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MICROBALLOONS: A NOVEL APPROACH IN GASTRO-RETENTION FLOATING DRUG DELIVERY SYSTEM (FDDS)

Snehal Patel[*1], Chintan Aundhia[2], Avinash Seth[2], Nirmal Shah[2], Kartik Pandya[2], Chainesh Shah[2], Vinod Ramani[2], Ankur Javia[2]

[1]II[nd] M. Pharm (Pharmaceutics), Department of Pharmacy, Sumandeep Vidhyapeeth, Piparia, Vadodara
[2]Department of Pharmacy, Sumandeep Vidhyapeeth, Piparia, Vadodara

ABSTRACT

Oral controlled release dosage forms face several physiological restriction like inability to retain and position the controlled drug delivery system within the targeted region of the gastrointestinal tract (GIT) due to fluctuation in gastric emptying. This results in non‐uniform absorption pattern, inadequate medication release and shorter residence time of the dosage form in the stomach. As the fallout of this episode there is inadequate absorption of the drug having absorption window predominantly, in the upper area of GIT. These contemplations have provoked to the development of oral controlled release dosage forms with gastroretentive properties. Microballoons (Hollow microspheres) hold certification as one of the potential approaches for gastric retention. Microballoons are spherical empty particles without core and can remain in the gastric region for delayed periods. They significantly increase the gastric residence time of medication, thereby enhance bioavailability, improves patient compliance by reducing dosing frequency, lessen the medication waste, enhance retention of medication which solubilize only in stomach, enhance solubility for medications that are less soluble at a higher pH environment. The present review preparation methods, characterization, advantages, disadvantages, mechanism of drug release from microballoons, applications and list of the drugs formulated as microballoons are discussed.

KEYWORDS: Microballoons, Gastro-retention, Floating drug delivery system (FDDS).

INTRODUCTION

Microballoons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballoons are in strict sense, spherical empty particles. These microballoons are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Gastro-retentive Microballoons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Microballoons to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved.

Enhanced absorption of drugs which solubilise only in stomach, Gastric retention time is increased because of buoyancy.[1]

Advantages[2, 3]

✓ Improves patient compliance by decreasing dosing frequency.

✓ Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

✓ Gastric retention time is increased because of buoyancy.

✓ Enhanced absorption of drugs which solubilise only in stomach

✓ Drug releases in controlled manner for prolonged period.

✓ Site-specific drug delivery to stomach can be achieved.

✓ Superior to single unit floating dosage forms as such microballoons releases drug uniformly and there is no risk of dose dumping.

✓ Avoidance of gastric irritation, because of sustained release effect.

✓ Better therapeutic effect of short half-life drugs can be achieved.

Disadvantages[2, 3]

✓ Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin,theophylline, corticosteroids, iron (ferrous sulfate), oral contraceptives, and tricyclic antidepressants.

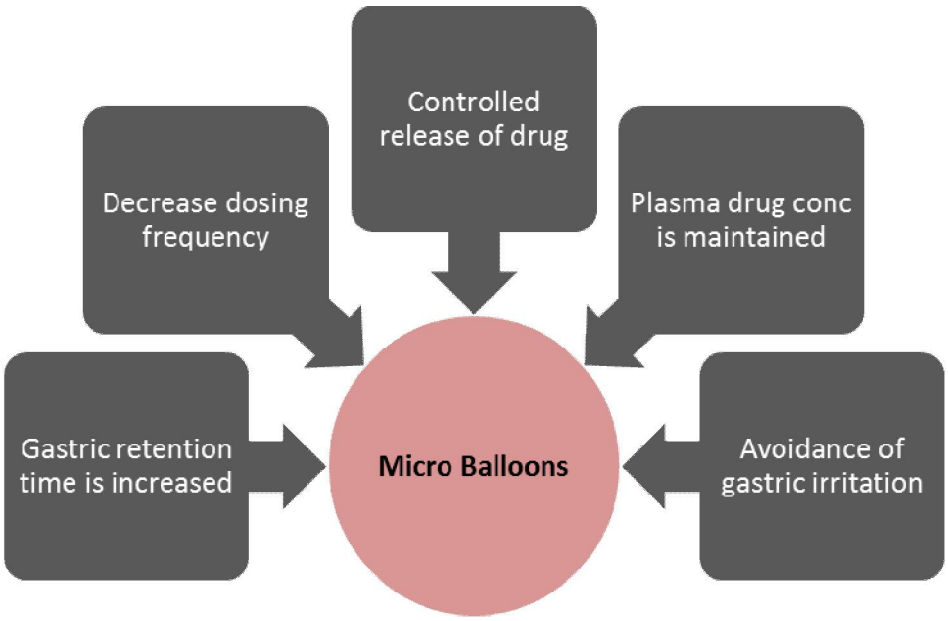
✓ Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.

✓ They are not suitable candidatesfor drugs with stability or solubility problem in stomach.eg.ranolazine

✓ Single unit floating capsules or tablets are associated with an “all or none concept,” but this can be overcome by formulating multiple unit systems like floating microballoons or microballoons.

✓ FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200-250 ml) of water to be taken together with FDDS.

RATIONALE BEHIND MICROBALLOONS



MECHANISM OF FLOATING MICROBALLOONS

When microballoons come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier 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 the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microballoons. However a minimal gastric content needed to allow proper achievement of buoyancy. Microballoons of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent development[4]

FACTORS AFFECTING GASTRIC RETENTION[5, 6]

Density

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm.

Shape

The dosage form with a shape tetrahedron and ring shape 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.

Fed or Unfed State

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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. 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.

Nature of the meal

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

Caloric Content

GRT can be increased between 4 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

Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.

Age

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

Posture

GRT can vary between supine and upright ambulatory states of the patients.

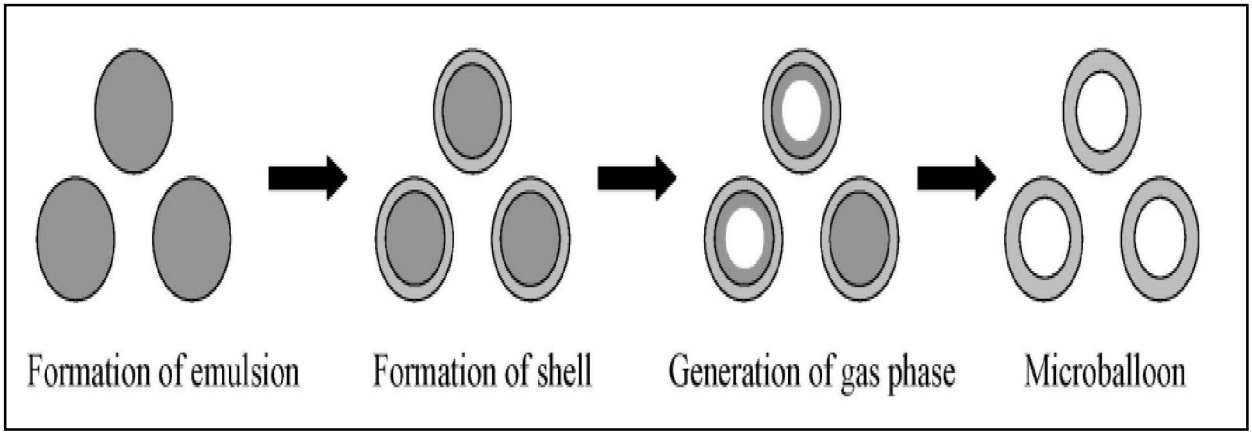
Diseased state of the individual

Biological factors also affect the gastric retention e.g. Crohn's disease, gastrointestinal diseases and diabetes. Concomitant drug administration: Anti-cholinergics like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.(1-7)

LIST OF POLYMERS USED IN HOLLOW MICROBALLOONS

Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene oxide etc.

PROCESS OF FORMATION OF MICROBALLOONS



TECHNIQUES USED IN THE PREPARATION OF MICROBALLOONS[7-9]

The different methods used for various microballoons preparation depends on route of administration, duration of drug release and particle size. The various methods of preparations are

Emulsion solvent evaporation technique

The drug is dissolved in chloroform and then dissolved in polymer and the resulting solution is added to aqueous phase containing 0.2% sodium of PVP as emulsifier. This mixture was stirred at 500 rpm then the drug and polymer (Eudragit) was transformed into fine droplet which solidified into rigid microballoons by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. For these techniques, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

Oil in water solvent evaporation technique

In this technique, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer. The polymer is dissolved in an organic solvent such as dichloromethane, methanol and chloroform. The drug is either dissolved or dispersed into polymer solution and this solution is emulsified into an aqueous phase to make an oil-in water emulsion by emulsifying agent. After that the organic solvent is decanted and the micro particles are separated by filtration.

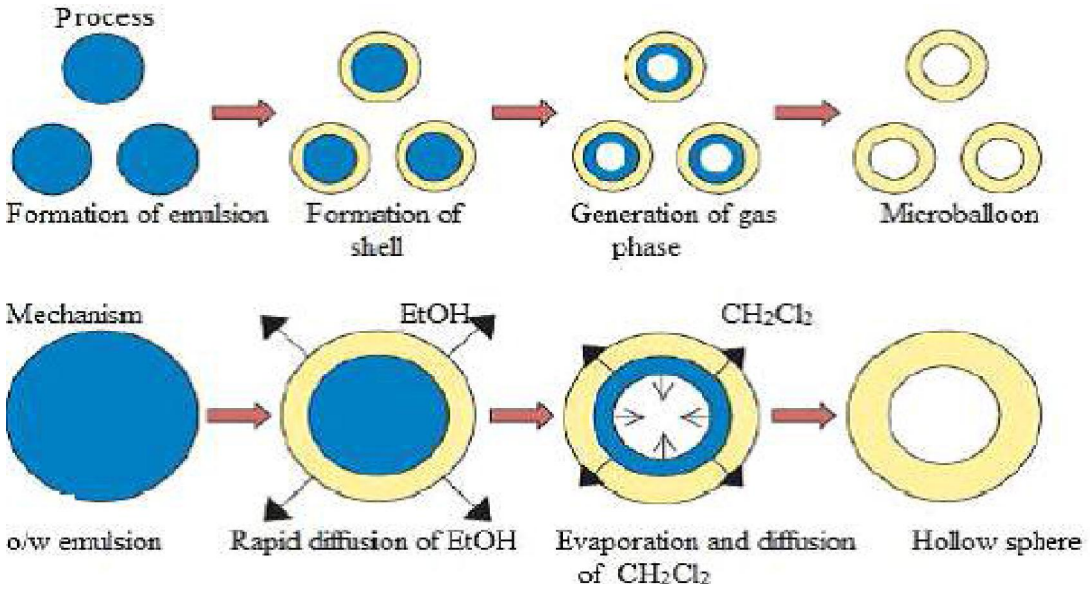
Water-in-oil emulsification solvent evaporation technique

This water-in-oil emulsification process is also known as non-aqueous emulsification solvent evaporation. Drug and polymers are co dissolved at room temperature with vigorous agitation to form uniform drug–polymer dispersion. This mixture is poured into the dispersion medium consisting of light / heavy liquid paraffin in the presence of oil soluble surfactant such as Span. Then this mixture is stirred using propeller agitator at 500 rpm over a period of 2–3 h to ensure

complete evaporation of the solvent. The liquid layer is decanted and micro particles are separated by filtration through a Whitman filter paper, washed with n-hexane and dried for 24 h and subsequently stored in desiccators.

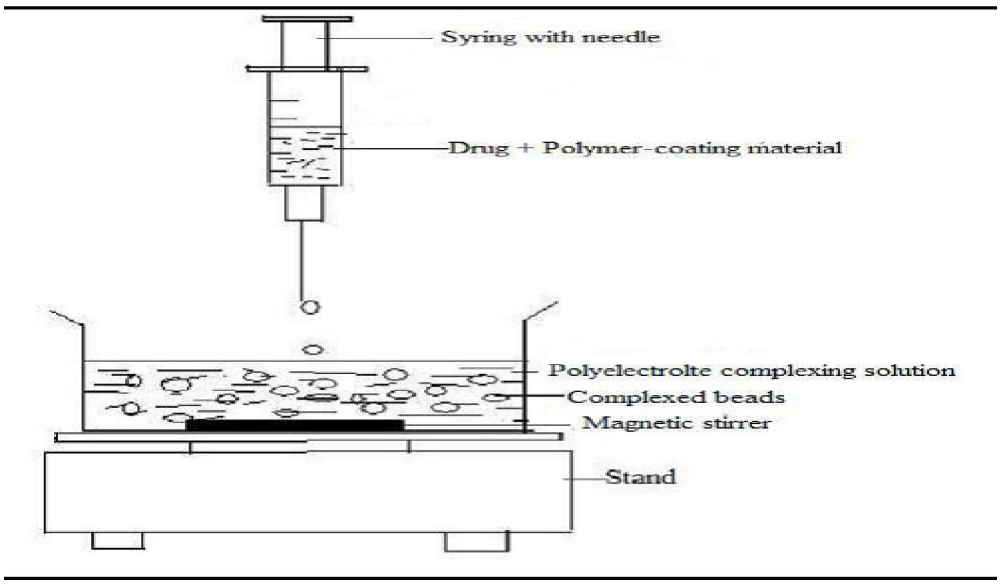
Emulsion-solvent diffusion technique

The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hour and formed floating microballoons were washed and dried in a desiccator at room temperature.



Ionic gelation technique

The drug was added to 1.2% (w/v) aqueous solution of sodium alginate and continue stirring is preferred for complete solubility. After that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solutionin acetic acid Microballoons were kept in original solution for 24 hr for internal gellification followed by filtration for separation . The maximum release of the drug was obtained at pH 6.4-7.2. Alginate/ chitosan particulate system for diclofenac sodium release was prepared using this technique.



Single emulsion technique

Micro particulate carriers of natural polymers (proteins and carbohydrates) are prepared by single emulsion technique. The natural polymers (proteins and carbohydrates) are dispersed in aqueous media followed by dispersion in non-aqueous medium like oil with the help of cross linking agent.

Double emulsion technique

Double emulsion technique is the formation of the multiple emulsions or the double emulsion such as w/o/w.

Coacervation phase separation technique

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug was dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles.

Polymerization technique

The polymerization techniques conventionally are mainly classified as:

a. **Normal polymerization:** It is carried out using different techniques of polymerization like bulk, suspension, precipitation, emulsion and micellar polymerization processes.

b. **Interfacial polymerization:** This technique involves the reaction of a range of monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

c. **Spray drying and spray congealing:** These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone and methanol etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This mixture is then atomized in a stream of hot air. The atomization prompts the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microballoons in a size range 1-100 µm. Depending upon the removal of the solvent or cooling of the solution are named spray drying and spray congealing respectively.

FACTORS TO BE CONSIDERED DURING FORMULATION

1. Addition of polymer solution

As reported that, the high surface tension of water caused the solidification and aggregation of polymer on the surface of aqueous phase. To minimize the contact of polymer solution with the air-water interface and to develop a continuous process for preparing microballoonss, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microballoonss and reduced the extent of aggregate formation.

2. Effect of rotation speed

It is obvious that the rotation speed of propeller affects yield and size distribution of microballoonss. As the rotation speed of propeller increases, the average particle size decreases.

3. Effect of temperature

The temperature of the dispersing medium is an important factor in the formation of microballoonss as it controls the evaporation rate of the solvents. Microballoonss prepared at low temperature (10ºC) were crushed and irregularly shaped. The shell of the microballoons turns translucent during the process, due to slower diffusion rate of ethanol and dichloromethane. At higher temperature (40ºC), the shell of the microballoons became thin and it might be due to the faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium.

EVALUATION OF FLOATING MICROBALLOONS[2, 10]

Micromeritics

Microballoons were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausner‟s ratio.

Particle size

The particle size of the microballoons was measured using an optical microscopic method and mean microballoons size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm3)

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Volume of sample}}$$

Tapped density

Accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm3)

$$\text{Tapped density} = \frac{\text{Weight of sample}}{\text{Tapped volume}}$$

Carr's index (%)

The Carr‟s index is frequently used as an indication of the flowability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability and below 15% of good flowability. Flow property of blend depends upon Compressibility index. The Carr‟s index is an indication of the compressibility of a powder. It is calculated by the formula. (Values as given in Table 1)

$$\text{Carr's index}(\%) = \text{Tapped density} - \text{Bulk density} \times 100 / \text{Tapped density}$$

Table 1: Carr's index as an indication of powder flow

Carr's index	Type of Flow
5-15	Excllent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Extremely Poor

Angle of repose (θ)

The angle of repose is indicative of flowability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by (Values as given in Table 2.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, θ is angle of repose,

h is height of the pile;

r is the radius of the pile.

Table 2: Relationship between angle of repose (θ) and flowability

Angle of Repose(θ)	Flowability
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Hausner's ratio

The Hausner"s ratio is an indication of the compressibility of a powder. It is calculated by the formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

The Hausner"s ratio is frequently used as an indication of the flowability of a powder. A Hausner"s ratio greater than 1.25 is considered to be an indication of poor flowability. The observations for the flow properties determinations were recorded.

Percentage yield

Percentage yield of floating microballoons was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microballoons and is represented by following formula.

% yield = (actual weight of product/total weight of drug and Excipients) ×100

Drug entrapment efficiency (DEE)

The amount of drug entrapped was estimated by crushing the microballoons 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 microballoons was calculated by the following formula:

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

In vitro Buoyancy

Floating behavior of hollow microballoons was studied using a USP dissolution test apparatus II by spreading the microballoons (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microballoons were collected separately. The microballoons were filtered, dried and weighed. The percentage of floating microballoons was calculated using the following equation

% buoyancy of microballoons = (weight of floating microballoons/initial weight of floating microballoons) x 100

Dissolution test (in vitro-drug release) of microballoons

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Microballoons equivalent to the drug dose are added to 900 ml of the dissolution medium and stirred at 100 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy.

Morphological Study using SEM

The external and internal morphology of the microballoons were studied by scanning electron microscopy (SEM) .

Stability Studies

Optimized formulation was sealed in aluminum packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the physical appearance and drug content.

APPLICATIONS OF FLOATING MICROBALLOONS[1, 11, 12]

Floating microballoons are very effective approach in delivery of drugs that have poor bioavailability because of their limited absorption in the upper GIT. These systems efficiently maximize their absorption and improve the bioavailability of several drugs. e.g Furosemide, Riboflavin etc.

The floating microballoons can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.

Gastro retentive floating microballoons are very effective in the reduction of major adverse effect of gastric irritation; such as floating microballoons of nonsteroidal anti inflammatory drugs i.e. Indomethacin are beneficial for rheumatic patients.

Floating microballoons are especially effective in delivery of 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. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microballoons may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as Verapamil hydrochloride. The gastro-retentive floating microballoons will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

Hollow microballoons 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 microballoons are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin frusemide and misoprostol. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

These microballoons systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microballoons of tranilast are fabricated as a floating controlled drug delivery system.

The drugs recently reported to be entrapped in hollow microballoons include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem, verapamil and riboflavin, aspirin, griseofulvin, ibuprofen, terfenadine.

There are several others significant applications of FDDS as summarized below:

Sustained Drug Delivery

HBS systems can remain in the stomach for longer 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. Such 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 thus the passage from the pyloric opening is prohibited.

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.

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.

CONCLUSION

Floating microballoons has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microballoons as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. Optimized multi-unit floating microballoons are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse diseases. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Increased sophistication of this system will ensure the successful advancements in the avenue of gastro retentive microballoons therapy so as to optimize the delivery of molecules in a more efficient manner.

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