REVIEW ARTICLE

Floating Microspheres: A Prevailing Trend in the Development of Gastroretentive Drug Delivery System

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Abstract

One of the complex processes in the human body is gastric emptying, as it is highly variable which makes the *in vivo* performance of the drug delivery systems uncertain. To overcome this variability, a controlled drug delivery system with a prolonged gastric residence time of >12 h in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. Various gastroretentive drugs are available in the form of tablets, capsules, laminated films, floating microspheres, granules, and powders. The use of microparticulate drug delivery for the oral delivery of drugs has become a prominent method in the present days. Such systems are more beneficial than the single-unit dosage forms. One of the approaches to increase the gastric retention time through multiparticulate drug delivery is floating microspheres. The floating microspheres are gaining attention which results in more reproducible drug absorption and reduced risk of local irritation. These systems give a prolonged and uniform release of the drugs in the stomach. The present review brings together the recent literature with respect to the methods of preparation, characterization, and various parameters affecting the performance of the floating microspheres for the oral route of administration. Microballoons are advantageous when compared to the other floating drug delivery systems as they do not possess a floating lag time.

Key words: Buoyancy, gastric emptying, gastric retention, microballoons, multiparticulate system

INTRODUCTION

The oral route of administration of drugs has achieved most of the attention among all the routes of drug administration. The ease of administration offers more flexibility to the oral dosage-form designs than most other routes which has made the oral route of administration of drugs quite successful. To achieve a predictable and increased bioavailability of drugs, the short gastric residence times, unpredictable gastric emptying times, and other physiological adverse conditions must be overcome.[1] These considerations led to the design of oral controlled drug delivery systems with prolonged gastric residence time. This is priorly important for the drugs with absorption window in stomach and duodenum and the drugs with stability problems.[2]

Different techniques such as bioadhesive drug delivery systems, size-controlled drug-delivery systems, and gastric floating drug delivery systems are adopted for this purpose. However, there are few problems associated with bioadhesive systems as they deliver a large amount of drug at a particular adhesive site of the gastrointestinal tract, which leads to local irritation.[3-5] As for the size controlled drug-delivery system, when they come in contact with the gastric fluid, the matrix swells and expand the size, therefore, retard the passage through the pylorus. The use of passage-delaying agents exerts an influence on the transit of the drug-delivery systems, and this is due to the lipid vehicles, primarily the fatty acids which reduce the motility of the stomach.[6]

Large single-unit dosage forms were also reported to increase the gastric retention time. After the oral administration of these systems, their size will increase to inhibit the gastric emptying

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even at an uncontractile state of the pyloric sphincter by the swelling of balloon; hydrogels are examples of such delivery systems. Another approach for improving gastric residence time is to incorporate the drug into a floating device that is less dense than the gastric fluid. Floating single-unit dosage forms, also called hydrodynamically balanced systems, are being studied extensively in the recent days.[7] These single-unit dosage forms have the disadvantage of a release all-or-nothing emptying process because if the gastric emptying takes place even before the floating of the drug, there would not be any required therapeutic activity of the drug.[8]

However, multiparticulate systems are not associated with any such problems. The uniform distribution of the multiparticulate dosage in the gastric content could result in more reproducible absorption and a reduced risk of local irritation than single-unit dosage forms.[9] Such prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug. The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids will float.[10] Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. Posture and nature of the meal also have an effect on gastric emptying.

Most of the multiple-unit systems are effervescent ones that use matrices prepared with swellable polymers and effervescent components, such as sodium bicarbonate, calcium carbonate, and citric, or tartaric acid. The disadvantage of these systems is their delayed response as the gas generation takes some time. The other forms of multiple-unit dosage forms are floating microspheres or the microballoons. The main advantages of floating microspheres are: (1) Enhancement of the bioavailability of the drug, despite first pass effect, because fluctuations in plasma drug concentration can be avoided, and a desirable plasma drug concentration is maintained through continuous drug release, (2) floating microspheres are always superior to single-unit floating dosage forms as the release of drugs is uniform and there is no risk of dose dumping, (3) enhanced absorption of drugs that solubilize only in the stomach can be attained through the floating microspheres, (4) site-specific drug delivery to the stomach can be achieved, (5) avoidance of gastric irritation, due to the sustained release effect, (6) better therapeutic effect of short half-life drugs can be achieved. Microballoons are advantageous when compared to the other floating drug delivery systems as they do not possess floating lag time.[11]

MECHANISM OF BUOYANCY OF MICROBALLOONS

Microballoons are low-density systems that have sufficient buoyancy to float over gastric fluid and remain in the stomach for a prolonged period of time. As the system floats over the gastric fluid, the drug is released slowly at a desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. When microballoons come in contact with gastric fluid, the gel forms 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 outer 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 makes the density lower than the gastric fluid and confers buoyancy to the microspheres. However, a minimal gastric content needed to allow proper achievement of buoyancy.[12,13] Adherence to the wall of the stomach will be possible during the emptying process in both fed and the fasted state, assuming that the mucoadhesive properties of the particles have not been modified by the stomach contents, in particular, non-adherent mucus. Hollow microspheres (microballoons) of acrylic resins, Eudragit, hypromellose, polyethylene oxide, cellulose acetate, polystyrene floatable shells, polycarbonate floating balloons, and Gelucire floating granules are the recent advancements [Figure 1].[14]

FORMULATION METHODS OF HOLLOW MICROBALLOONS

O/W type is the most common emulsion developed for the preparation of microbaloons.[15-17] Active pharmaceutical ingredient, polymer system, solvent system, and emulsifier are the major formulation constituents in the microballoons for this method. In this method, the polymer should be first dissolved in the selected solvent system, in which, the API is either dissolved or dispersed. This mixture of API and polymer in the solvent serves as the organic phase.[18] On the other hand, the aqueous phase is to be prepared by dissolving the selected emulsifier in water (pH can be maintained by adding buffers if desired). Then, the above organic phase is to be added slowly drop by drop into the aqueous phase which should be kept under constant stirring using either a mechanical or magnetic stirrer to obtain o/w emulsion. Based on the type of solvents used, the microballoons can be further prepared by two methods.

Emulsion-solvent evaporation method

Formation of microballoons involves two steps. In the first step, one of the solvents of the solvent system is rapidly evaporated so as to rigidize the outer layer of the globules

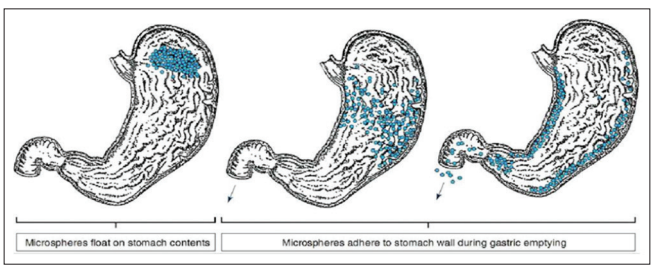

Figure 1: Mechanism of floatation of microballoons

in the emulsion and still contain the solvent inside the globules. In the second stage, the solvent inside the globules is gradually evaporated by subjecting the emulsion to temperature under stirring so that inside hollowness is created.[19] Thus, the obtained hollow micron-sized particles are termed as microballoons, which should be separated by filtration followed by drying to obtain dried free flowing microballoons [Figure 2].

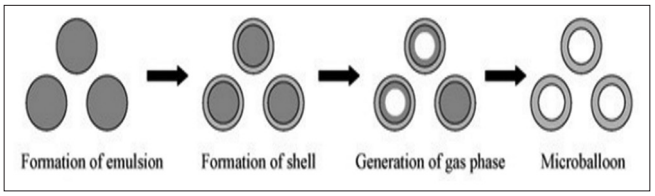

Figure 2: Solvent evaporation method

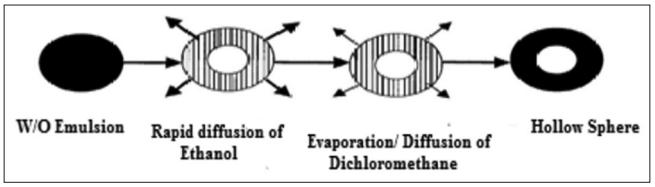

Figure 3: Solvent diffusion method

Characteristics of the materials used in the emulsion-solvent evaporation method

Solvent systems

Formation of microballoons majorly depends on the nature of the solvent system. To obtain the rigid outer layer on the globules immediately after their formation, the primary solvent in the solvent system should be a low boiling (highly volatile) water immiscible solvent. Examples of such solvents are dichloromethane and diethyl ether.[19,20] To form hollowness inside the globules, the second solvent should be slowly evaporating solvent which is water-miscible solvent and may be volatile so as to hasten the solvent removal process. These solvents can be either true solvents or non-solvents for the API.

Polymer system

The selected polymer(s) should be soluble in the primary solvent and may or may not be soluble in the second solvent. To form immediate rigid layer on the globules on evaporation of the primary solvent, the polymer should preferably be insoluble in the second solvent.[21,22] The polymer(s) should be insoluble in the outer aqueous phase so as to maintain the rigidity and allow collecting the particles easily.

Emulsion-solvent diffusion technique

O/W emulsion-solvent diffusion technique is similar to the solvent evaporation technique in which the formation of microballoons involves two steps. In the first step, one of the solvents of the solvent system is rapidly evaporated, so that the outer layer of the globules in the emulsion is Rigidized and still containing the solvent inside the globules. In the second stage, the solvent inside the globules is gradually diffused by subjecting the emulsion to continuous stirring for a longer period of time so as to create hollowness inside the microspheres.[23-26] Thus, the obtained hollow micron-sized particles are termed as microballoons, which can be separated by filtration followed by drying to obtain dried free flowing microballoons. The emulsifiers[19] commonly used for this method of the preparation of microballoons are tween 80, span 80 and SLS are used [Figure 3].

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Factors affecting the physicochemical characteristics of microballoons

Stirring rate

It is obvious that the stirring rate affects the size of the microsphere. When the organic phase is added to an aqueous phase with continuous stirring, the internal phase is prone to size reduction when the stirring speed is high as more energy is applied to the dispersion. Thereby with an increase in the agitation, higher energy is produced which helps in breaking the particles and thereby a fine size reduction can be obtained.[27,28]

Temperature of preparation

The study of optimum preparation temperature with respect to microsphere cavity formation can be carried out in the following manner. The solution drug and polymer are poured into an aqueous solution of polyvinyl alcohol at various temperatures, that is, 20, 30, 40, and 50°C. They conclude that preparation at 20 or 30°C provided porous microspheres having higher porosity with a surface so rough as to crumble on touching. As the preparation temperature increases, particle size decreases. This is because at high temperature, the emulsion is less viscous and it becomes much easier for the emulsion to be broken down into smaller droplets at the same power of mixing input.[29] Microspheres formed at higher temperature gives very slow release rates after their initial drug release.

Plasticizers

Due to the addition of plasticizer, it gives elasticity and flexibility to the wall of material so that it never gets brittle or ruptured under pressure. It is also observed that the release of the drug increased significantly with the increase of plasticizer concentration.[30]

Volume of aqueous phase (continuous phase)

The formation of hollow microspheres can be effected by the volume of the aqueous phase used. When the volume of aqueous phase increases, the particle size decreases and thus buoyancy increases. Use of large volumes of the external aqueous phase reduces the required stirring times. The solubility of dichloromethane in water is 1% w/v. Using a larger volume (400–500 ml), the diffusion of dichloromethane into the aqueous phase, and hence the solidification of particles, occurred faster, when compared to a volume of 200 ml.[31]

Solvent ratio

The bridging liquid plays a key role in microsphere preparation. Very small volume of the bridging liquid gives irregularly shaped microspheres while very large volume of bridging liquid prevents from solidifying of the emulsion droplets. Therefore, the amount of solvent needs to be carefully controlled.[32] Faster rate of solvent evaporation gives smooth surface, spherical shape, and lower encapsulation.

Amount of polymer and viscosity

Smaller microballoons are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium giving faster release of drug.[33]

Effect of solvent

The formation of microspheres by the solvent evaporation method can be effected by the use of different organic solvents. Dichloromethane is employed as a polar internal organic solvent phase for preparation of microspheres because it is a good solvent for most of the polymers and drugs. However, it is observed that the microspheres obtained are not at all spherical in shape. To solve this problem, methanol is used, along with dichloromethane, in the preparation of microspheres. The microspheres so obtained will be a spherical, but lack of smooth texture. To avoid this problem, various solvents are critically screened on the basis of the boiling points, such as dichloromethane (39.75°C), acetone (56.5°C), methanol (64.7°C), and ethanol (78.4°C). It is observed that the boiling point increased from dichlorometahne (DCM) to ethanol and so instead of DCM/methanol, ethanol is tried. Most of the water-soluble drugs and water-insoluble polymers are dissolved in ethanol, and it is non-toxic and considered as a good solvent. The high boiling point of ethanol in relation to other organic solvents such as dichloromethane, acetone, methanol etc., prevents the immediate polymer precipitation. The researchers observed that the microspheres so obtained were completely spherical, with a smooth surface.[34]

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

Carr's index	Type of flow
5–15	Excellent
12–16	Good
18–21	Fair to passable
23–35	Poor
33–38	Very poor
≥40	Extremely Poor

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

Angle of repose(θ)	Flowability
<20	Excellent
25–30	Good
30–40	Passable
>40	Very poor

Emulsifier concentration

The particle size and size distribution increase when the surfactant concentration is reduced. The role of the emulsifier (surfactant) is to decrease the interfacial tension between the dispersed droplets and the continuous phase, as well as to protect the droplets from collision and coalescence.[35] At lower emulsifier concentrations, droplets are more likely to collide and fused to form larger globules; it is insufficient to shield the entire droplet surface. At higher concentration of emulsifier, it reduces the encapsulation efficiency. Hence, the optimum concentration of 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).

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

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.

$$\text{Carr's index}(\%) = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

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,

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

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,

$$\text{Swelling ratio} = \frac{\text{Weight of wet formulation}}{\text{Weight of dry formulation}}$$

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.

$$\%\text{Yield} = \frac{\text{Actual weight of product}}{\text{Total wt.of drug excipients}} \times 100$$

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.

$$\text{DEE} = \frac{\text{Amount of dug present}}{\text{Amount of drug taken}} \times 100$$

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.

$$\%\ \text{Buoyancy} = \frac{\text{Weight of floated microballoons}}{\text{Initial weight of microballoons}} \times 100$$

Buoyancy is influenced by process parameters and formulation parameters such as 1 solvent composition, 2 amount of polymer, 3 emulsifier concentration, 4 temperature, and 5 stirring rate. In general, with the increase in the amount of polymer, an increase in the buoyancy can be observed. The increase in the buoyancy percentage may be attributed to air and gel-forming polymer.

In vitro drug release of microbaloons[37]

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

Drug release kinetics

Data obtained from *in vitro* release studies[39] are fitted to various kinetic equations to find out the mechanism of drug release. The kinetic models used are:

$Q_t = K_0\, t$ (zero-order equation)

$ln\ Q_t = ln\ Q_0 - K_1\, t$ (first-order equation)

$Q_t = K_h\, t_{1/2}$ (Higuchi equation)

Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the microsphere, and K_0, K_1, and K_h are rate constants of zero-order, first-order, and Higuchi equations, respectively. Further to confirm the mechanism of drug release, the first 60% of drug release was fitted in the Korsmeyer-Peppas model.

$$M_t/M_\infty = k\ tn$$

Where M_t is the amount of drug release at time t and M_∞ is the amount released at time $t = \infty$, thus M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent which can be used to characterize both mechanisms for both solvent penetration and drug release.

Stability studies[40]

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 are analyzed for the physical appearance and drug content.

In vivo floating efficiency (X-ray) study[41]

The *in vivo* study was carried out by administering floating beads to rats and monitoring them by a radiological method. Six healthy albino rats of either sex, weighing 200–300 g are used for the present study. The animals should be housed in individual cages, and the experiments are conducted in a sanitized room at a temperature maintained at around 27°C. Food was withdrawn 12 h before the study with water *ad libitum*. To make the beads radiopaque, 500 mg of barium sulfate was incorporated into polymeric solution (the same optimized formulation composition was used to prepare radiopaque beads) and radiopaque beads are to be prepared using a similar procedure to that mentioned in the preparation of beads. Beads are to be administered through the oral gastric tube with 2 ml water in the fasted state. The animals are not allowed to eat or drink throughout the study (up to 6 h). In total, 1 ml of water should be administered to animals every hour throughout the study. The position of the bead in the rat's stomach is monitored by X-ray photographs of the gastric region at varying time intervals (at 1, 4, and 6 h).

Experimental design

Several formulations and process parameters influence the different characteristics of microballoons. The optimization of these parameters can be achieved effectively only by the application of different statistical techniques.[42] The various experimental designs that can be applied in the optimization of the parameters include empirical models, factorial designs, fractional factorial designs, simplex optimization, and response surface methodology. The final experimental results are expressed as mean standard deviation and are statistically treated using Student's *t*-test and analysis of variance to check significant differences in different formulations. The hypothetical statistical differences are considered to be significant at $P < 0.05$.

CONCLUSION

In the current review, we hereby conclude that the floating hollow microspheres show an effective gastroretentive controlled release delivery system which ensures a potential approach for gastric retention. Microballoons possess a low-density which favors buoyancy to float over gastric contents and retain in the stomach for a prolonged period. The drug is released at a predetermined rate when it floats over gastric contents thereby reducing the fluctuations in plasma drug concentration. Microballoons are efficient means of enhancing the bioavailability. Optimized microballoons will find the prior place in novel drug delivery. Microballoons prove to be more advantageous than the other floating gastro retentive drug delivery systems as they do not require lag time and floating time for the buoyancy as they retain on the gastric fluid as such, unlike the single-unit floating drug delivery systems and effervescent floating drug delivery systems which possess floating lag time.

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