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Floating Microspheres: A New Development in Gastroretentive Drug Delivery System

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Abstract

Gastric emptying is a complicated process in the human body that is extremely changeable, making the in vivo performance of drug delivery devices unclear. A regulated drug delivery system with a prolonged gastric residence period of >12 h in the stomach might be of major practical value for medications with an absorption window in the ugastro retentivestine to overcome this variability. Tablets, capsules, laminated films, floating microspheres, granules, and powders are all forms of gastroretentive medications. The use of microparticulate drug administration for oral medication delivery has become a popular approach iniscent years. Such methods are more advantageous than single-unit dosing forms. One strategy for increasing gastric retention Floating microspheres are used to deliver multiparticulate drugs over time. Floating microspheres are gaining popularity, resulting in more repeatable medication absorption and a lower risk of local discomfort. These methods provide a scharacterizationsistent release of medications in the stomach. The current review compiles the most recent research onMicro balloonses of production, characterisation, and numerous criteria influencing the performance of floating microspheres for oral administration. Microballoons are superior to conventional floating medication delivery devices because they do not have a floating lag period.

Introduction

A medicine that is released from a dosage form in the stomach in a regulated manner will recognized fluids and have the wholutilizede area of the small intestine available for absorption[1]. For decades, oral medication delivery has been recognised as tutilizedextensively utilised method of administration of the systemic delivery routes investigated. The oral route is the most convenient and widely utilised method of medication delivery. If the controlled release system cannot remain near the absorption point, it has limited uses. The capacity to be kept in the stomach is referred to as a gastro retentive medication delivery mechanism. They can aid in the optimization of oral controlled medication administration. "absorption window" ensures excellent bioavailability by continuously releasing the medication prior to the absorption window for an extended length of time. Gastric emptying happens both while fasting and when fed. The pattern of motility, however, differs between the two phases. Stomach emptying investigations demonstrated that orally administered controlled release dosage forms face two major challenges: short gastric residence period and variable gastric emptying rate[2].

Controlled release medication administration system Table 1: Comparison between conventional and gastro retentive drug delivery system [3]

Parameters	**Gastroretentive Drug Delivery System**	**Conventional Drug Delivery System**
Risk of toxicity	Lower	Higher
Patient compliance	High compliance level	Less compliance level
Dose dumping	High risk	No risk
Drugs	**Beneficial for drugs:** That have rapid GI absorption Degrade in colon	**Not beneficial for drugs:** That have low GI absorption Degrade in colon

GRDDS is required.

• Traditional oral administration is commonly employed in the pharmaceutical industry to treat ailments. However, traditional delivery has numerous limitations, the most significant of which being non-site specificity.

• Some medications are exclusively absorbed at a specific place. They need release at a specified spot or release in such a way that the maximal amount of medicine reaches the targeted site.

• The pharmaceutical industry is increasingly focused on medications that require site specificity.

• Gastro-retentive delivery is a site-specific delivery method for delivering medications to the stomach or intestine. It is achieved by maintaining the dose form in the stomach and releasing the medicine in a controlled manner to a specified spot in the stomach, duodenum, or intestine [4].

Physiology of the Gastrointestinal Tract

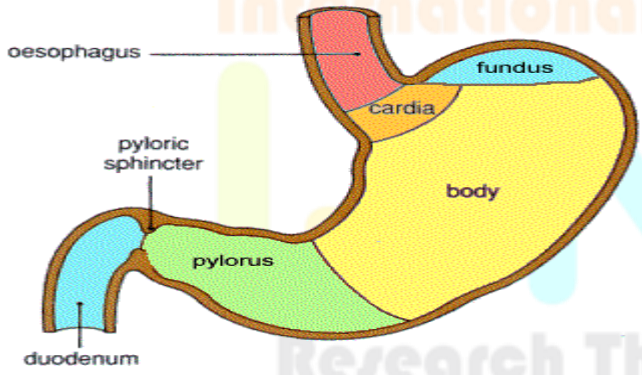

Figure 1 depicts the anatomy of the gastrointestinal system.

1. Phase I (base phase) lasts 40-60 minutes with occasional contractions.

2. Phase II (preburst phase) lasts 40 to 60 minutes and is characterised by intermittent action potential and contractions. The intensity and frequency steadily rise as the phase advances.

3. The third phase (burst phase) lasts 4 to 6 minutes. It consists of brief periods of severe and regular contractions. All undigested material is carried out of the stomach and into the small intestine by this wave. The housekeeping wave is another name for it.

4. Phase IV lasts between phases III and I of two consecutive cycles and lasts 0 to 5 minutes.

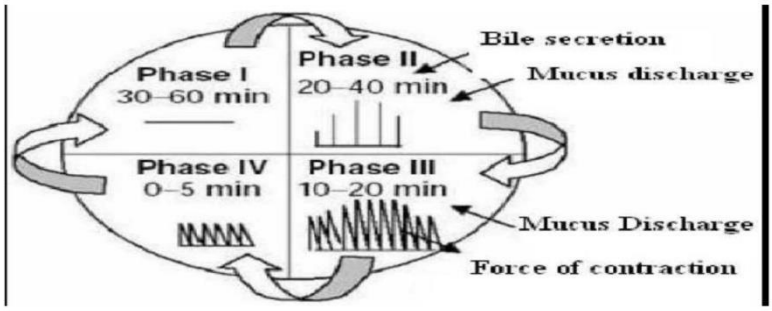

Figure 2 shows a schematic illustration of interdigestive motility.

Following the intake of a mixed

fundus,body,antrum(pylorus). The fundus and body of the proximal section function as a storage for undigested material, whereas the antrum is the primary site for mixing motions and works as a pump for stomach emptying by pushing activities. 13 Gastric emptying happens both while fasting and when fed. However, the motility pattern differs between the two states. Fasting causes an interdigestive series of electrical events that cycle through the stomach and intestine every 2 to 3 hours. 14 This is known as the interdigestive myloelectric cycle (IDMC) or migrating myloelectric cycle (MMC), and it is separated into four phases as defined by Wilson and Washington.

Approaches for GRDDS [8-10]

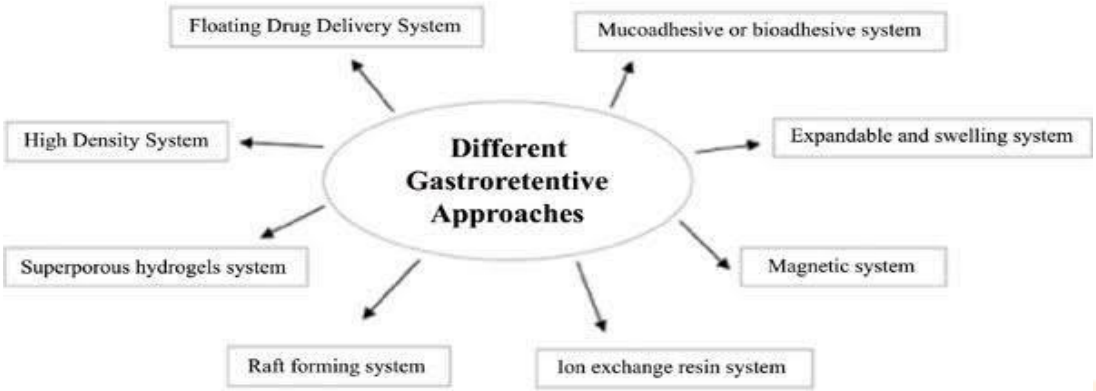

Fig.3 Different Gastroretentive approaches

HOLLOW MICROBALLOONS FORMULATION METHODS

The most frequent emulsion created for the production of microbaloons is the O/W type.

[15-17] The key formulation ingredients of the microballoons for this approach include active pharmaceutical ingredient, polymer system, solvent system, and emulsifier. In this procedure, the polymer is first dissolved in the solvent system of choice, after which the API is either dissolved or dispersed. The organic phase is a solvent-based combination of API and polymer. [18] The aqueous phase, on the other hand, has to be created by dissolving the specified emulsifier in water (pH can be maintained by adding buffers if desired). The aforesaid organic phase is then progressively dropped into the aqueous phase, which should be kept under continuous pressure. To create an o/w emulsion, use a mechanical or magnetic stirrer. The microballoons can be made in two ways, depending on the solvents utilised.

Method of evaporation using an emulsion-solvent

Microballoons are created in two phases. In the first stage, one of the solvents in the solvent system is quickly evaporated to rigidify the globules' outer layer.

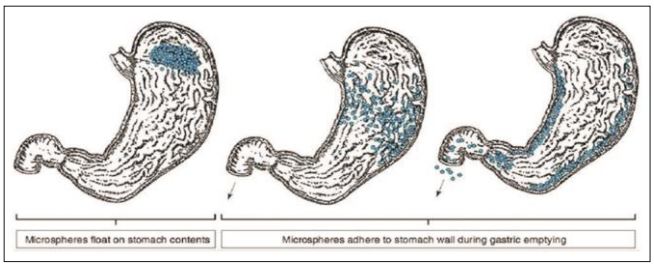

Figure 4: Mechanism of microballoon flotation in emulsion while retaining solvent inside globules. The solvent inside the globules is gradually evaporated in the second step by submitting the emulsion to temperature while stirring, resulting in interior hollowness. [19] Thus, the produced hollow micron-sized particles are referred to as microballoons, which should be separated by filtration and drying. to produce dry, free-flowing microballoons **[Figure 2].**

Material properties employed in the emulsion-solvent evaporation technique

System of solvents

The type of the solvent solution has a large impact on the formation of microballoons. The principal solvent in the solvent system should be a low boiling (very volatile) water immiscible solvent to achieve the stiff outer layer on the globules shortly after their creation. Dichloromethane and diethyl ether are two examples of such solvents. [19,20] To generate hollowness inside the globules, the second solvent should be a slowly evaporating solvent that is water-miscible and may be volatile to speed up the solvent removal process. These solvents can be either real solvents or API non-solvents.

The polymer system

The chosen polymer(s) must be soluble in the main solvent. is progressively disseminated by continuously swirling the emulsion for a prolonged length of time, creating hollowness inside the microspheres. [23-26] As a result, the generated hollow micron-sized particles are referred to as microballoons, which may be separated by filtering followed by drying to produce dried free flowing microballoons. The emulsifier should be identified.

Characterization of floating microballoons

Micromeritics

Microballoons

are characterized for their micromeritic properties such as particle size, angle of repose, compressibility index, and Hausner's ratio. The micromeritic properties[36] of the microspheres are to be priorly considered so as to study their flow properties during the filling of microballoons into the capsules.

Particle size

The particle size of the microballoons is measured using an optical microscopic method, and the mean microballoons size is calculated by measuring 100 particles with the help of a calibrated ocular micrometer. Particle size is influenced by process parameters and formulation parameters such as solvent composition, amount of polymer, emulsifier concentration, temperature, and stirring rate.

Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. 10 g of a sample of microballoons is to be placed into 25 ml graduated measuring cylinder. The volume occupied by the microballons is observed without disturbing the cylinder, and the bulk density is calculated using the equation (values expressed in g/cm^3).

$$\text{Bulkdensity} = \frac{\text{weight of sample}}{\text{volume of sample}}$$

Tapped density

About 10 g of microballoons is placed in 25 ml measuring cylinder. The cylinder is dropped at 2 s intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume is recorded, and the tapped density is calculated by the following equation (values expressed in gm/cm^3).

weight of sample

Tapped density = ——————tapped volume

Carr's index (%)

Carr's index is frequently used as an indication of the flowability of a powder. Flow property of blend depends on compressibility index.[37] The Carr's index is an indication of the compressibility of a powder. A high Carr's index is indicative of the tendency to form bridges between the particles. Smaller the Carr's index, better will

be the flow properties. The flowability with respect to the Carr's index is represented in Table 1. It is calculated by the formula.

Carr·sindex %( ) = ——————————tapped density−bulk density ×100 tapped density

Angle of repose (θ)

The angle of repose is indicative of flowability of the substance. A funnel is fixed to a burette stand in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample is allowed to flow from the funnel, until the height of the pile just touches the tip of the funnel. The radius of the pile is determined by drawing a boundary along the circumference of the pile and taking the average of radius of the circumference from three trials. The relationship between the angle of repose and flowability is given in Table 2. The angle of repose is calculated by

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

Where, θ is angle of repose, h is height of the pile, and r is the radius of the pile.

Hausner's ratio

The Hausner's ratio is an indication of the compressibility of a powder. A Hausner's ratio >1.25 is considered to be an indication of poor flowability. It is calculated by the formula,

Hausner sratio· = ——————Tapped density ×100 Bulk density

Morphological study using scanning electron microscopy (SEM)

SEM technique[38] is used for determining the surface morphology of the microballoons. The SEM sample is prepared by sprinkling the powder on the tape stuck attached to an aluminum stub. The stubs are coated using the mixture of gold and palladium at a thickness of 250–450Å under an argon atmosphere in a high vacuum evaporator at a voltage of 20 KV, current 10 mA, and low pressure. Photomicrographs are taken on the random screening of coated samples using

SEM.

Swelling studies[39]

These studies are performed to calculate the molecular parameters of swollen polymers. Swelling studies are determined using dissolution apparatus, optical microscopy, and other sophisticated techniques, which include HINMR imaging, confocal laser scanning microscopy, and cryogenic SEM. It is calculated by the following formula,

Weight of wet formulation

Swelling ratio = ——————————

Weight of dry formulation

Percentage yield[37]

Percentage yield of floating microballoons was calculated by dividing the actual weight of the product to the 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 ×100

Total wt.of drug excipients

Drug entrapment efficiency (DEE)[37]

The amount of drug entrapped is estimated by crushing the microballoons and extracting with aliquots of suitable solvent taken repeatedly. The extract is transferred to a 100 ml volumetric flask, and the final volume is made using a suitable solvent. The solution is filtered, and the absorbance is measured by spectrophotometer against appropriate blank.

Amount of dug present

DEE = ×100

Amount of drug taken

In vitro buoyancy[37]

Floating behavior of hollow microballoons is 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 a surfactant. The medium is agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 h, both the floating and the settled portions of microballoons are collected separately. The microballoons are filtered, dried, and weighed.

% Buoyancy = Weight of floated microballoons ×100 Initial weight of microballoons

CONCLUSION

In this research, we conclude that floating hollow microspheres provide an efficient gastroretentive controlled release delivery method, indicating a possible solution for gastric retention. Microballoons have a low density, which allows them to float over gastric contents and remain in the stomach for an extended length of time. When the medication floats over stomach contents, it is released at a controlled rate, limiting changes in plasma drug concentration. Microballoons are an effective method of increasing bioavailability. Microballoons that have been optimised will take the lead in innovative medication delivery. Microballoons outperform conventional floating gastro retentive medication delivery methods since they do not require lag time or floating time for buoyancy as they retain on the stomach wall. As such, they are fluid, as opposed to single-unit floating drug delivery systems and effervescent floating drug delivery systems, which have floating lag time.

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