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Microballoon: Novel Gastroretentive Floating Drug Delivery System

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Abstract

Oral route is the most widely used way of drug administration. Controlled oral drug delivery system, which overcomes the physiological adversities like short gastric residence time and unpredictable gastric emptying time, has been developed nowadays largely. Different approaches for gastroretention of drugs which includes high density, low density (floating), bioadhesive, mucoadhesive, expandable, unfoldable, super porous hydrogel, magnetic system etc. Floating drug delivery systems are low density systems which floats over the specific region like stomach and proximal small intestine and is used to improve bioavailability, improved therapeutic activity and better patient compliance. Floating systems can be of two types : Efferevescent systems and Non efferevescent systems. Microballoons are the novel gastroretentive drug delivery system based on non efferevescent approach. Microballoons are characteristically free flowing powders constituting proteins, or synthetic polymers having size range of 200µm. These are also called hollowspheres, porous smooth in nature and shows good floating properties[1].

Keywords;Gastroretentive drug delivery system, microballoons, hollowspheres, efferevescent, floating system

INTRODUCTION

Oral route is the most promising and widely used route of drug delivery. Drug absorption through the oral route can be affected by several factors like gastric emptying, GI transit, drug release from dosage form and site of absorption of drugs. Recent research and development focuses on the development of sustained drug delivery systems to achieve required therapeutic concentration with low dose frequency. Gastrointestinal transit time may vary in individuals which can lead to incomplete drug release and shorter residence time of dosage form in the stomach. Many drugs are well absorbed in the gastrointestinal tract but this high variability amoung individuals may lead to incomplete absorption absorption and bioavailability. A drug delivery which is able to control and prolong gastric emptying time and deliver the drug in the absorption site is beneficial. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site specific drug release in GIT. It can remain in stomach for prolonged period of time and thus increases the gastric retention time (GRT) of drugs. Drugs well absorbed in stomach have short life and eliminate quickly. To overcome the dosing frequency of these drugs, oral sustained controlled release formulation is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in blood. It improves bioavailability, increases the duration of drug release, reduces drug waste and improves the bioavailability of drugs which are less soluble in high pH environment. Gastroretentive dosage forms greatly improves pharmacotherapy of GIT through local drug release, leading to high concentrations at gastric mucosa, useful in the treatment of gastric and duodenal ulcers, oesophagitis etc. Gastroretentive drug delivery systems include high density (sinking), low density (floating), mucoadhesive systems, unfoldable, extendible or swelling systems, superporous hydrogel system, magnetic systems etc. Microballoons are low density (floating) drug delivery system based on efferevescent approach. Microballoons are spherical vesicles without core which are characteristic free flowing powders having size of 200µm. It has sufficient buoyancy to float over the gastric fluid for prolonged period of time[2].

Factors affecting gastric retention

- Size of dosage form

Dosage form unit with diameter of more than 7.5mm have increased GRT compared with a diameter of 9.9m.

- Shape of dosage form

Shape and size are important in designing dosage forms. Ring shaped and tetrahedron shaped devices have better GRT (90-100% at 24hr) as compared with others.

- Density of dosage form

Dosage forms having density lower than gastric contents can float in the gastric fluids and provide gastroretention while high density systems sink to bottom. Both dosage form isolate the dosage system from the pylorus.

- Food intake and its nature

Food intake, viscosity and volume of food, caloric value, frequency of feeding have effect on gastroretention of dosage forms. Presence of food increases GRT. A heavy meal containing high proteins and fats can increase GRT by 4-10 hours.

- Effect of gender, posture and age

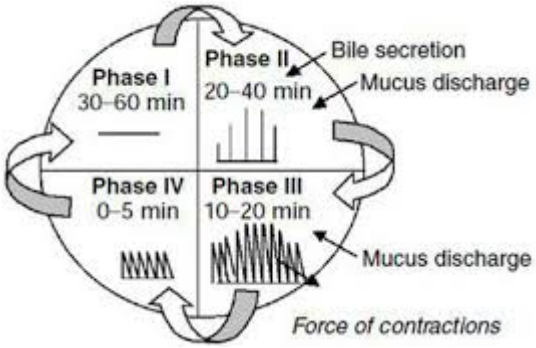
Females have slower gastric emptying rates than male. Upright, ambulatory, and supine state doesnot have any significant difference in GRT. Gastric emptying will slow down in elderly patients[2].

Physiology of stomach

Stomach is anatomically divided into fundus, body and antrum. Proximal part of fundus and body acts as reservoir for undigested material. Antrum is an important site for mixing and act as a pump for gastric emptying by propelling action. Gastric emptying will occur in both fasting and fed states. During the fasting state an interdigestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hr. It

is called interdigestivemyloelectric cycle or migrating myloelectric cycle (MMC) divided into 4 phases[4].

- Phase I (basal phase)- lasts from 30 to 60 min with rare contractions.
- Phase II (preburst phase)- lasts for 20 to 40 min with intermittent action potential and contraction. Intensity and frequency also increases as the phase progresses.
- Phase III (burst phase)- lasts for 10 to 20 min. It includes intense and regular contraction for short period. It is called housekeeper wave.
- Phase IV- lasts for 0-5 min and occur between phases III and 1 of 2 consecutive cycle.



Floating drug delivery system

Floating drug delivery system are the low density system with sufficient buoyancy to float over the gastric contents. The drug will release slowly over a prolonged period of time and residual system will emptied from the stomach. It will increase gastric retention time, reduce fluctuation in plasma concentration and enhances bioavailability[3].

It can be classified into two types,

- Efferevescent system
  a. Volatile liquid containing system
  b. Gas generating systems
- Non efferevescent system
  a. Colloidal gel barrier
  b. Microporous compartment system
  c. Alginate beads
  d. Hollow microsphers

Mechanism of Floating system

Floating drug delivery systems (FDDS) have a bulk density lower than gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a long duration. While the system is floating on gastric contents, the drug released slowly at desired rate from system. After release of drug, the residual system is eliminated from the stomach. It results in increased GRT and better control over fluctuation in plasma concentration. A minimal gastric content and a minimal level of floating force is needed to allow the proper achievements of the buoyancy retention effect[4].

Mechanism of floating microballoons

The gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier when microballoons come in contact with gastric fluid, that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of adjacent hydrocolloid layer. The air trapped by swollen polymer lowers the density and confers the buoyancy[9].

MATERIALS AND METHODS

- Drugs

Drugs having narrow therapeutic window in GI tract, absorbed from stomach and upper part of GIT, locally acting on stomach, degrade in colon, disturb normal colonic bacteria.

Eg : Aspirin, Salicylic acid, Ethoxybenzamide, Furosemide etc.

- Polymers

Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylaten, Carbopol, Agar etc.

- Solvents

It should have good volatile properties. It should easily come out from emulsion leaving hollow microspheres.

Eg : Ethanol, Dichloromethane (DCM), Acetonitrile, Acetone, Isopropyl alcohol, Dimethyl formamide (DMF)

- Processing medium

It is used to harden the drug polymer emulsified droplets when the drug polymer solution is poured into it, shouldnot interact with former; mainly used in processing medium are liquid paraffin, polyvinyl alcohol and water.

- Surfactant

These are stabilizers/ emulsifiers used to harden the microspheres.

Eg: Tween 80, Span 80 and SLS

- Cross linking agent

Chemical crosslinkers include Formaldehyde, glutraldehyde or by using di acid chlorides such as terephthaloyl chloride.

- Hardening agent

It is used to harden microspheres.

Eg: n-hexane, Petroleum ether

METHOD OF PREPARATION

a. Solvent evaporation method.

Aqueous solution of drug is prepared. Polymers are dissolved in organic solvent like chloroform with stirring. Drug solution is mixed with polymer solution to form an emulsion. Formed emulsion is added to large amount of water containing emulsifier to form multiple emulsion. Emulsion is constantly stirred till organic solvent completely evaporates to give microspheres. Hollow microspheres are washed and dried.

b. Emulsion solvent diffusion method.

The solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of PVA. Ethanol rapidly partition into the external aqueous phase and polymer precipitate around methylene chloride droplets. Evaporation of entrapped methylene chloride leads to formation of internal cavities within microparticles.

c. Single emulsion technique

Aqueous solution or suspension of polymer dispersed in organic phase like oil or chloroform by stirring or

sonication. Dispersion which undergoes heat denaturation or chemical crosslinking to give microspheres in organic phase. Hollow microspheres are obtained by centrifugation, washing and separation.

d. Double emulsion technique

Aqueous solution of protein or polymer is prepared. Dispersion of oil phase into aqueous solution by homogenisation will give first emulsion (w/o). To this add aqueous solution of polyvinyl alcohol results in formation of multiple emulsion. Hollow microspheres are obtained by denaturation, separation, washing and drying.

e. Coacervation phase separation technique

Polymer is dissolved in aqueous or organic solvent. Drug is dispersed or dissolved in polymer solution. Polymer rich globules are obtained by phase separation induced by different means. By hardening hollow microspheres in aqueous or organic phase are obtained. Hollow microspheres are obtained by separation and drying.

f. Spray drying and Spray congealing

Spray drying :- The coating solidification can be done by rapid evaporating of solvent in which coating material is dissolved.

Spray congealing :- The coating solidification can be done by thermally congealing a molten coating material. The solvent is removed by sorption, extraction or evaporation[1].

Drug candidates suitable for gastroretentive drug delivery

- Drugs having narrow absorption window in GIT
  Eg: L Dopa, p-aminobenzoic acid, furosemide, riboflavin
- Drugs those are locally active in stomach
  Eg: Misoprostol, antacid
- Drugs those are unstable in intestinal/ colonic environment
  Eg: Captopril, ranitidine HCl, metronidazole
- Drugs that disturb normal colonic microbes
  Eg: Antibiotics used for the eradication of Helicobactor pylori, such as tetracycline, clarithromycin, amoxicillin.
- Drugs that exhibit poor solubility at high pH values
  Eg : Diazepam, chlordiazepoxide, verapamil[8]

CHARACTERIZATION OF HOLLOW MICROSPHERES

1. Micromeritic properties

Determination of bulk density, tapped density and particle density is done. Different fractions of the optimized formulation (1g) were taken into a 10 ml graduated measuring cylinder separately and volume was noted down. The measuring cylinder was then tapped for 50 times using the USP bulk density apparatus. The bulk density and tapped densities were determined using the formulae,

$$Bulk\ density = \frac{Weight\ of\ the\ floating\ microballoons}{Intial\ volume}$$

$$Tapped\ density = \frac{Weight\ of\ the\ floating\ microballoons}{Final\ volume\ after\ tapping}$$

$$Compressibility\ Index, I = \frac{Bulk\ volume - Tapped\ volume}{Tapped\ volume} \times 100$$

$$Angle\ of\ repose\ (\theta), Tan\theta = \frac{2H}{D}$$

where $\frac{2H}{D}$ is the surface area of free standing height of the heap.

2. Particle size analysis

It was carried out by using optical microscopic method with the help of a caliberated eye piece microscope micrometer. Size of around 100 particles was measured and median diameter was measured and median diameter was measured.

3. Scanning electron microscopy (SEM)

Scanning electron microscopy was performed for morphological characterization of microspheres using scanning electron microscopy. Sample were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film under reduced pressure.

4. *Invitro* drug release study

A USP basket apparatus has been used to study *invitro* drug release study. It was studied by using USP dissolution apparatus type I at 100rpm in distilled water and 0.1ml hydrochloric acid (pH 1.2) as dissolution fluid (900ml) maintained at 37±0.5^{0}C. Samples were withdrawn and analyzed spectrophotometrically. The volume was replaced with same amount of fresh dissolution fluid to maintain sink condition.

5. Buoyancy percentage

Calculated amount of microballoons were placed in 900 ml of 0.1N hydrochloric acid. Mixture was stirred at 100rpm in a dissolution apparatus for 8hrs. After 8hrs, the layer of buoyant microspheres were pippetted and separated by filtration. Particles in sinking particulate layer separated by filtration. Particles were dried in a dessicator until constant weight. Both the fractions of microspheres were weighed and buoyancy determined by,

$$\%\ Buoyancy = \frac{Weight\ of\ floating\ microspheres}{Weight\ of\ settled\ microspheres} \times 100$$

6. *Invivo* studies

Invivo floating behaviour can be determined by Xray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The *invitro* drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The *invivo* plasma profile can be obtained by performing the study in suitable animal models.

7. Stability study

Accelerated stability studies were performed where the product is stored under extreme conditions of temperature. Optimized formulation were sealed in aluminium package coated with polyethylene inside, and various samples were kept in the humidity chamber maintained at 40^{0}C and 75% RH for 2 months. At the end of studies, samples were analyzed for physical appearance,drug content and drug release[10][6].

ADVANTAGES

- Reduces dosing frequency and improve patient compliance.
- Improve bioavailability and reduces the intensity of adverse effects and despite first pass effect because fluctuation in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continous drug release.
- It is used to decrease material density and gastric retention time is increased because of buoyancy.
- Absorption of drugs which solubilise only in stomach is enhanced.
- Drug releases in controlled manner for prolonged period.
- Site specific drug delivery can be achieved.
- Better therapeutic effect of drugs having short half life can be achieved[1].

APPLICATIONS

- Microballoons can be used as additives to lower the density of a material.
- It improve the pharmacotherapy of stomach through local drug release, leading to high drug concentration at gastric mucosa, thus eradicating Helicobactor pylori from submucosal tissue of stomach and is useful in treating stomach and duodenal ulcers, gastritis and oesophagitis.
- These microballoons provide sustained drug release behaviour and release the drug over a prolonged period of time.
- Floating microspheres are effective in delivery of sparingly soluble and insoluble drugs.
- Floating microspheres can be used as carriers for drugs with so called absorption windows, these substances, for eg antiviral, antifungal and antibiotic agents.
- Hollow microspheres of non steroidal anti-inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation[3].

FUTURE POTENTIAL

- Design of an array of gastroretentive drug delivery systems, each have narrow GRT for use according to the clinical need eg: dosage and state of diseases.
- The quantitative efficiency of gastroretentive drug delivery systems in the fasted and fed states.
- Determination of minimal cut off size above that dosage forms retained in the GIT for prolonged period of time.
- Design and development of gastroretentive drug delivery systems as a beneficial strategy for the treatment of gastric and duodenal cancers.
- Development of various anti reflux formulation utilizing gastroretentive technologies.
- Exploring the eradication of Helicobactor pylori by using various antibiotics.
- Design and development of gastroretentive drug delivery systems for drugs, which are potential to treat parkinson's disease.
- Study of the effect of various geometric shapes in a more excessive manner than previous studies.
- Design and synthesis of novel mucoadhesive agents to develop bioadhesive drug delivery systems for improved gastroretention.
- Design of novel mucoadhesive delivery using various natural mucoadhesive agents according to their clinical and pharmaceutical need[5].

CONCLUSION

Floating drug delivery system (FDDS) release drug at desirable rate for prolonged time by increasing the gastric retention time of drugs. Amoung various floating drug delivery systems, microballoons are emerging as innovative, most reliable drug delivery system. Microballoons are useful especially for drugs that can't withstand acidic pH of stomach. The drug is released slowly at desired rate when it floats over gastric contents resulting reduced fluctuations in plasma drug concentration. It is an efficient means of enhancing bioavailability. Optimized microballoons will be placed at the central position in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective *invivo* delivery. Therefore floating microspheres may be effective strategy for the development of easy, reproducible and cost effective method to prove its potential for safe and effective oral drug delivery therapy.

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