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MICROSPONGE: A NOVEL APPROACH IN GASTRO-RETENTION DRUG DELIVERY SYSTEM (GRDDS)

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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. Microsponge hold certification as one of the potential approaches for gastric retention. Microsponge are porous 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. In the present review method of preparation, characterization, advantages, disadvantages and applications of floating microsponge are discussed.

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INTRODUCTION

A Microsponge Delivery System (MDS) is "Patented, highly cross-linked, porous, polymeric microspheres that can entrap wide range of actives and then release them onto the skin over a time and in response to trigger"(Kilicarslan,2003). By Won in 1987, microsponge technology was developed and the original patents were assigned to highly developed polymer systems. Microsponges are porous microspheres having many of consistent voids of particle size ranging between 5-300 µm. To control the release rate of active agents to a programmed site in human body has been one of the biggest challenges faced by drug industry. 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. These microsponges have ability to entrap broad range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infectives and are used as a topical drug delivery system. These porous microspheres consist of active ingredients can be incorporated into formulations like creams, lotion, powders, and tablet for drug delivery. Microsponge is one of the modern and new approach to deliver a drug for longer period of time in a sustained manner.The microsponge drug delivery system is widely applicable to the 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 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. Microsponge 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.

The microsponge for oral delivery

Microsponges are porous polymeric microspheres that are used typically for topical and recently for oral administration. In oral applications, the microsponge drug delivery system 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 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.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 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.

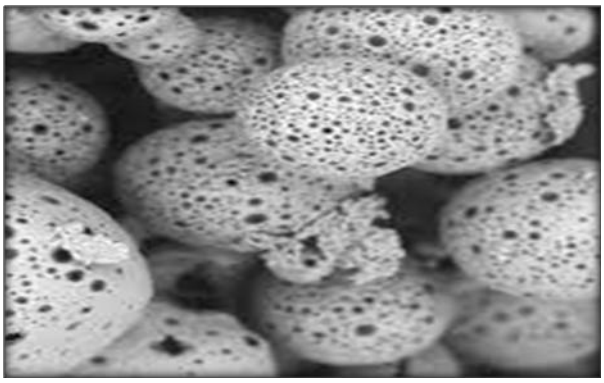

Figure 1: Diagram of Microsponge.

Ideal Characteristics of Microsponge

a. Microsponge formulations are stable over range of pH 1 to 11.
b. Microsponge formulations are steady at the temperature up to 130°C.
c. Microsponge formulations are compatible with the major vehicles and ingredients.
d. Microsponge formulations are self sterilizing as their average pore size is 0.25µm where bacteria cannot enter.
e. Microsponge formulations have superior loading capacity (50 to 60%), still free flowing and can be cost effective.
f. Microsponges are non-allergic, non-irritating, non-mutagenic and non-toxic.
g. Microsponges can absorb oil up to 6 times their weight without drying.

Characteristics of Materials That Can Are Entrapped In Microsponges

a. Most liquid or soluble ingredients can be entrapped in the particles and active ingredients that can be entrapped in microsponges must assemble following requirements.
b. It should be also completely miscible in monomer or capable of being made miscible by adding together of small amount of a water immiscible solvent.
c. It should be water immiscible or at most only slightly soluble.
d. It should be inert to monomers.
e. It should be steady in contact with polymerization catalyst and environment of polymerization.
f. The spherical structure of microsponges should not disintegrate.

Formulation Aids

Various polymers can form a microsponge 'cage'. These include ethyl cellulose, eudragit RS100, and polystyrene. In addition to actives, some microsponges contain plasticizer that helps to stabilize their structure.

Advantages

a. Oil control: Microsponges can absorb oil up to 6 times its weight without drying.
b. Extended release: It provides continuous action up to 12 hours i.e. extended release.
c. Improved product elegancy.
d. Lessen the irritation and better tolerance that leads to increase in patient compliance.
e. They have better thermal, physical and chemical stability.
f. These are non-irritating, non-mutagenic and non-toxic.
g. MDS allows the incorporation of immiscible products.
h. They have greater formulation flexibility.
i. In contrast to other technologies like microencapsulation and liposomes, MDS has wide range of chemical stability, higher payload and are easy to formulate.
j. Liquids can be converted into powders improving material processing.
k. It has flexibility to enlarge novel product forms.
l. MDS can improve bioavailability of same drug.
m. It can also improve efficacy in treatment.
n. Site specific action produce on target organ.

Limitations

a. The preparation method usually use organic solvents as porogen, which pose an environmental hazard, as some may be highly inflammable, posing a safety hazard.
b. In some cases, the traces of residual monomers have been observed, which may be toxic and hazardous to health.

PREPARATION OF MICROSPONGES[4, 5]

Drug loading in microsponges can take place in two ways, one-step process or by two-step process, as discussed in liquid-liquid suspension polymerization and quasi emulsion solvent diffusion techniques which based on physico-chemical properties of drug to be loaded. If the drug is typically an inert non-polar material, will create the porous structure it is called porogen. Porogen drug, which neither hinders the polymerization nor become activated by it and stable to free radicals is entrapped with one-step process.

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 polymerisation the monomer is dissolved along with the active ingredient in suitable solvent and then added in 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 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. (Reaction vessel are shown in fig. 2)When the drug is sensitive to the polymerization conditions, two-step process is used. The polymerization is performed using substitute porogen and is replaced by the functional substance under mild experimental conditions.

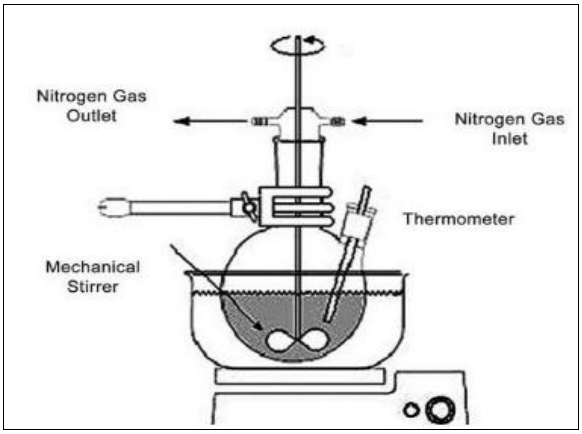

Figure 2: Reaction vessel.

The various steps in the preparation of microsponges are summarized as

a. Selection of monomer or combination of the monomer
b. Formation of chain monomer as polymerization begins
c. Formation of monomer ladder as result of cross linkage between chain monomer
d. Folding of monomer ladder to form spherical particles
e. Agglomeration of microsphere lead to formation of bunches of microsphere
f. Binding of bunches lead to formation of microsponge.

Quasi-emulsion Solvent Diffusion

This is a two step process where the microsponges can be prepared by quasiemulsion solvent diffusion method (Figure 3) using the different polymer amounts. To prepare the inner phase, Eudragit RS 100 was dissolved in ethyl alcohol. Then, drug can be then added to solution and dissolved under ultrasonication at 35^{o}C. The inner phase was poured into the PVA 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^{o}C for 12 Hr and weighed to determine production yield.

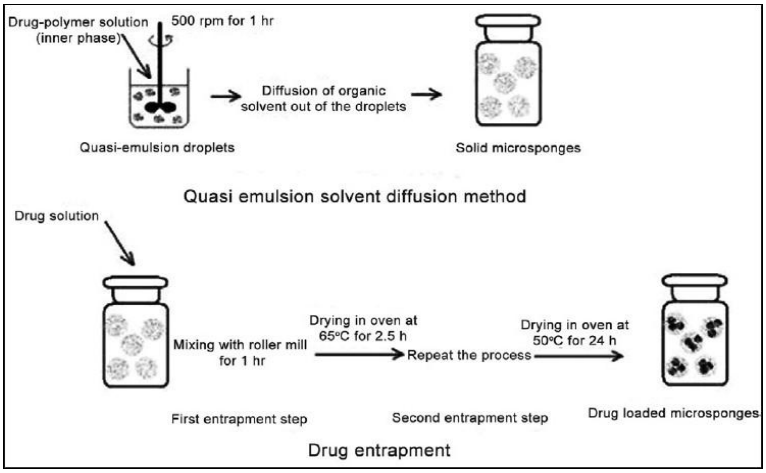

Figure 3: Quasi-emulsion Solvent Diffusion.

EVALUATION OF FLOATING MICROSPONGE[6-8]

Micromeritics

Microsponge 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 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. 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,

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

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 microsponge was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microsponge 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 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:

DEE = (amount of drug actually present/theoretical drug load expected) × 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 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 microsponge were collected separately. The microsponge were filtered, dried and weighed. The percentage of floating microsponge was calculated using the following equation

% buoyancy of microsponge = (weight of floating microsponge / initial weight of floating microsponge) 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 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 microsponge 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.

APPLICATION OF MICROSPONGE[3, 5, 8]

Table 3: Application Of Microsponge.

Active Agents	Applications
Anti-inflammatory e.g. hydrocortison	Long lasting activities with lessening of skin allergic response and dermatoses
Anti-fungals	Sustained release of actives
Anti-pruritics	Extended and improved activity
Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficiency and aesthetic appeal
Sunscreens	Long lasting product efficacy with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
Anti-dandruffs e.g. selenium sulfide, zinc pyrithione	Reduced unpleasant odour with with reduced irritation and sensitization
Anti-acne e.g. Benzoyl peroxide	Maintained efficacy and reduced skin irritation and sensitization.
Rubefacients	Prolonged activity with reduced irritancy, greasiness and odour.

CONCLUSION

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

LIST OF ABBREVIATIONS

GRDDS : Gastro-Retention Drug Delivery System
GIT : Gastrointestinal Tract
MDS : Microsponge Delivery System
PVA : olyvinyl Alcohol

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