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Review Article

Microsponges: A Promising Novel Drug Delivery System

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ABSTRACT

Microsponge is recent novel technique for control release and target specific drug delivery system. More and more developments in drug delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Microsponges are polymeric delivery system containing porous microspheres having a size range from 5 to 300µm. Microsponge Delivery System (MDS) is a unique technology for controlled drug delivery. This review article mainly deals with Microsponge drug delivery along with its method of preparation, characterization, advantages and release mechanism of MDS. Microsponges are characterized by particle size, entrapment efficacy, true density, % drug content and % yield, dissolution studies, Resiliency, compatibility studies and in-vitro studies. Wide range of applications is also preferred to develop drug with enhanced safety and efficacy.

Keywords: Microsponge, Porous microspheres, Control release, Colon.

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INTRODUCTION:

Drug delivery system that can specifically control the release rate and target drugs to specific locations of the body have a major impact on the health care system [1]. They are polymeric and has large porous surface with a tiny sponge like spherical particles. Moreover, they reduce side effects, enhance stability and modify drug release favorably. Microsponge technology makes it a versatile drug delivery vehicle as it has many techniques. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product [2]. Microsponges are also capable of delivering pharmaceutical active ingredients efficiently at a minimal dose to targeted site, which reduces severe systemic degradation [3, 4].

Microsponge delivery system (MDS) also known as solid phase porous microspheres as it is a patented micro particulate system, (Figure 1)[5] highly comprising cross-linked, polymeric porous microspheres having numerous interconnected voids in the particle, loaded with active agent [6] within a non-collapsible structure [7] with large porous surface to entrap wide range of active agents with varying pharmacological activities administered in different doses that can be released at the desired site for absorption [8]. The size of the micro sponges ranges from 5-300µm in diameter and sphere can have up to 250000 pores. Microsponges are designed to deliver a pharmaceutical active ingredient efficiently at minimum dose, reduce side-effect, enhance stability and also to modify drug release profile This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent[9-11].

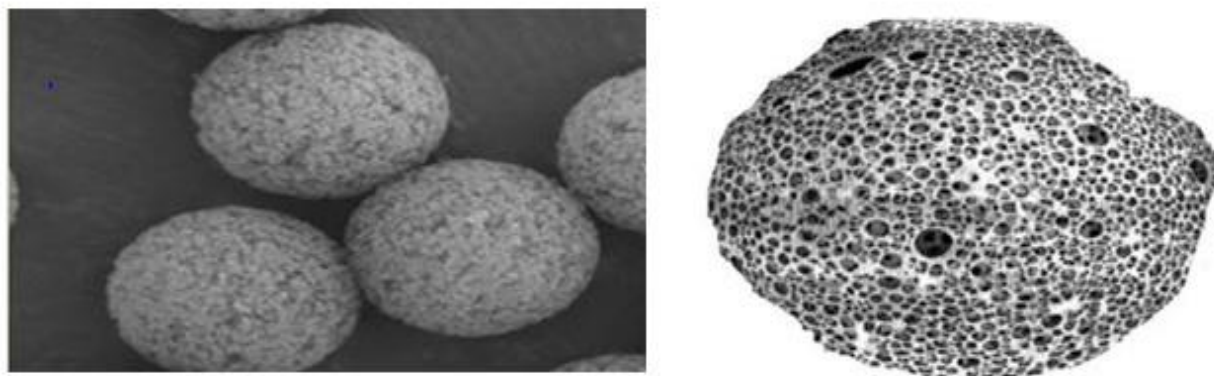


Fig.1: Highly porous nature of microsponges

Potential features of microsphere drug delivery systems [12-15]:

1. Have stability at pH extending from 1 to 11.
2. They are stable at temperature 130°C.
3. Have self-sterilization due to pore size 0.2 μm which prevents penetration of bacteria, thus they not require addition of a preservative.
4. Have high loading capacity ranging from 50 to 60%.
5. Free flow properties and can be productive in relation to its cost.
6. Offer good compatibility with different vehicles and ingredients.
3. Gives elegance to product. It can be incorporated into different formulation.
4. Has good thermal, physical and chemical stability.
5. Non-irritant, non-mutagenic, non-toxic and non-allergenic.
6. Converts fluids into powders to improve material handling.
7. Improves drug bioavailability.
8. Improves treatment efficiency.
9. In contrast to other technologies like liposome and microencapsulation, MDS has a wide range of chemical stability, higher payload and are easy to formulate.
10. Improved formulation flexibility.
11. Flexibility to develop novel product forms [20].

Characteristics of actives moieties that is entrapped into microsponges [16, 17]:

1. Active ingredients that are entrapped in microsphere can be incorporated into many products such as creams, gels, powders, lotions and soaps.
2. Certain considerations are taken into account while, formulating the vehicle in order to achieve desired product characteristics.
3. It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.
4. It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
5. It should be water immiscible or nearly only slightly soluble.
6. It should not collapse spherical structure of the microsponges.
7. It should be stable in contact with polymerization catalyst and also in conditions of polymerization.
8. The solubility of actives in the vehicle must be limited.
9. Payload and polymer design of the microsponges for the active must be optimized for required release rate for given period of time.

Advantages of microsphere drug delivery system [18, 19]:

1. Enhances product performance.
2. Decreases irritation and increases patient compliance.

Advantages over other formulations:

Microsponges have several advantages over other preparations available in the market.

Conventional formulations: Conventional formulations of topical drugs are aimed to work on the outer layers of the skin. Such products after application release their active ingredients. They deliver a layer of concentrated active ingredient which gets rapidly absorbed. This results in excessive accumulation of ingredients within the epidermis and the dermis. Microsphere system can significantly minimize the side effects of drug like irritation without decreasing its efficacy through delivering the active ingredient gradually to the skin, like MDS Benzoyl peroxide formulations which have excellent efficacy with minimal irritation [21].

Microencapsulation and liposomes: The MDS has potential features over other technologies like microencapsulation and liposomes. The rate of release of actives usually cannot be controlled in microcapsules. The actives contained within microcapsules will be released once the wall is ruptured. Liposomes have limited capacity, difficult formulation, restricted chemical stability and microbial instability.

Ointments: Patient compliance with ointment is reduced due to its aesthetically unattractive, viscous and greasy nature. Ointments have low efficiency as drug delivery systems, thus they cause irritation and sensitization because these compounds need high concentrations of active ingredients for effective treatment. Another drawback of

topical formulations is the bad odor, uncontrolled evaporation of active ingredient and potential incompatibility of drugs with vehicles. The microsphere system, however, increases time during which an active resides either within epidermis or on skin surface.

PREPARATION OF MICROSPONGES:

Method of preparation:

Method of preparation involves two ways: one is liquid-liquid suspension polymerization and the other is quasi emulsion solvent diffusion technique, respectively that is based on physico-chemical properties of drug to be loaded [22].

Liquid-liquid suspension polymerization:

In this method the monomers which are immiscible with each other, are first dissolved along with active ingredients in a suitable solvent, then they are dispersed in aqueous phase consists of surfactant or suspending agents to facilitate formation of suspension. The polymerization is then activated by increasing temperature, irradiation, or addition of a catalyst. The polymerization process results in the formation of a reservoir type of system with spherical structure. After the polymerization process, the solvent is removed leaving the microstructure, i.e., microsponges (Fig.2) [23-25].

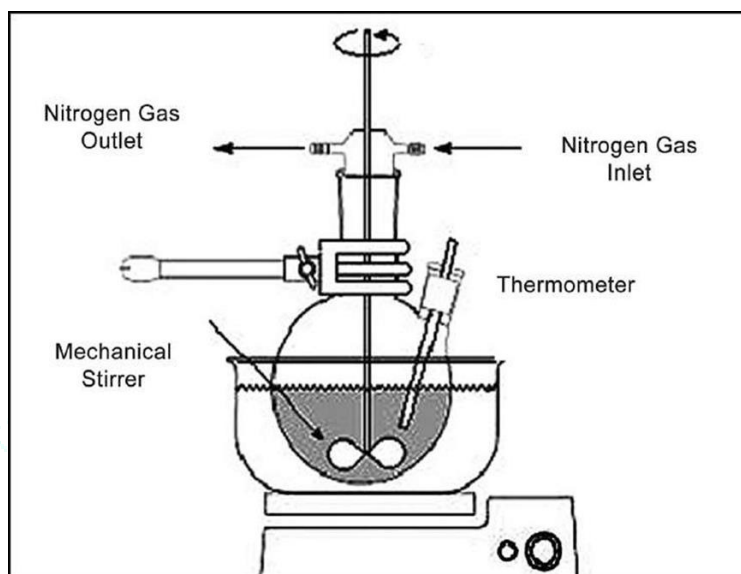


Fig.2: Microsponge preparation by liquid-liquid suspension polymerization

Quasi-emulsion solvent diffusion:

Microsponges were also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing a polymer, such as Eudragit, dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35°C. A plasticizer such as Tri ethyl citrate (TEC) was added

in order to aid the plasticity. The internal phase is then poured into an external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hours. Then, the solution is filtered to separate the micro sponges. The product (micro sponges) was washed and then dried in an air- heated oven at 40°C for 12 hours (Fig.3) [23-28].

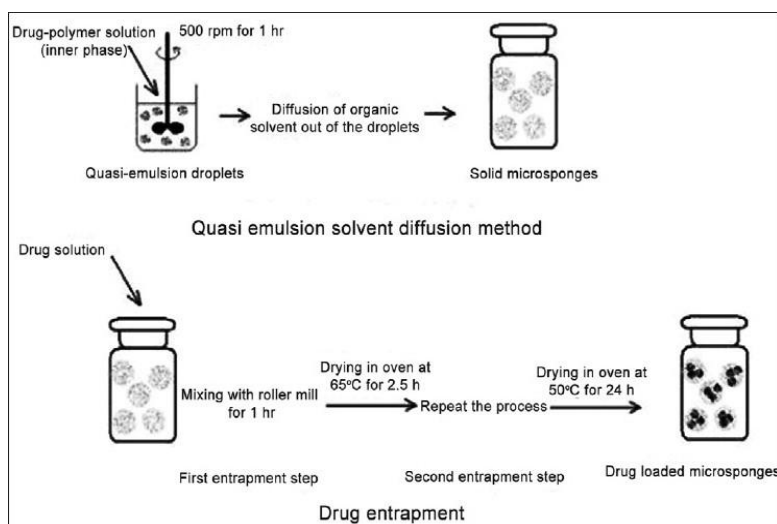


Fig.3: Preparation of Microsponges by Quasi- emulsion solvent diffusion method

Table 1: Preparation of microsponges by Quasi emulsion solvent diffusion

Method	Advantages	Disadvantages
Liquid—liquid suspension polymerization	It can be suitably modified to one step or two step methods for drug loading.	Probable entrapment of unreacted monomers and solvent traces. Non uniform structure. Requires long time for the reaction of monomers. Requires two-step method for thermo sensitive drugs that has low drug loading efficiency.
Quasi-emulsion solvent diffusion	No monomer entrapment. Low solvent traces. High drug loading. No exposure of drug to ambient condition. Size of microsponges can be easily controlled by controlling the stirring.	Cannot be used for the loading of water-soluble drugs. Requires long time for the reaction of monomers. Drug should be soluble in a volatile water-soluble solvent.

Polymers and formulation aids in microsponges:

Polymers studied for the fabrication of microsponges for the oral purposes include Eudragit RS-100, Eudragit RSPO, Eudragit S-100, poly lactide-co-glycolic acid, polylactic acid, poly divinyl benzene and polyhydroxyl butyrate. Eudragit RS-100 formed the most widely used polymer due to its versatility enabling the researchers to employ it in various ways. It was mostly exploited for the development of colon-targeted microsponges due to its high transition pH (above 7) which enabled to protect the release in lower pH. Eudragit RSPO also modulated the drug release along with enhancing the solubility of the drug by forming a solid dispersion like structure. Poly lactide-co-glycolic acid and Poly lactic acid were studied for delivering the proteins and peptides. Microsponges fabricated with these polymers also possessed floating ability due to the hydrophobicity of the polymer which limited the wetting of the particles with aqueous media, thus these microparticles can be employed for fabricating floating microsponges. The use large variety of polymers for the fabrication of the microsponges showed that the method of preparation of microsponges can be modified as per the requirement. In addition to polymers and active ingredients, some researchers also used tri ethyl citrate as plasticizer that help to stabilize the resilient property of the microsponges [29]. During the preparation of microsponges by quasi-emulsion solvent diffusion method, it is reported that the presence of an emulsifier having tendency to maintain the viscosity of aqueous phase is compulsory [30]. Researchers attempted the use of cellulose ethers and PVA for such role and found the use of PVA as a better emulsifier.

Colon targeted drug delivery:

Colon offers advantages on account of a near neutral pH, much longer transit time, greater responsiveness to absorption enhancers and reduced digestive enzymatic activity [31, 32]. Colon specific drug delivery systems have been focused on increasing interest due to the importance of this region i.e. gastrointestinal tract. Additionally, colonic delivery of drugs may be extremely useful when a delay in drug absorption, e.g. in case of diurnal asthma, angina pectoris and arthritis is required from a therapeutic point of view. Several triggering mechanisms utilizing the gastrointestinal transit time of various formulations and the change in pH, pressure in the gastrointestinal tract, bacterial concentration have been reported to achieve colon specific drug delivery [33].

Every system has advantage as well as shortcoming. Prodrugs, being considered as a new chemical entity from regulatory perspective, the similarity in pH between colon, small intestine and retention times make the mentioned

strategies less reliable [34]. However, microflora-activated systems formulated making use of non-starch polysaccharides are highly promising because the polysaccharides remain undigested in the stomach and the small intestine and can only be degraded by the vast anaerobic microflora of the colon. Furthermore, this strategy exploiting the abrupt increase of the bacteria population (400 distinct species of bacteria) and corresponding enzyme activities will also accomplish greater site-specificity of initial drug release [35]. The polysaccharides are also inexpensive, naturally occurring and abundantly available for colonic drug delivery [36].

APPROACHES TO DELIVER THE MOLECULE TO THE COLON:

Coating with polymers:

The intact molecule can be delivered to the colon by coating of the drug molecule with the suitable polymers without absorbing at the upper part of the intestine, which degrade only in the colon [37].

Coating with pH-sensitive polymers:

The pH-dependent systems exploit pH of the human, GIT increases to (pH 7-8) in the distal ileum and it increases progressively from the stomach (pH 1-2 which increases to 4 during digestion, small intestine (pH 6-7) at the site of digestion, it increases to 7-8 in the distal ileum. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid [38].

Coating with biodegradable polymers:

The bio environment inside the human GIT is characterized by the presence of complex microflora especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary component or other materials. Drugs which are coated with the polymers, are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting [39].

EVALUATION TESTS OF MICROSPONGES:

Particle Size and Size Determination [40, 41]

Morphology and surface topography [42]

Determination of pH [43]

Determination of loading efficiency and production yield [44]

Determination of true density [45]

Characterization of pore structure [46]

Dissolution Test [47]

Compatibility Studies [48]

Kinetics of release [49]

Scanning Electron Microscopy (SEM) [50]

Fourier transform infrared spectroscopy (FTIR) [51]

APPLICATIONS OF MICROSPONGES:

Microsponges can be used in variety of applications. It is used mostly for topical and recently for oral administration [52-56]. Several patents have reported that it can be used as an excipient due to its high loading capacity and sustained release ability.

In oral drug delivery:

The oral route is considered the most common route of administration due to its ease of access, high capability of dissolving many drugs, and low toxicity. Although it is easy and safe, it is not compatible with all administered drugs, as drugs that have short life time that are excreted rapidly after administration, drugs that destroyed by the acidity of the stomach or bile juice secreted in the intestine, or drug that are needed to be in the colon to treat some medical condition. This made to developing methods for controlling the release of the drug [57-61]. In oral applications, the microsphere system has been shown to increase the rate of solubilisation of poorly water soluble drugs by entrapping such drugs in the microsphere system's pores. Controlled oral delivery of ibuprofen microspheres is achieved with an Eudragit RS, acrylic polymer, by changing their intraparticle density. Sustained release formulation of chlorpheniramine maleate, microspheres is prepared by the dry impact blending method, for oral drug delivery. Controlled oral delivery of Ketoprofen is prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 polymer and afterwards tablets of microspheres were prepared by the direct compression method. Colon-specific, controlled delivery of Flurbiprofen and Eudragit RS 100 were prepared by quasi-emulsion solvent diffusion method. FLB was entrapped into a commercial Microsphere 5640 system using entrapment method [62]. Curcumin loaded microspheres were prepared by quasi emulsion solvent diffusion method using Eudragit polymer and water soluble porogen. Microspheres were optimized using 3² full factorial design. Studies revealed that microspheres prevented the premature release of curcumin in upper GIT and specifically released the drug at colonic pH [63]. Prednisolone-loaded microspheres for colon specific drug delivery were prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 as a polymer. Oral controlled release of Prednisolone-loaded microspheres is formulated to minimize the proximal absorption, allow high drug concentration in the colon and reduced side-effect [64]. Sustained release of 5-Fluorouracil (5-FU) is prepared by Oil in oil emulsion solvent diffusion method with Eudragit RS100 polymer for treatment of colon cancer. The formulation of 5-FU Microspheres is used to enhance the entrapping efficiency of more than 95% [65].

Topical:

Many topical formulations are based on microsphere drug delivery system. As microsphere is polymer-based, allows binding or sustaining a large content of drug. Although they are microscopic in size, these systems are too large to pass through the stratum corneum when incorporated into topical products [66-72]. Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of

acne, skin irritation as a common side effect. It has been shown that controlled release of Benzoyl peroxide as a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Benzoyl Peroxide is prepared by emulsion solvent diffusion method, aqueous phase containing polyvinyl alcohol to this add organic internal phase which contains ethyl cellulose and dichloromethane by suspension polymerization of styrene and divinyl benzene. The prepared microspheres were dispersed in gel base and they are evaluated for anti-bacterial and skin irritancy. The system containing free BPO can release the drug at greater rate than the entrapped system. Topical delivery system was successfully developed with reduced irritancy.

Microsphere for Bone and Tissue Engineering Bone-substitute

By mixing the pre polymerized powders of polymethyl methacrylate and liquid methyl methacrylate monomer with two aqueous dispersions of calcium deficient hydroxyapatite powders and tricalcium phosphate grains compounds were obtained. The final composites appeared to be porous and acted as microspheres. According to the biodegradation of the sponge matrix, when collagen sponge sheet was incorporated in the mouse sub-cutis, basic fibroblast growth factor (bFGF) was sustained released and exhibited local angiogenic activity in a dose-dependent manner. These suggest the significance and therapeutic utility of the type I collagen as a reservoir of bFGF [73-81].

CONCLUSION:

Microspheres are identified as potential, novel targeting for controlled release of drug molecule to the various parts of GIT including ascending colon and stomach. Based on the research work in the microspheres reveals that it can able to manage the dosing frequency effectively. Apart from the above medicinal advantage, microspheres can able to deliver the drug at specific site on specific rate with a improved, safety and reduced toxicity. In this view, we exclusively reviewed about different methods to prepare the microspheres. Further the characterizations of microspheres were effectively revealed. Microsphere delivery technology is more likely to become valuable for various therapeutic applications in the future. Microspheres has got a lot of potential and is a emerging field which is needed to be explored soon with extensive research work for the proper development of this technology, as this system has a vast scope for development of various novel pharmaceutical applications.

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