 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.

Biological factors: Diabetes and Crohn's disease.

Approaches to Gastric Retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include:

A. Floating systems
B. Bioadhesive systems
C. Swelling and expanding systems
D. High density systems and
E. Modified systems

A. Floating drug delivery systems: Floating drug delivery system is also called the hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a 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. This delivery system is further divided into in to noneffervescent and effervescent (gas-generating system).

(A) Non-effervescent systems

i. Colloidal gel barrier systems

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20- 75%w/w) of

one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

ii. Micro porous compartment systems

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un dissolved drug.

iii. Multiparticulate system:

Floating Beads Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet.

iv. Microballoons

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric microballoons as carrier for drugs. Hollow microspheres are known as the microballoons. Microballoons were floatable in vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movements.

(B) Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

i. **Volatile liquid containing systems** These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.
ii. **Gas generating systems**: These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate CO2, have also been developed. The system consists of a sustained release (SR) pill as seed,

surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swell able membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, carbon-dioxide is released, causing the beads to float in the stomach.

Advantages of FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery

Disadvantages of FDDS

- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
- High variability in gastric emptying time due to its all or non-emptying process.
- Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size.
- Therefore patients should not be dosed with floating forms just before going to bed.

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