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Gastroretentive Floating Microsponges an Updated Review

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JICKY T PANICKER[1]*, SHAIJU S DHARAN[1], SOJAN ABRAHAM JOSHUA[1], JULIE E JAMES[1], BINEESHA K B[1]

[1]Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyatinkara-695124, Thiruvananthapuram, Kerala.

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ABSTRACT

Gastro retentive dosage forms (GRDFs) are being used for a very long time to improve therapy with several essential drugs. Floating drug delivery (FDDs) permit prolonged and continuous release of the drug to the upper part of Gastrointestinal tract (GIT) and this expressively extends the duration of drug release and improve the bioavailability of drugs that have a narrow therapeutic window. Floating microsponges greatly improve the therapy of stomach by releasing the drug locally and thus used for drug targeting at a particular organ. This can be sustained over a longer duration of time. Floating Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release.

INTRODUCTION

Drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. The size of the microsponges can be varied, usually from 5 – 300 µm in diameter, although the microsponge size may vary, a typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsponge, which can be loaded with up to its weight of active agent [1].

Microsponge polymers have the flexibility to load a wide range of actives providing the benefits of improved product efficacy, tolerability, mildness and extended wear to a wide range of skin therapies. Improved in formulation stability to ensuring long term product efficacy and extended shelf life. Microsponge is one of the modern and new approaches to deliver a drug for a longer period in a sustained manner. The microsponge drug delivery system is widely applicable to transdermal drug delivery products. But MDS also expands its application in oral drug delivery, bone, and tissue engineering, in detecting the diseases and in RNAi silencing.

Gastro-retentive Microsponge is low-density systems that have sufficient buoyancy to float over gastric contents and remain in the stomach for a prolonged period. The drug is released slowly at the desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Microsponges improve patient compliance by decreasing dosing frequency, the better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilize only in the stomach, Gastric retention time is increased because of buoyancy[2].

Floating microsponge drug delivery system (FMDDS) has been shown to enlargement of the rate of solubilization of poorly water-soluble drugs in the microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significantly increased surface area so that increase in the rate of solubilization. An added

advantage is that the time it takes the microsponge system to cross the small and large intestine is significantly increased thus maximizing the amount of drug that is absorbed[FigureI]. Conventional oral dosage forms are unsuccessful in delivering drugs to the colon due to absorption or degradation of the active ingredient in the upper gastrointestinal tract. A microsponge system offers the potential to grip active ingredients in a protected atmosphere and supply controlled the delivery of oral medication to the lower gastrointestinal tract, where it will be released upon contact to specific enzymes in the colon. Potentially, the microsponge system can decrease extensively the irritation of efficient drugs without reducing their effectiveness [3].

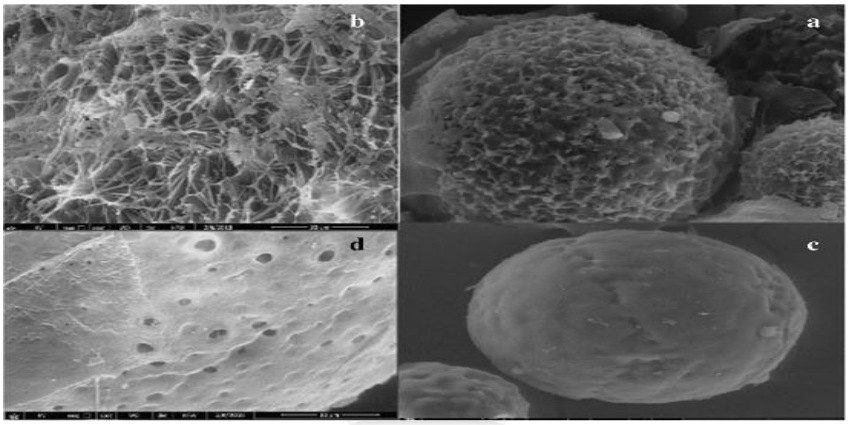

Figure No 1: Floating microsponges

IDEAL CHARACTERISTICS OF FLOATING MICROSPONGES

a. They are stable over the range of pH 1 to 11.

b. They are steady at the temperature up to 130°C.

c. They are compatible with the major vehicles and ingredients.

d. They are self-sterilizing as their average pore size is 0.25µm where bacteria cannot enter.

e. They have superior loading capacity (50 to 60%), still, free-flowing and can be cost-effective.

f. They are non-allergic, non-irritating, non-mutagenic and non-toxic.

g. They can absorb oil up to 6 times their weight without drying.

ADVANTAGES OF FLOATING MICROSPONGE DRUG DELIVERY

1. This system is especially advantageous for those drugs which are absorbed from the stomach or the proximal part of the small intestine, e.g., furosemide and riboflavin.

2. The fluctuations in plasma drug concentration are minimized and side effect associated with concentration is also minimized.

3. Complete absorption of the drug from the floating formulation is expected even at alkaline pH of intestine. The dissolution occurs in gastric fluid and after emptying of the stomach contents the dissolved drug is available for absorption in the small intestine [4]. Because of site-specific absorption from the upper part of the GIT, Drugs that have poor bioavailability are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

4. FDDS improves patient's compliance by reducing dosing frequency.

5. The better therapeutic effect achieved from short half-life drugs.

6. Because of buoyancy gastric retention time in increased.

7. Increase absorption of drugs which are only solubilized in stomach.

8. Because of the sustained release effect, floatability and uniform release of drug through multi- particulate system avoiding gastric irritation.

MATERIALS THAT CAN BE ENTRAPPED IN FLOATING MICROSPONGES

Most liquid or soluble ingredients can be entrapped in the particles and active ingredients that can be entrapped in microsponges must assemble the following requirements.

a. It should be also completely miscible in the monomer or capable of being made miscible by adding together the small amount of a water-immiscible solvent.

b. It should be water-immiscible or at most only slightly soluble.

c. It should be inert to monomers.

d. It should be steady in contact with the polymerization catalyst and environment of polymerization.

e. The spherical structure of microsponges should not disintegrate [5].

PREPARATION OF FLOATING MICROSPONGES

Drug loading in microsponges can take place in two ways, one-step process or by a two-step process, as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which based on Physico-chemical properties of the drug to be loaded.

Polymerization

Porous microsphere prepared by the polymerization method i.e. Liquid-liquid suspension polymerization. They are conveniently prepared by this method. In this method of polymerization, the monomer is dissolved along with the active ingredient in a suitable solvent and then added in an aqueous phase containing additives i.e. surfactant, suspending agents, etc. The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation. Polymerization of styrene or methyl methacrylate is carried out in round bottom flask. A solution of the non-polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete droplets of the desired size is established, by activating the monomers either by catalysis or increased temperature. When the drug is sensitive to the polymerization conditions, the two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental condition [Figure no 2].

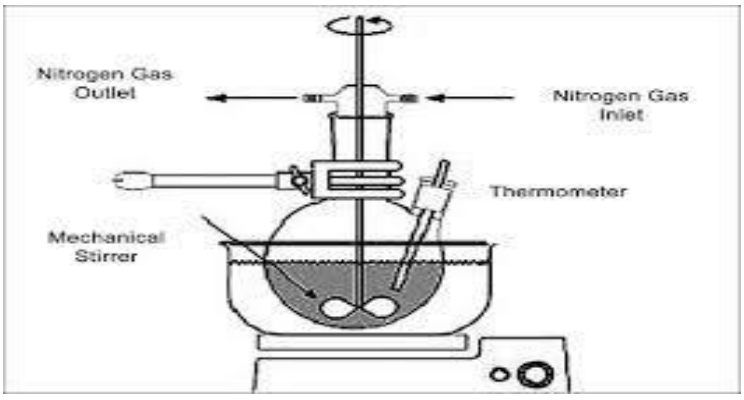

Figure no 2: Reaction vessel

Quasi-emulsion Solvent Diffusion

This is a two-step process where the microsponges can be prepared by quasi emulsion solvent diffusion method using the different polymer amounts [Figure no 3]. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, the drug can be then added to the solution and dissolved under ultrasonication at 35°C. The inner phase was poured into the Polyvinyl alcohol solution in water (outer phase). Following 60 min of stirring, the mixture is filtered to separate the microsponges. The microsponges are dried in an air-heated oven at 40° C for 12 Hr and weighed to determine production yield. [5]

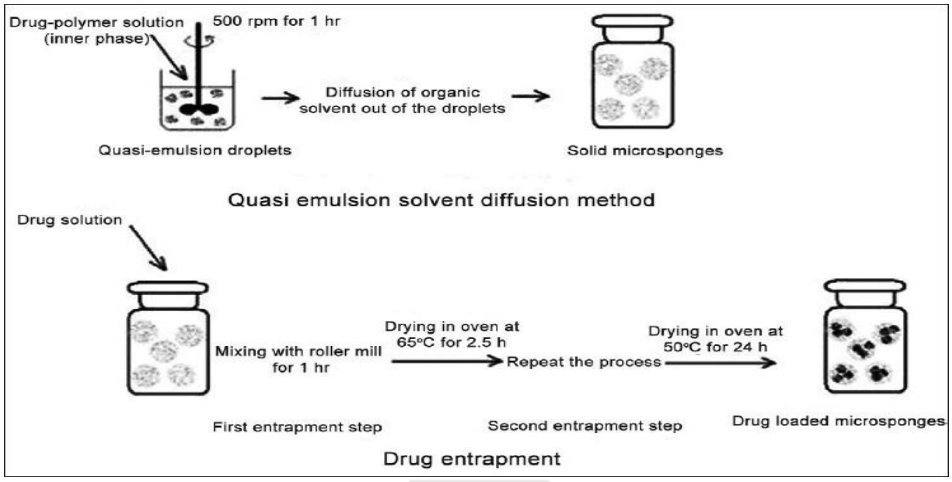

Figure no 3: Quasi emulsion solvent diffusion method

EVALUATION OF FLOATING MICROSPONGES

Floating Microsponges were characterized for their micromeritic properties such as particle size, angle of repose, compressibility index and Hausner`s ratio.

Particle size

The particle size of the microsponge was measured using an optical microscopic method and mean microsponge 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. The volume occupied

by the granules was noted without disturbing the cylinder and the bulk density was calculated using the equation (values expressed in gm/cm^3).

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

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/cm^3).

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

Carr's index (%)

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. Carr`s index is an indication of the compressibility of a powder.

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

The angle of repose (θ)

The angle of repose is indicative of flowability of the substance. The 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

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

Where θ is the angle of repose, his height of the pile; r is the radius of the pile.

Hausner's ratio

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

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

Percentage yield

The percentage yield of floating microsponge 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 microsponge and is represented by the following formula.

$$\%\ \text{yield} = \frac{\text{Actual weight of product}}{\text{total weight of drug and excipients}} \times 100$$

Drug entrapment efficiency (DEE)

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

$$\text{DEE} = \frac{\text{amount of drug present}}{\text{theoretical drug load expected}} \times 100$$

***In vitro* Buoyancy**

Floating behavior of microsponge was studied using a USP dissolution test apparatus II by spreading the microsponge (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as a 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 microsponges were collected separately. The microsponges were filtered, dried and weighed. The percentage of floating microsponge was calculated using the following equation.

$$\%\ \text{Buoyancy of microsponge} = \frac{\text{weightoffloatingmicrosponge}}{\text{initialweightoffloatingmicrosponge}} \text{ x } 100$$

Dissolution test (*in vitro*-drug release) of microsponge

In vitro dissolution studies can be carried out in a USP paddle-type dissolution assembly. Microsponge equivalent to the drug dose is 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 microsponges 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 the studies, samples were analyzed for physical appearance and drug content [6].

CONCLUSION

Floating microsponges has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Floating microsponge 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 microsponge is 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 microsponge therapy to optimize the delivery of molecules more efficiently.

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