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FLOATING MICROSPHERES: A GENERAL APPROACH FOR GASTRORETENTION

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ABSTRACT

There are several problems encountered during formulation of any drug delivery system. Gastric emptying and gastric resident time are two important parameters which have a major effect on the therapeutic efficacy of drug and it causes variability in the retention time of the drug. Therefore to overcome from these problems various gastroretentive drug delivery systems has been approached and floating microspheres is one of the most reliable and innovative techniques of gastroretentive drug delivery system to overcome from these problems.

KEYWORDS: Gastric emptying, buoyancy, gastroretention time, floating microspheres, non effervescent.

INTRODUCTION

FLOATING MICROSPHERES

Oral drug delivery system is one of the most reliable and preferred route for drug administration as it is easy to administered, patient compliance, no need of assistance but it has several limitation such as fluctuation in peak plasma concentration, frequent dosing etc therefore to overcome these limitation it is important to deliver drug to target organ in optimal amount to achieved desired therapeutic efficacy.[1]

One such approach is the development of oral controlled release drug delivery system but the major obstacle in this approach is gastric emptying and alteration of pH at different parts of gastrointestinal tract and gastric transit time. Therefore to prolong the gastric residence several approach has been made one such approach is gastroretentive drug delivery system.

APPROACHES USED IN GASTRORETENTIVE DRUG DELIVERY SYSTEM

GRDDS (Gastro-retentive drug delivery system) has ability to retain in the gastric region for longer period of time therefore increasing the gastric retention time of drugs having poor oral bioavailability. There are several approaches which has been used to prolong the gastric retention rime such as.[2,5]

1) **High density systems**
2) **Swelling and expanding systems**
3) **Mucoadhesive & bioadhesive systems**
4) **Floating systems**

FLOATING DRUG DELIVERY SYSTEM[6]

Due to low density of the floating drug delivery system than gastric fluid they tend to float in the stomach for longer period of time without affecting the gastric emptying rate therefore it result in slow release of the drug maintaining desired plasma drug concentrations.

ADVANTAGES[7,10]

- Increased bioavailability of the drugs having shorter half life or especially drugs which get metabolized in the upper git region.
- Increased in gastric residence time of the drug result in sustained release of the drug therefore this result in the improved action at the local sites of the stomach and intestine.
- Fluctuation in the peak plasma concentration reduced as compared to the conventional oral drug delivery system.
- Floating drug delivery system delivered the drug specifically to the site of action therefore side effects are minimized.
- FDDS are advantageous for drugs meant for local action in the stomach e.g.: Antacids
- Avoidance of gastric irritation, because of sustained release effect.
- Enhanced absorption of drugs which are only soluble in stomach.
- Inter and intra variability are less observed as compared to other formulation.

DISADVANTAGES[11]

- Drugs which causes stability and solubility problems in the gastric fluid are not considered as a candidate for this delivery system.
- Drugs that cause irritation and lesion to gastric mucosa are not desired candidate for floating drug delivery system.

- Drugs which under goes first pass metabolism are not suitable for this type of drug delivery.

IDEAL DRUGS SUITABLE FOR FLOATING DRUG DELIVERY SYSTEM[12,15]

- Drugs which have poor colonic absorption are ideal characters for the FDDS.
- Drugs which shows narrow window absorption window in the GIT e.g., Riboflavin and Levodopa.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

FDDS has been classified into 2 categories i.e.:

- EFFERVESCENT FDDS
- NON-EFFERVESCENT FDDS
- EFFERVESCENT FDDS:

These types of dosage forms when come in contact with the gastric environment of stomach it releases carbon dioxide and then trapped in the swollen hydrocolloids, this provides buoyancy to the dosage forms (Shweta Arora et al, 2005, Gangadha-rappa H.V, 2007).

NON-EFFERVESCENT FDDS

It works on the principle of swelling of polymers resulting in adhesion of polymer to the mucosal layer of GIT. The most commonly used excipients for the preparations of non-effervescent FDDS are gel forming or swellable type hydrocolloids, poly-saccharides and matrix forming polymers like polyme-thacrylates, polycarbonates, polyacrylates polystyrenes and bioadhesion polymers like chitosan and carbopols. One of the approaches in the development of such floating dosage forms involves thorough mixing of drug and gel forming hydrocolloids. After oral administration, the dosage form comes in contact with gastric fluids and gets swollen, form a gelatinous barrier at the surface. The swollen dosage form maintains a relative integrity of shapes and bulk density less than 1.0. The air entrapped within the swollen polymer matrix imparts buoyancy to the dosage form.[17]

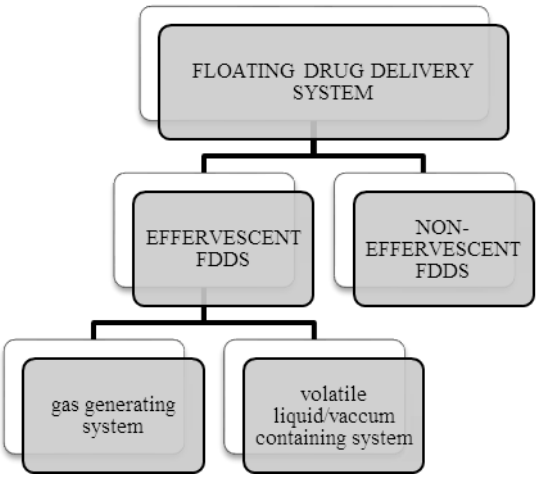

Fig 1: Classification of floating drug delivery system.

ANATOMY AND PHYSIOLOGY OF STOMACH

The stomach is a muscular, J-shaped organ located in the upper part of the abdomen. It is part of the digestive system, which extends from the mouth to the anus.

STRUCTURE

Stomach is divided into five main regions which are (fig.2):

- the cardia.
- fundus.
- body or corpus.
- antrum and
- pylorus.

The **cardia** (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped **fundus**. Below the fundus is the **body**, the main part of the stomach. The funnel-shaped **pylorus** connects the stomach to the duodenum. Fundus and corpous are the acid secreting glands of the stomach whereas antrum is alkaline secreting gland of stomach.[18]

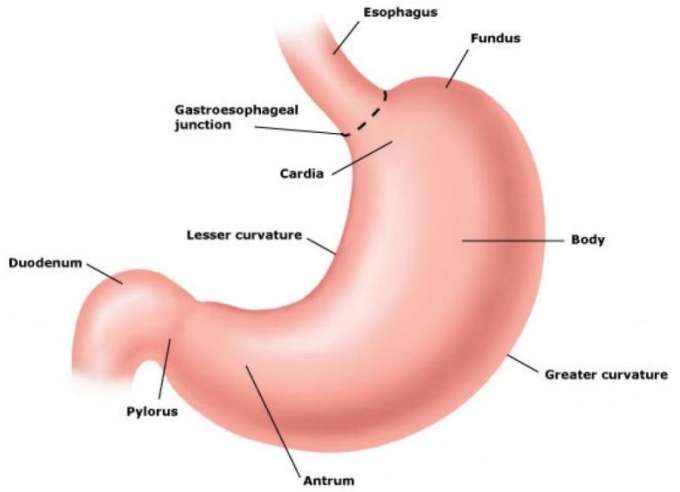

Fig 2: Structure of stomach.

FUNCTION OF STOMACH

Stomach play important role in following ways such as:

- storage of food after entering in stomach through esophagus for 2 hour.
- Digestion of food with the help of chyme, acid and pepsin and pepsin have important role in the breakdown of macromolecules such as proteins into smaller parts.

The daily gastric secretions of gastric juice is about 2-3 litre.

Table 1: Various gastric secretions.

Gastric juice	pH	function
Hcl	0.8-3.5	Activate pepsin, denature proteins and kills bacteria
Intrinsic factor(glycoprptein)	-	Absorption of vitamin B.
Pepsinogen	1.5-3.4	Breakdown of proteins, inactive form of pepsin
Mucin	-	Mucin covers the walls of stomach and act as barrier and protect stomach from the Hcl

Gastric emptying is defined as the movement of food and other contents from stomach to intestine and it occurs in fasting and fed conditions. However the pattern of motility is different in both stages. During fasting conditions undigested food are cleared off by housekeeping waves and interdigestive series of electrical series occur. It is also known as migrating myloelectric cycle (MMC). (Vedha hari b.n.et al, 2010). This cycle consists of following 4 phases:

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

2. 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.

3. Phase III (burst phase) lasts for 4 to 6 minutes. Here intense and regular contraction occurs for short period. In this phase these waves clears off all undigested material from stomach to intestine and also known as the housekeeper wave.

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

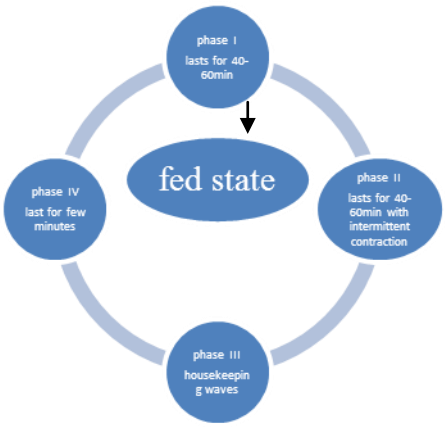

Fig 2: Interdigestive series in stomach.

FLOATING MICROSPHERES- AN APPROACH FOR GASTRIC RETENTION

Gastroretentive drug delivery system is a type of controlled drug delivery system which remain unaffected in the gastric region for longer period of type therefore prolong the gastric residence time. Benefits of increasing gastric resident time is that it improves the bioavailability, solubility of those drugs which are unstable in pH of gastric environment and local delivery of drug in the gastric region. Floating microspheres is an innovative approach of GRDDS.

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm).[19]

Floating microspheres are gastroretentive drug delivery systems based on a non-effervescent approach. It is also known as hollow microspheres, microballons and floating microparticles. These are free flowing particles having particle size range from 1 to 1000 µm.[20]

Kawashima *et al*. (1992) have developed non-effervescent hollow polycarbonate microspheres by using an emulsion solvent evaporation method. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than one. This property results in delayed transit through the stomach. The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

ADVANTAGES OF FLOATING MICROSPHERES[21,23]

- Problem associated with poor stability of drug in acidic environment of stomach get improved therefore they can remain stable for longer period of time.
- Controlled delivery of the drug at desired site of action without affecting gastric emptying.
- Drugs having shorter half life results in improved bioavailability after oral delivery.
- Frequency of dosing are reduced resulting in improved patient compliance.
- Due to improved bioavailability of the drug it shows better pharmacokinetic and dynamic profile.
- Drugs which have problem of narrow absorption window shows improved absorption.
- Improved therapeutic action due to buoyancy.

FLOATING MICROSPHERES: FORMULATION TECHNIQUES

There are various methods for formulation of floating microspheres. Some of the techniques used in the formulation are as follows:

- Solvent Evaporation Method
- Emulsion Solvent Diffusion Method
- Ionotropic Gelation Method
- Emulsion Cross Linking Technique
- Spray Drying Technique

SOLVENT EVAPORATION METHOD[24]

- Solvent evaporation involves the formation of an emulsion between polymerisation and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.
- This process is carried out in a liquid manufacturing vehicle.

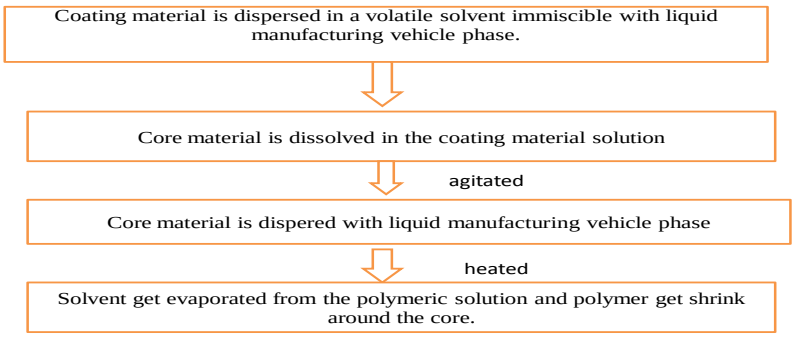

Fig3. steps involved in solvent evaporation method

EMULSION SOLVENT DIFFUSION METHOD[24]

In this method, first the drug is dissolved in suitable polymer solution in ethanol and dichloromethane. This drug polymer solution is added drop wise to sodium lauryl sulphate (SLS) solution, stirred by propeller type agitator at room temperature at 150 rpm for 1 h, washed and dried in desiccator at room temperature.

IONOTROPIC GELATION METHOD[25]

Ionotropic gelation is based on the ability of poly electrolytes to cross link in the presence of counter ions to form beads. Since, the use of alginates, gellan gum, chitosan and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. The natural poly electrolytes in spite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations.

EMULSION CROSS-LINKING TECHNIQUES[26,27]

This method is used for microparticles of natural carriers. The natural polymers are dissolved or dispersed in aqueous medium followed by addition of non-aqueous medium. The drug is dissolved in aqueous solution of carrier such as gelatin which is previously heated for 1hr at 40ºC. The resultant solution is added drop wise to oil phase such as liquid paraffin containing a suitable surfactant at a stirring speed of 1500 rpm for 10 min at 3ºC. This resultant w/o emulsion is further stirred for 10 min at 15ºC. The microspheres are washed with suitable

organic solvents such as acetone and isopropyl alcohol and air dried. The formed microspheres are cross linked by dispersing in 5 ml of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs, further treated with 100 ml of 10mM glycine solution containing 0.1% w/v of tween 80 at 37ºC for 10 min to stop the cross linking.

SPRAY DRYING[28,29]

The polymer is first dissolved in a suitable volatile organic solvent such as dichloro methane, acetone etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenisation. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporate instantaneously leading to the formation of the microspheres in a size range 1-100micrometers, thus formed microspheres are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. The major advantage of this process is feasibility of operation under aseptic condition, this process is rapid and this leads to the formation of porous microparticles.

EVALUATION PARAMETERS

Following parameters are carried out for the characterization or evaluation of floating microspheres:

- Micromeritics study
- Encapsulation efficiency
- Buoyancy study
- In-vitro drug release study
- Scanning electron microscopy:

MICROMERITICS STUDY

Micromeritics properties of floating microspheres involved particle size, flow property, density, angle of Repose Hausner's Ratio, compressibility index.

- **Particle size**[30]

Particle size is measured by using optical microscopy by measuring the mean particle size of 200-300 particles with the help of calibrated optical micrometre. Particle size is determined by optical microscopy using a quantity of dried microspheres suspended in glycerin.

- **Compressibility index**[31]

I= vb-vt /vb.100

Where vb= bulk volume.

Vt= tapped volume.

ENTRAPMENT EFFICIENCY[32]

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank.

The amount of drug entrapped in the microspheres was calculated by the following formula:

%entrapment = (amount of drug actually present/theoretical drug load expected) × 100

BUYOUNCY STUDY[33]

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hrs. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

% BUOYANCY: $\mathbf{W_f / W_f+W_s *100}$

Where W_f is weight of floated microspheres and

W_s is weight of settled microspheres

IN-VITRO DRUG RELEASE STUDY[34]

For such type of studies USP dissolution apparatus at particular speed is used. Distilled water and dissolution fluid is maintained at 37±10C. Samples withdrawn at periodical intervals and are analyzed spectrophotometrically. The volume was replenished with the same amount of fresh medium to maintain the sink condition.

SCANNING ELECTRON MICROSCOPY[35]

Scanning electron microscopy was used to investigate external and internal morphology of microspheres. The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of

about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The stub containing the coated samples was placed in the scanning electron microscope. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 20 kV, original magnification 30´ to investigate the internal morphology, and microspheres were divided into two pieces by using a knife.

APPLICATION OF FLOATING MICROSPHERES[36,39]

1. Floating microspheres results in improved bioavailability of drugs which have low absorption in the upper GIT. E.g. furosemide
2. Floating microspheres is an effective approach for the controlled delivery of non steroidal anti-inflammatory drugs and helps in the reduction of the gastric irritation.
3. It overcome the problems which are associated with gastric resident time in the GIT therefore sustained release of drug is achieved
4. It helps in the local treatment of the diseases associated with GIT as it provide controlled delivery of drug to stomach as floating microspheres results in prolonged gastric resident time e.g. riboflavin
5. Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. The development of such systems allow administration of nonsystemic, controlled release antacid formulations containing calcium carbonate and also locally acting antiulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
6. Many drugs are reported to be entrapped in the floating microspheres such as prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem, verapamil and riboflavin.
7. Drugs having narrow absorption window can be targeted to specific sites of GI mucosa as floating microspheres can be used as carrier to deliver drug at targeted sites. for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracycline

Table no. 2: Marketed formulation of floating drug delivery system.

PRODUCT	DRUG DELIVERY SYSTEM	MANUFACTURER
Valrelease	Floating capsules	Hoffmann-LaRoche
Madopar HBS (Propal HBS)	Floating CR capsules	Roche Products, USA
Conviron	Colloidal gel forming FDDS	Ranbaxy, India
Cifran OD	Gas generating floating form	Ranbaxy, India
Cytotech	Bilayer floating capsule	Pharmacia, USA

CONCLUSION

There are several factors which affect the bioavailability of drugs resulting in low therapeutic action of the drug. Many drugs are unstable and insoluble in the gastric environment and to overcome from these limitation various gastroretentive approaches has been developed and one such approach is floating microspheres. Floating microspheres has been emerged as a potential technique used to improve poor bioavailability, poor aqueous solubility, and stability of many drugs. Floating microspheres also improve gastric retention therefore it is most widely used as gastroretentive drug delivery system.

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