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Novel Approach for Drug Delivery System: "Micro-Sponge"

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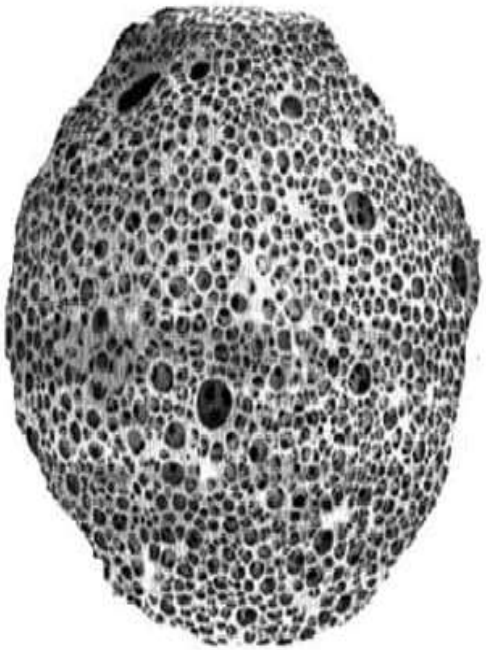
ABTRACT : Micro-sponges are based on polymeric delivery systems composed of porous microspheresMicro-spongesconsisting of porous microspheres having a size range from 5 to 300 micron. They are spherical particles with large porous surface appearing looks like tiny sponge. Moreover, they may amplifies stability, reduce side effects and improves drug release favourably. Thismake it a versatile drug delivery vehicle. Micro-sponge Systems are mainly 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 such as a gel, cream, liquid or powder.



MICROSPONGE

The outer surface is usually porous, allowing a sustained flow of substances out of the sphere. Micro-sponges are porous, polymeric microspheres that are used widely for topical use and have recently been used for oral administration. Micro-sponges are designed to deliver of pharmaceutical active ingredient efficiently at the minimum dose and also to enhance the stability to reduce side effects, and modify drug release.

[Keywords: Micro-sponge, Liquid–liquid suspension polymerization, Quasi-emulsion solvent diffusion]

I. INTRODUCTION

Micro-sponge technology arises from the experienced difficulty of conventional formulation in releasing poorly soluble active ingredients especially in the caseof extendedrelease dosage form. Micro-sponges are introduced into the topical drug products to avoid direct unleash of drug to the systemic circulation.

Anyway the oral drug delivery through the micro-sponges is additionally associate inevitable drug delivery system. Today numerous products of micro-sponges are marketed for the topical application. Micro-sponges have various interconnected pores. From the pores itself the drug are emancipate to the specific site and make the action of drug. Micro-sponges are pored microspheres. The active agents are entangled in the porous surface and provide extended release of drug. Various studies are connected for oral drug delivery for colon targeting micro-sponges. It additionally has the capacity to scale back side effects, improved stability, and also improve formulation flexibility.

Micro-sponge formulations are versatile carrier system, they are stable over the vary of physiological pH and additionallythey are stable over the vary of 13 degree C. Micro-sponges restricts the penetration of the micro-organisms, with the average pore size 0.25µm from this it act as a self-sterilizing formulation. Its porous surface helps the dissolution media into the drug loaded concentration and also they improves the solubility of poorly soluble drug. Within the case of topical drug delivery of micro-sponges reduce accumulation of active agents in to epidermis and dermis towards this avoids the irritation of skin. In oral drug delivery floating micro-sponges provide

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prolonged release of drug by escaping from the gastric emptying procedure and make the drug in a comfort zone. The prolonged unleash conditions cut back the toxicity and hypersensitivity.

MICROSPONGE HISTORY

The micro-sponge technology was developed by Won in 1887, and the original patent were assigned to advanced polymer system. Inc. This company developed a large number of variation of techniques and applied those to the cosmetic as well as OTC and physician prescribed product.

PREPARATION

Liquid–liquid suspension polymerization:

Generally, a solution is made comprising of monomers and the functional or active ingredients, that square measure are immiscible with water. This phase is then suspended with agitation in a liquid phase, usually consists additives, such as surfactants and dispersants, to assist suspension.

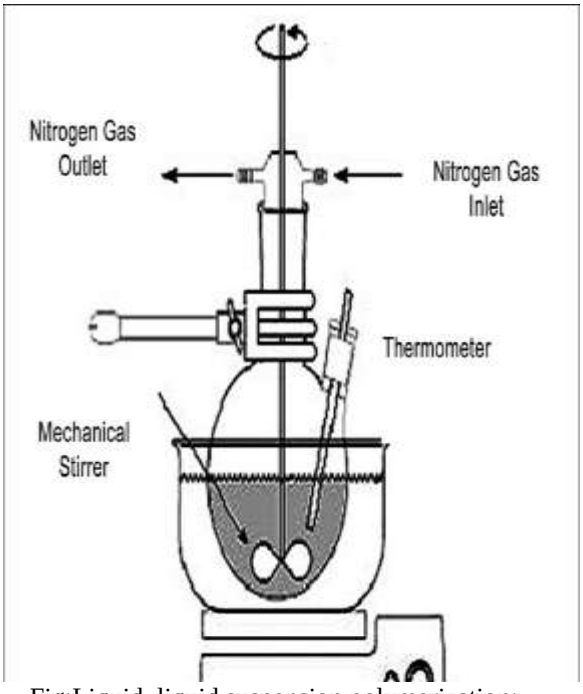

Fig:Liquid–liquid suspension polymerization:

Once the suspension is established with distinct droplets of the specifiedsize, polymerization is accomplished by activating the monomers either by catalysis, accrued temperature or irradiation. As the polymerization process continues, a spherical structure is created containing thousands of micro-sponges bunched together like grapes, forming interconnecting reservoirs. Once the polymerization is complete the solid particles that result from the method area unit recovered from the suspension. The particles are then washed and processed till they are substantially ready for use. The micro-sponge products are made by using styrene and divinyl benzene or methyl methacrylate and ethylene glycol dimethacrylate as beginning maters.

Quasi-emulsion solvent diffusion:

To make the inner organic phase, Eudragit RS 100 is dissolved in ethyl alcohol.

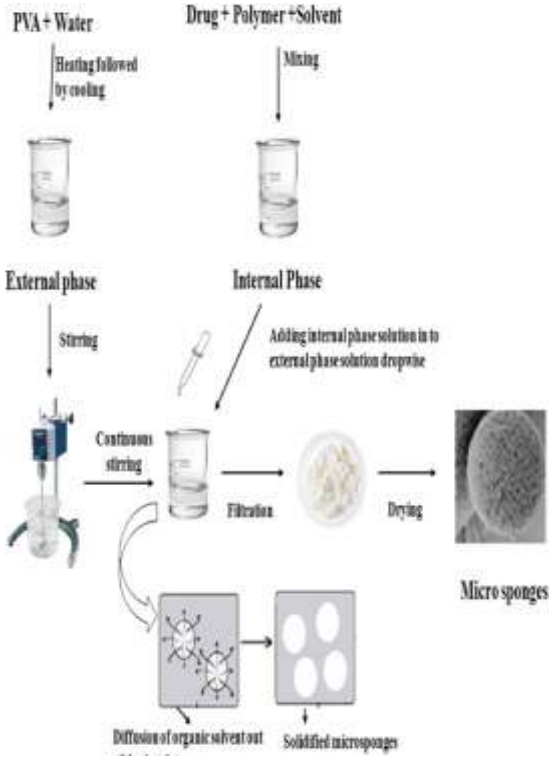

Fig: Quasi-emulsion solvent diffusion

Next, the drug is added to the solution and dissolved underneath ultrasonication at 35°C. The inner section is poured into the polyvinyl alcohol solution in water (outer phase). Following 1hour of stirring, the mixture filtered, to separate the micro-sponges. The micro-sponges are dried in an air-heated appliance (oven) at 40°C for 12 hours. Ingredients are often entangled in micro-sponge polymers either at the time of synthesis, or if too labile to face up to polymerization conditions, they be post-loaded once the microsphere structure has been pre-formed. In general, the latter method is that the well liked mode, as many cosmetic ingredients, and most pharmaceutical ones, would

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decompose at the temperatures utilized for polymerization.

Multiple-emulsion Solvent Diffusion:

This novel method was developed to organize perishable porous microspheres. During this method, an internal aqueous phase containing an emulsifying agent like span, poly-ethylene-imine,and stearyl amine was dispersed in organic polymeric solution. Thereafter, this water in oil emulsion was once more spread in external phase containing Poly Vinyl Alcohol to form a double emulsion. This methodology has the advantage of entrapping both water-soluble and water-insoluble drugs. It may be used for entrapping thermo-labile materials like proteins. Some authors additionally delineated the xanthan gum as an emulsifier to stabilize the interior water in oil emulsion.

Addition of Porogen:

Duringthis technique interior multiple emulsions was replaced by a porogen like hydrogen peroxide or bicarbonateof soda. For this, the porogen was dissolved within the polymeric solution to form a single-phase system that was redispersed in aqueous phase containing Poly Vinyl Alcohol. An instigator was then added to the multiple emulsion and the organic solvent was allowed to evaporate to leave the micro-particles for producing micro-sponges. The result of incorporating hydrogen peroxide resulted within the formation of equally distributed and interconnected pores with diameters ranging from 5 to 20 μm.

Oil in Oil Emulsion Solvent Diffusion:

In distinction to w/o/w technique, oil in oil (o/o) emulsion was prepared using volatile organic liquid because the internal phase that was allowed to evaporate slowly at a minimum rate with continuous stirring. As noted the technique used dichloromethane because the solvent for internal phase, poly-lactide glycolic acid as polymer and amixture of fixed oil (corn or mineral) and dichloromethane containing span 85 as external phase. The interior phase was value-added drop-wise to form the dispersion medium with continuous stirring to induce the micro-sponges. This methodwas utilized for development of hydroxyzine Hydro chloric loaded Eudragit RS-100 micro-sponges using acetone as dispersing solvent and liquid paraffin as the continuous medium. Selection of the organic solvent and external phase depend on the physicochemical properties of the drug and the polymer used for fabrication of micro-sponges.

Lyophilization:

Lyophilization as the methodwas used for changing the microspheres madeby gelation technique, to porous microspheres. During this methodology the microspheres were incubated within the resolution of chitosan: hydrochloride and then lyophilized. Fast removal of solvent lead to formation of pores within the microspheres. This technique is fast and rapid however has the disadvantage of manufacturing cracked or shrunken microparticles due to fast elimination of solvent.

Vibrating Orifice Aerosol Generator Method:

Vibrating orifice aerosol generator (VOAG) was initially reported for the preparation of lipid bilayered mesoporous silica particles. The technique involved the synthesis of porous particles by evaporation-driven surfactant templating in microdroplets by a VOAG method. For the preparation of core particle tetraethylorthosilicate, ethanol, water and dilute hydrochloric acid were refluxed to arrange stock solution. The stock solution was diluted with the solvent containing surfactant and stirred to permit the formation of monodisperse droplets using VOAG. The microspheres produced were encapsulated in the liposomes. These encapsulated particles are used for targeted drug delivery of actives.

Ultrasound-Assisted Production:

This technique was developed by modifying the liquid-liquid suspension polymerization. The micro-sponges are synthesis by utilizing the monomer betacyclodextrin (BCD) and cross-linking agent diphenyl carbonate. Size management of the microparticles was accomplished by heating and sonication of the reaction mixture. Then reaction mixture was allowed to cool, the product obtained was milled to give rough particles that were washed with distilled water and then by ethanol. The porous microparticles of cross-linked β-CD can serve as carrier for efficient loading of drugs. However, this method has the limitation of entrapment of residues of the cross-linking agents that can be potentially toxic.

Electro-hydrodynamic Atomization Method:

Porous microsphere of chitosan was produced by this method. Chitosan resolution was sonicated to come up withbubbles and the resultant bubble suspension was drawn into a syringe, perfused through a steel capillary employing a syringe pump and finally subjected to electro-hydrodynamic atomization. The diameter of the

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capillary was chosen to retain all bubbles within the suspension where as it flowed through it. The voltage utilized in the experiments entirely depends on the concentration of chitosan within the solution. The combination of flow rate and applied voltage resulted in the stable mode in each case, except once highest concentration was used that was tough to electrospray. The chitosan microspheres were cross-linked by 4% w/v sodium hydroxide aqueous solution.

ADVANTAGES:

1. Advanced oil control, absorb up to 6 times its weight without drying
2. Improved product elegancy
3. MDS permits the incorporation of immiscible products.
4. Extended unleash
5. Reduced irritation formulas
6. Permits novel product form.
7. These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
8. Improved product aesthetics
9. Extended unharness, continuous action up to 12 hours
10. Reduced irritation, higher tolerance means broader consumer acceptance
11. Upgraded product aesthetics, gives product an elegant feel
12. Upgrades stability, thermal, physical and chemical stability
13. Permits incorporation of immiscible products
14. Upgrades material processing e.g. liquid can be converted to powders

EVALUATION OF MICROSPONGE:

1) Particle size determination:

Laser light diffractometry or any other appropriate way are using to Particle size analysis of loaded and unloaded micro-sponges. The values can be expressed for all formulations, size range. Accumulative proportion of drug release from micro-sponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30 µm can impart gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in final topical formulation.

2) Scanning electron microscope study:

For morphology and surface topography, prepared micro-sponges is coated with gold palladium beneath an argon atmosphere at room temperature and then the surface morphology of the micro-sponges can be studied by scanning electron microscopy (SME). SEM of a broken micro-sponge's particle can be taken its ultrastructure.

3) Determination of loading potency and production yield:

The loading potency (%) of the micro-sponges can be calculated according to the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Micro-sponge}}{\text{Theortical Drug Content}} \times 100$$

4)Production yield:

The production yield of the micro particles can be determined by calculative accurately the initial weight of the raw materials and also the last weight of the microsponge obtained.

$$\text{Production Yield (PY)} = \frac{\text{Practical Mass of Micro-sponges}}{\text{Theortical Mass (Polymer +Drug)}} \times 100$$

5) Determination of True Density:The true density of Micro-sponges will be measured using an ultra-pycno-meter under helium gas and is calculated from a mean of perennial determinations.

6)Compatibility Studies:

Compatibility of drug with reaction adjuncts will be studied by thin layer chromatography (TLC) and Fourier Transform Infrared spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC).

7) Polymer/monomer composition:

Factors like microsphere size, drug loading, and polymer composition govern the drug unleash from microspheres. Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the micro-sponge system and hence have direct influence on the release rate of entrapped drug. Unleash of drug from micro-sponge systems of different polymer compositions can be studied by plotting cumulative % drug release against time.

Release Mechanism:

The active ingrediententrapped in the micro-sponges may release by four mechanisms:

A) Pressure Triggered Release Mechanism: The entrapped drug is released from micro-sponge when they are pressurized or rubbed. The amount released depends upon the size and number of pore available on the sponge.

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B) Temperature triggered Release Mechanism:
The active ingredients loaded in micro-sponges are viscous at storage temperature. On the application onto the skin by the means of rubbing or increase in temperature reduces the viscosity the active drug may flow out vigorously the skin. Sometimes by increasing the temperature of the skin may enhance the fluidity of drug. The release of the drug is easily modulated by changing the temperature.
C) pH Triggered Release Mechanism:
In this mechanism micro-sponge is coated with the pHdependent polymers. On the specific pH these polymers either swelled or leached out from the micro-sponges. After leaching of pH-dependent polymer the drug released from the Micro-sponges. Coating of the micro-sponge increases the application of drug delivery to site-specific delivery.
D) Solubility Triggered Release Mechanism:
When water-soluble drug loaded in micro-sponge it release only in presence of water. The rate of drug release from micro-sponge can be triggered by the amount of aqueous medium.

APPLICATIONS OF MICROSPONGES DRUG DELIVERY SYSTEM

Micro-sponges are designed to deliver the pharmaceutically active ingredient with efficiency at the minimum dose and additional to boost stability, reduce side effects and modify drug release. Microsponges are porous, polymeric microspheres that are used mostly for topical however recently used for oral administration.

A) Micro-sponge for Topical Delivery: The micro-sponge systems are based on microscopic, polymer-based microspheres that can bind, suspend or entangled a wide variety of substances and then be incorporated into a developed product, like a gel, cream, liquid or powder. A single micro-sponge is as tiny as a particle of talcum powder, measuring less than one-thousandth of an inch in diameter.

Like a true sponge, every microsphere consists of a myriad of interconnecting voids inside a non –collapsible structure which will accept a wide variety of substances. The outer surface is usually porous, permitting the controlled flow of drugs into and out of the sphere. Many primary characteristics, or parameters, of the micro-sponge system, will be defined throughout the production phase to get spheres that are tailored to specific product applications and vehicle compatibility. Micro-sponge systems are made of biologically inert polymers. Extensive safety studies have demonstrated that the polymers are non-irritating, non-mutagenic, non-allergenic, nontoxic and non-biodegradable. As a result, the human body cannot convert them into other substances or break them down. Though they are microscopic in size, these systems are overlarge to pass through the stratum carenum when incorporated into topical products.

B) Micro-sponge for Oral Drug Delivery:

In oral applications, the micro-sponge system has been shown to extend the rate of solubilisation of poorly water-soluble drugs by entrapping such drugs within the micro-sponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly will increases the rate solubilisation.

Controlled oral delivery of ibuprofen micro-sponges is achieved with an acrylic polymer, eudragit RS, by ever-changing their intra-particle density 50. Sustained release formulation of chlorpheniramine maleate, using powder-coated micro-sponges, is prepared by the dry impact blending methodology, for oral drug delivery 54. Controlled oral delivery of Ketoprofen prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and later on tablets of microsponges were prepared by the direct compression methodology. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like micro-sponge structure, manufacturing mechanically strong tablet 55.

C) Micro-sponge-based Delivery Systems for Bone and Tissue Engineering:

Bone-substitute compounds were obtained by mixing prepolymerized powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of tricalcium phosphate grains and calcium-deficient hydroxyapatite powders. The ultimate composites loooed as if it would be porous and acted as micro-sponges. The basic fibroblast growth factor incorporated during asponge sheet was sustained unleashwithin the mouse sub-cutis according to the biodegradation of the sponge matrix and exhibited local angiogenic activity in a dose-dependent manner. Intramuscular injection of collagen micro-sponges incorporating fibroblast growth factor, induced a significant increase in the blood flow, in the murine ischemic hind limb, which could never have been attained by the bolus injection of T fibroblast growth factor these results

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recommended the significance and therapeutic utility of the kind I collagen as a reservoir of fibroblast growth factor.

II. CONCLUSION

The micro-sponge delivery system is a unique technology for the controlled unleash of macroporous beads, loaded with active agent, offering a potential reduction in side effects, while maintaining their therapeutic efficacy. The micro-sponge drug delivery system offers entanglement of its ingredients and is believed to contribute toward reduced side effects, enhance stability, increased elegance, and enhanced formulation flexibility. Additionally, varied studies have confirmed that micro-sponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic. This technology is being used presently in cosmetics, over-the-counter skin care, sunscreens, and prescription products. This kind of drug delivery technology might cause a much better understanding of the healing of many diseases. Hence, the micro-sponge based drug delivery technology is probably to become a valuable drug delivery matrix substance for varied therapeuticapplications in the future.

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