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FLOATING MICROSPHERES FOR GASTROINTESTINAL DISORDERS

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Abstract:
Drug absorption in the gastrointestinal tract is a highly variable process. Floating microspheres are promises to be a potential approach for gastric retention enhances 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 microspheres 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. 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. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

Keywords: *Gastro Retention, Hollow microspheres, Floating microspheres, Short halflife, Solvent Diffusion, Floating drug delivery system (FDDS).*

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INTRODUCTION:

Gastroretentive Drug Delivery System: Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of gastrointestinal tract (GIT) due to variable gastric emptying and motility [1-4]. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine, can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control on placement of a variety of important drugs through appropriately designed drug delivery system (DDS) in a specific region of the GI tract offers advantages particularly for those having a narrow absorption window in the GIT or those with stability problems. These considerations have led to the development of a unique oral controlled release dosage form with Gastroretentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine [6-10].

Gastric emptying is a complex process, one that is highly variable and that makes *in vivo* performance of drug delivery systems uncertain. A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. Floating or hydrodynamically controlled drug delivery systems are useful in such applications. Various gastroretentive dosage forms are available, including tablets, capsules, pills, laminated films, floating microspheres, granules and powders. The dosage form comprises a plurality of buoyant particles, each comprising an inner drug-containing core, an intermediate layer surrounding said core and a release rate-controlling outer coating. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation.

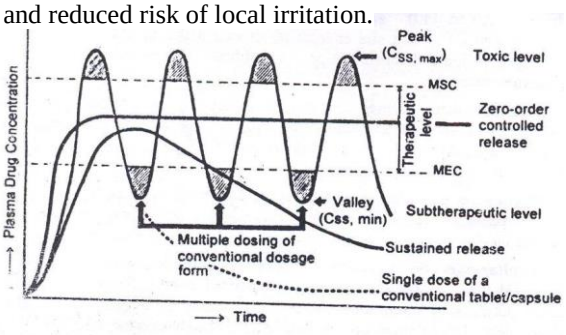

Figure 1: Drug blood level versus time profiles

Mechanism:

Most of the floating systems are single-unit systems, which are generally unreliable and non-reproducible in prolonging the GRT, in virtue of their unpredictable all-or-nothing emptying process. On the other hand, multiple-unit dosage forms appear to be better suited, since they claim to reduce inter-subject variability in absorption and have a lower dose-dumping probability. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave way to the development of gastroretentive floating microspheres [11-13]

Floating microspheres are gastroretentive drug delivery systems based on a non-effervescent approach. Hollow microspheres, microballoons or floating microparticles are terms used synonymously for floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core. These are free-flowing particles, with size ranging from 1 to 1000 µm. non-effervescent hollow polycarbonate microspheres are developed 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 [14].

Advantages of floating microspheres:

1. Bioavailability enhances, despite first pass effect, because fluctuations in plasma drug concentration are avoided, and a desirable plasma

drug concentration is maintained by continuous drug release.
2. Superior to single-unit floating dosage forms, as such microspheres release drugs uniformly and there is no risk of dose dumping.
3. Enhanced absorption of drugs that solubilise only in stomach.
4. Site-specific drug delivery to the stomach can be achieved.
5. Avoidance of gastric irritation, due to sustained release effect.
6. Better therapeutic effect of short half-life drugs can be achieved.

Disadvantage
Reproducibility of the particle size of the formulation.

Methods of Preparation of Hollow Microspheres:
Hollow microspheres are prepared through the **solvent diffusion and evaporation method** to create the hollow inner core. The solvent is evaporated either by increasing the temperature under pressure or by continuous stirring.
The floating microspheres are prepared by the emulsion solvent diffusion method, utilizing enteric acrylic polymers dissolved with drug in a mixture of dichloromethane and ethanol. The above solution was introduced in the aqueous solution of polyvinyl alcohol at 40 ºC with constant stirring to form an oil-in-water (o/w) emulsion. After agitating the system for 1 hour, the resulting polymeric particulate systems were sieved between 500 and 1000 mm and then dried overnight at 40 ºC to produce hollow microspheres.
A novel two step manufacturing process of hollow, poly-butyl-2-cyanoacrylate (PBCA) microspheres in an aqueous phase was developed to synthesize gas-filled hollow microspheres. These microspheres have an organic shell. The first step is the polymerization process of *n*-butyl-2-cyanoacrylate (BCA) to form nanoparticles. During the second step, the nanoparticles attach on a microbubble precursor and finally form hollow microspheres.
Cellulose acetate, chitosan, Eudragit, Acrycoat, Methocel, polyacrylates, polyvinyl acetate, Carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide are some of the polymers used in the preparation of hollow microspheres.

Mechanism of formation of hollow microspheres
Ethanol and methanol have been found to be good solvents for most drugs and polymers. Dichloromethane and chloroform are good bridging liquids due to the good linkage between the drug and polymers and to their immiscibility in the external phase. Water-insoluble polymers, mentioned above, show higher solubility in dichloromethane than ethanol. However, ethanol has higher solubility in water. As soon as the polymer solution was added to the aqueous medium, the ethanol diffuses rapidly from the droplets of the polymer solution. Simultaneous diffusion of water inside the sphere further decreased the ethanol concentration, hence the polymer precipitated, resulting in the formation of microspheres. Dichloromethane remaining as the central core diffused slowly due to its low water solubility. Therefore, the diffusion of ethanol played an important role in determining the size and shape of the microspheres.

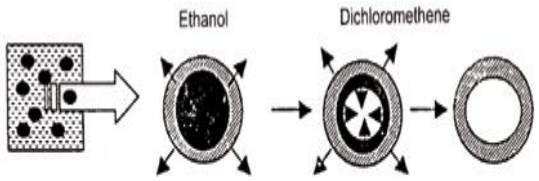

FIGURE 2 - Formulation of floating microspheres (Kawashima *et al.*, 1991).

Mechanism of gastro retention
When microspheres 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 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 microspheres. However, a minimal gastric content is needed to allow proper achievement of buoyancy.

Characterization/evaluation of floating microspheres

Particle size
Size is measured using an optical microscope, and mean particle size is calculated by measuring 200–300 particles with the help of a calibrated ocular micrometer

Tapped density and compressibility index
The tapping method is used to determine the tapped density and percentage compressibility index, as follows

$$Tapped\ density = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

$$\%\ \text{compressibility Index} = \left[1 - \frac{V}{V_0}\right] \times 100$$

where V and V_o are the volumes of the sample after and before the standard tapping, respectively.

Floating behaviour

The floating test on the microspheres is carried out using the dissolution method II apparatus, specified in the USP XXII. The microspheres are spread over the surface of the dispersing medium (900 ml), which is agitated by a paddle rotated at 100 rpm. Disintegration test solution No. 1 (pH 1.2), containing Tween 20 (0.02%, w/v), is used as a dispersing medium to simulate gastric fluid. After agitation for a previously determined interval, the hollow microspheres that floated over the surface of medium and those that settled to the bottom of the flask are recovered separately. After drying, each fraction of the hollow microspheres is weighed. The buoyancy of the hollow microspheres is represented by the following equation.

$$buoyancy\ (\%) = \frac{Q_f}{Q_f + Q_s} \times 100 \quad (7)$$

where Q_f and Q_s are the weights of the floating and settled hollow microspheres, respectively.

***In vitro* release studies**

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Microspheres 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 or HPLC, etc.

In vivo *studies*

In vivo studies are generally conducted in healthy male albino rabbits weighing 2-2.5 kg. The animals are fasted for 24 hours before the experiments; however, they are given free access to food and water during the experiments. Blood samples (2 mL) are collected from the marginal ear vein into heparinized centrifuge at an appropriate time interval

Applications of floating microspheres

1. Floating microspheres can be used as carriers for drugs with so-called absorption windows
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.

2. Hollow microspheres of non-steroidal anti-inflammatory drugs are very effective for controlled release, and reduce the major side effect of gastric irritation. For example, floating microspheres of indomethacin are quite beneficial for rheumatic patients.

3. Floating microspheres are especially effective in the 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 transit time becomes a significant factor affecting drug absorption.

4. The gastroretentive floating microspheres will beneficially alter the absorption profile of the active agent, thus enhancing its bioavailability.

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.

CONCLUSION:

Floating microspheres 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 microspheres 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 microspheres 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 microspheres therapy so as to optimize the delivery of molecules in a more efficient manner.

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