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Microsponges as Smart Carriers in Pharmaceutical Science: Its Formulation, Characterization and Therapeutic Applications

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A B S T R A C T

The pharmaceutical industry has demonstrated a strong interest in microparticulate medication delivery technologies. They make it possible to decrease adverse effects and improve the therapeutic efficiency of drugs. A variety of active substances can be entrapped in microsponges, a novel type of porous polymer microsphere. Characterisation of the system is essential during development, and drug release analysis is one of the most used tests. They are associated with therapeutic efficacy and can show how a medicine behaves in a particular location under specific application conditions. Therefore, this review provides an overview of microsponges methods of preparation, Characterisation and its various applications for drug delivery

Introduction

Most of traditional dosage forms, including tablets, capsules, creams, lotions, and gels with rapid release, are simple but have several drawbacks, including low bioavailability, gastrointestinal and skin discomfort and harmful consequences of the active ingredients. The microsponge drug delivery system improves the health of humans and provides a number of benefits (like sustained, controlled, and site-specific release) over conventional dosage forms, modified drug release technology is therefore one of the most developing fields of pharmaceutical sciences. The diameter of the microsponges varies from 5 to 300 µm, and a typical 25 µm sphere can have up to 2,50,000 pores. The original patents for Won's 1987 invention of microsponge technology were given to Advance Polymer Systems, Inc. The effectiveness of medications given topically is enhanced by the using microsponges(1). These consist of non-destructible, porous structures that enable regulated release of active substances. These active microsponges offer a variety of advantages and can be added to formulations like tablets, capsules, creams, gels, lotions, and powders(2). These spherical, sponge-like particles have a wide porous surface. They may also improve stability, lower the side effects, and positively change medication release. Composed of highly cross-linked, polymeric porous microspheres with number of interconnected voids in the particle, the Microsponge Delivery System (MDS), also called the Solid Phase Porous Microsphere, is a patented microparticulate system that is loaded with an active agent inside a collapsable structure with a large porous surface to entrap a variety of active agents with varying pharmacological activities administered in different doses that can be released at the site of absorption. (3)Because of their interconnected networks or pores, microsponges can trap large concentration of drugs(1,4).

These networks are in responsible for maintaining the microsponges structure. These polymeric particles are made to effectively distribute active ingredients at the lowest possible dosage, improve stability, and lessen adverse effects. Drug release studies showed microsponges can increase drug release rates due to their porous structure. The choice of dissolution fluid depends on the delivery system. Microsponges can be designed to release active ingredients over time based on external triggers like pressure, temperature, solubility and pH. High pressure can increase drug release for topical use, while food and contractions in the GIT can increase it orally. Factors to consider include physicochemical properties, microsponge system properties, and vehicle properties(5).

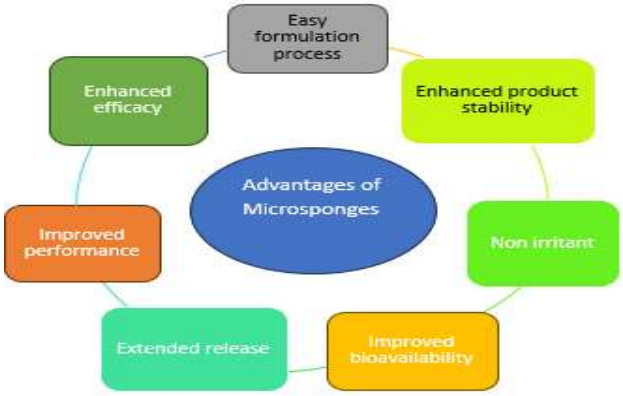

Figure 1- Advantages of microspheres

Polymers used in Microsponge preparation

Polymers used in microsponge preparation are broadly classified into biodegradable and non-biodegradable types. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polyglycolic acid (PGA) are widely used for controlled drug release due to their ability to degrade into non-toxic by products(6). PLGA, a copolymer of PLA and PGA, is FDA-approved and commonly used in injectable formulations and vaccine delivery. Natural biodegradable polymers like chitosan and gelatin offer advantages such as mucoadhesive properties and biocompatibility, making them suitable for targeted drug delivery and protein-based formulations(7). On the other hand, non-biodegradable polymers like ethyl cellulose, polymethyl methacrylate (PMMA), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) are used for long-term drug release. Ethyl cellulose is hydrophobic and commonly employed for sustained drug release, while PMMA is used in ocular implants and bone cement applications. PVA and PVP are water-soluble and enhance drug stabilization in controlled-release formulations. The selection of a polymer depends on factors such as biodegradability, hydrophilicity, molecular weight, and biocompatibility to achieve the desired drug release profile(8).

1. Methods for preparation of Microsponges

1.1. Quasi-Emulsion Solvent Diffusion Method

This method is widely used in pharmaceutical formulations due to its simplicity and efficiency. This procedure involves two phases, Internal Phase is prepared by dissolving a polymer (e.g., Eudragit, ethyl cellulose) in a volatile organic solvent like acetone or dichloromethane. The drug is then added to this solution under continuous stirring and plasticizer like dibutyl phthalate is added. External Phase Preparation includes an aqueous phase containing a stabilizer (e.g., polyvinyl alcohol) is prepared. The inner phase is then blended drop by drop in the external phase with the assistance of a mechanical stirrer for 8 hours at 1000 rpm to form an oil-in-water (O/W) emulsion. The organic solvent from the internal phase diffuses into the aqueous phase. As the solvent diffuses, the polymer precipitates out and forms microsphere-like structures. The drug remains trapped inside the polymer network. The solvent evaporates from the polymer matrix, leaving behind porous microsponges. The final microsponges exhibit an interconnected pore structure, which allows for controlled drug release over time. The formed microsponges are filtered, washed, and dried at a controlled temperature (e.g., 40°C) for 12 hours(1,9)

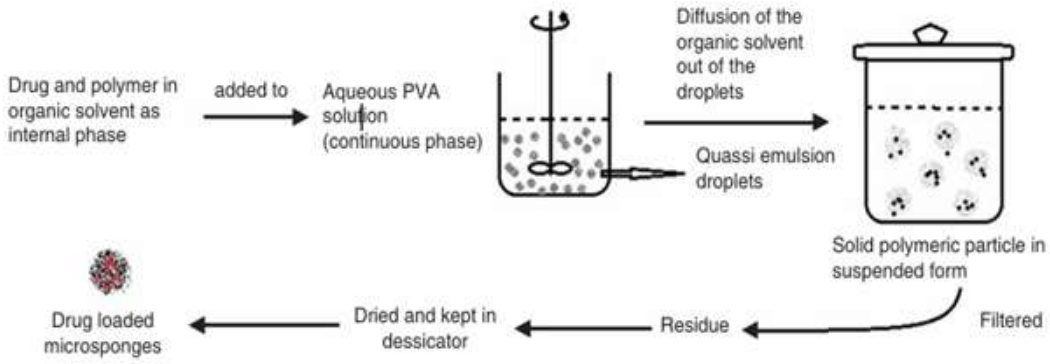

Figure 2 - Preparation of Microsponges by Quasi Emulsion Solvent Diffusion Method

1.2. Liquid-Liquid Suspension Polymerization

This method is commonly used for microsponges made from monomers like styrene, methyl methacrylate, and cross-linking agents. Monomers and the drug are dissolved in an organic solvent. An aqueous phase is prepared by dissolving surfactants or stabilizers (e.g., PVA) in an aqueous medium. A free radical polymerization is initiated using a polymerization initiator (e.g., benzoyl peroxide). The initiator produces free radicals, which start to link the monomers together, creating a polymer network. As the polymerization proceeds, cross-linking occurs between monomers, forming interlinked polymer chains. The polymerization results in the formation of porous microsponges, which encapsulate the drug, which are then collected, washed, and dried. The cross-linked structure of these microsponges is key for achieving controlled release and for encapsulating both hydrophobic and hydrophilic drugs(1,10)

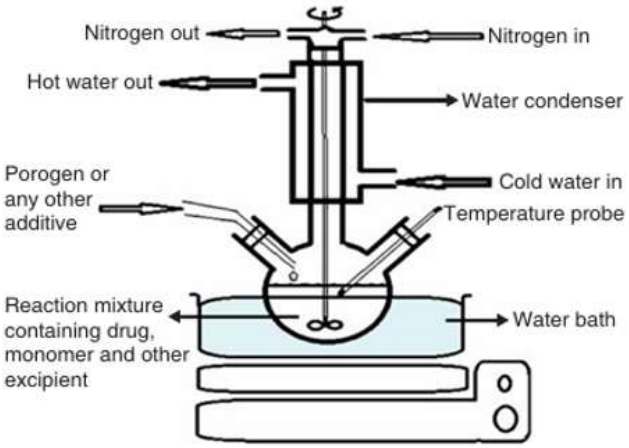

Figure 3- Preparation of Microsponges by Liquid Liquid Suspension Polymerisation

1.3. Solvent Evaporation Method

This method involves dissolving the drug and polymer in a volatile organic solvent. The organic solution (containing both drug and polymer) is then emulsified in an external aqueous phase using surfactants or stabilizers, forming a water-in-oil (W/O) or oil-in-water (O/W) emulsion. The solvent in the emulsion evaporates gradually (either under vacuum or room temperature conditions), causing the polymer to precipitate and solidify. As the solvent evaporates, the polymer encapsulates the drug, forming solid microsponges. The solvent's evaporation process results in microsponges with a porous structure, allowing for controlled drug release as the drug diffuses out of the porous network. The microsponges are then filtered, washed, and dried to remove any residual solvent(11,12).

1.4. Inclusion of a Porogen (for Highly Porous Microsponges)

The internal aqueous phase of the water in oil in water (w/o/w) emulsion was substituted with a porogen such as sodium bicarbonate or hydrogen peroxide. This was achieved by creating a homogeneous dispersion system with the porogen in the polymeric solution and then redistributing it with PVA in an aqueous phase. The microparticles were then left behind when an initiator was added to the w/o/w emulsion and the organic solvent was left to evaporate. When hydrogen peroxide is added, pores with sizes between 5 and 20 micrometre are distributed uniformly and linked(13).

1.5. Lyophilisation

To create porous microspheres, the gelation method was employed. This process involved incubating the microspheres in a solution of chitosan hydrochloride before lyophilising them. The microsponges developed pores as a result of the solvent being quickly eliminated. Although the solvent is quickly removed, this technique has the disadvantage of creating fragmented or shrunken microparticles(13,14).

1.6. Vibratory Orifice Aerosol Generator Method for Microsponges

This technique breaks a liquid jet containing dissolved polymer and medicament into homogeneous droplets using a vibrating aperture. The droplets solidify to produce microsponges. A syringe pump is filled with a polymer and medication suspension or solution. Using a piezoelectric device, the solution is driven through a tiny aperture, usually with a diameter of 10 to 100 µm, that vibrates at a regulated frequency. The liquid jet splits into uniformly sized monodisperse droplets as a result of the vibration. These droplets can be gathered as they harden (by cooling or solvent evaporation) and form homogeneous microsponges or microspheres. They are transported by an air stream. The orifice size, vibration frequency, and flow rate can all be changed to accurately control the particle size(15).

2. Characterisation of microsponges

2.1. Differential scanning calorimeter (DSC)

The Differential scanning calorimeter (DSC) equipped with an intercooler was used to get the thermogram of the drug microsponge formulation. For calibrating the DSC enthalpy and temperature scale, an indium standard was suggested. Microsponge samples were hermetically sealed in an aluminium pan and heated throughout a temperature range of 10-200°C at a constant rate of 10°C/min. Inert atmosphere was kept by purging nitrogen at a rate of 10 ml/min(16).

2.2. IR spectroscopy:

The KBr pellet method was used with a Fourier Transform Infrared In the wavelength range of 4000-400 cm^{-1}, FTIR Spectrophotometer (FTIR). spectra of drug, polymer, physical mixes of drug and polymer, and microsponge formulation were studied(16).

2.3. Determination of Entrapment efficiency, Production yield:

The quantity of core material that is successfully trapped in a formulation is known as entrapment efficiency. It can be determined indirectly by centrifuging a microsponge suspension for ten minutes at 2000 rpm. The amount of free drug present in the supernatant can be measured using HPLC or UV-visible spectroscopy after the supernatant has been appropriately diluted with an appropriate solvent. The formula below can be used to determine the drug entrapment efficiency (EE):

Entrapment efficiency (%) of the microsponges can be calculated by using (1)

$$\% \text{ Entrapment efficiency} = \frac{\text{Actual drug content in the microsponges}}{\text{Theoretical drug content}} \times 100$$

This method is used to determine entrapment efficiency in drug extraction from the formed microsponges.

% Production yield is determined by the weight calculation from the given equation (17)

$$\% \text{ Production yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer + mass)}} \times 100$$

2.4. Characterization of pore structure :

Characterization of pore is very important because presence of pore is a main characterization of microsponge. The pore structure can be determined by using Mercury- Intrusion porosimetry. Incremental intrusion volumes can be plotted against pore diameters that represent pore size distributions.

Pore diameter is determined by using Washburn Equation(13)

$D = -4\gamma COS\theta / P$

D = is the pore diameter [µm]

γ = the surface tension of mercury [485 dynes / cm]

θ=is the contact angle [130°C]

P= is the pressure [psig]

2.5. Internal porosity:

By adjusting the drug and polymer concentrations in the emulsion droplet, it is simple to control the internal porosity of the microsponge. The drug microsphere with a larger porosity is produced at a lower temperature. Internal porosity has a significant impact on drug release characteristics. These carrier systems drug release profiles are the most appropriate. Higuchi's concept suggests a reliance on internal porosity. Regardless of their surface porosity, crystals with similar internal textures had nearly identical tortuosity, as measured by Eq(13)

Porosity % = (Bulk volume −True volume) Bulk volume × 100

Where, V_p is the volume of the particles

V_b is the bulk volume of the particles

2.6. Actual drug content:

A precisely measured quantity (100 mg) of microsponges carrying the drug was continuously stirred in a 100 ml phosphate buffer solution (pH 7.4) for 12 h. Using a UV-visible spectrophotometer, filtered samples were further examined 276 nm in comparison to a blank. Using the following expressions, drug content and entrapment efficiency estimates were made for all batches.

$$\text{Actual drug content (\%)} = \frac{\text{actual content in weighed quantity of microsponges}}{\text{weighed quantity of microsponges}} \times 100$$

2.7. Scanning Electron Microscopy (SEM):

SEM is performed to analyse the surface morphology and topography of microsponges. Using double-sided tape, samples are placed on a metal stub, vacuum-coated with a thin coating of platinum/palladium alloy, and photographed at low voltages (e.g., 5 kV).Microsponges spherical structure and porous nature are confirmed by SEM pictures, which also show their shape, surface roughness, and porosity(18).

2.8. Particle size analysis:

A particle size analyser, such as the Malvern Mastersizer, is used to measure the particle size of microsponges. The examination is carried out at room temperature, often using laser light scattering, after the microsponges have been distributed in double-distilled water.The size at which 90% of the particles fall is known as the average particle size, and it is commonly expressed as d(0.9) μm(18).

2.9. X-ray diffraction study:

XRD is utilised to identify if microsponges are crystalline or amorphous, as well as to find any modifications to the drug's crystal structure following encapsulation. X-ray diffraction patterns were captured using a crystal monochromator, Cu, K radiation with a wavelength of 1.5405 nm, and an X-ray diffractometer. The instrument was run at 45 mV of voltage and 20 A of current, two diffraction patterns were run at 5-10 °C/min to characterise the crystal and physical state of drug(19).

3. Applications

3.1. Microsponges in Oral Drug Delivery

Because MDS can improve the release rate of medications that are poorly soluble in water by trapping these compounds in the microsponge's pore system, it is appropriate for oral drug administration. It controls the pH of the oral medication delivery microsponge. when a microsponge is taken due to enteric coating medication will not release shielding it from the stomach liquid pH (1-3). Colonic enzymes called glycosidases breakdown the coating in the stomach and medication release six hours later. The majority of medications are transported by MDS as they pass through the large intestine's descending colon. Additionally, the microsponge delivery system can accept medications in a restricted area and to carefully deliver active substances to the bottom part of the GIT. The main justification for employing the microsponge system as a carrier for colonic delivery is that active ingredients smaller than 200 μm are readily absorbed by macrophages in the colonic tissues, leading to efficient localised drug activity at the desired location(1).

3.2. Microsponges in Ocular delivery

Microsponges increase therapeutic efficacy, while ophthalmic delivery there of eliminates problems of primacy drug loss and systemic toxicity. Microsponges are capable of encapsulating hydrophilic as well as hydrophobic drugs, allowing controlled and released drug delivery onto the corneal surface, increasing contact time and therapeutic efficacy. There is no specialized microsponge-based ocular drug delivery system, to date, based on this review. But studies have explored formulations such as ketotifen microsponge-enriched gels for ocular application controlled release and in situ gels with acetazolamide-loaded microsponges for the management of glaucoma. These formulations with higher treatment efficacy and patient acceptability indicate commercialisation prospects in the near future(20).

3.3. Microsponges in topical delivery

Microsponges are utilized in topical drug delivery because of their ability to enhance drug stability, reduce side effects, and attain controlled release.

Several commercial products utilize microsponge technology in topical drug delivery, primarily in dermatology and cosmetics. Some examples include:

1. Retin-A Micro: A microsponge system containing tretinoin(0.1% and 0.04% Tretinoin, methyl acrylate/glycol dimethacrylate base is of aqueous gel used for the treatment of acne. Manufactured by Biomedic sothys. It provides controlled drug release, reducing fine lines, wrinkles, and decrease skin colouration due to ageing.

2. EpiQuin Micro: A microsponge system containing Hydroquinone and retinol, used to lighten areas of darkened skin such as freckles, age spots (21).

3. Carac Cream: A microsponge system containing 0.5% Fluorouracil, 0.35% methyl methacrylate glycol dimethacrylate cross-polymer and dimethicone, used to reduces fine lines and discolouration.

4. Lactrex : A microsponge system containing 12% Lactic acid, ammonium lactate, water, and glycerine, used to hydrate the skin.

5.Salicylic Peel 20 : A microsponge system containing salicyclic acid 20%, used to improve fine lines, reduces pigmentation and finelines.

They can be utilized in dermatological use, with longer drug retention in the skin surface and with the guarantee of minimum penetration(17,22).

3.4. Microsponges in the treatment of Parkinson's disease

There is growing interest in the possible application of microsponges in the treatment of Parkinson's disease (PD) because of a number of benefits that may improve therapeutic results. Microsponges Possible Use in the Treatment of Parkinson's Disease. Entacapone, Levodopa, dopamine agonists, and other antiparkinsonian medications can be released gradually or under control by microsponges, which lowers the frequency of dosing and lessens motor fluctuations and "on-off" effects(23). Improved Brain Targeting Microsponges may be designed to more effectively transmit drugs to the central nervous system (CNS) by altering their surface or employing appropriate polymers. Dyskinesia, a frequent adverse effect of long-term levodopa treatment, may be lessened by controlled release, which helps maintain a constant drug level in the brain. Combination Therapy like Levodopa and carbidopa or MAO-B inhibitors and dopamine agonists are two examples of medications that can be encapsulated in microsponges to produce synergistic effects. Nasal Delivery Potential of Microsponges can be investigated in nasal formulations for quick beginning of action and BBB bypass, making them perfect for an emergency therapy of Parkinson's "off" period. By shielding drugs that are prone to breakdown, such as dopamine, the porous matrix of microsponges can improve stability.

3.5. Microsponges in cancer treatment

Microsponges of Celecoxib were prepared in this study using a quasi-emulsion solvent diffusion approach, which resulted in stable and porous microsponges ,drug delivery system can be employed as an efficient method to increase the drug solubility, thereby increasing the drug's bioavailability and providing an extended-release profile that is advantageous over standard formulations s for Chemoprevention of Familial Adenomatous Polyps(24).

3.6. In Bone and tissue engineering

Microsponges have also been identified as a potential material for bone and tissue engineering because of their specific characteristics like controlled degradability, shape-memory, and high porosity. They are suitable for osteogenic differentiation, cell adhesion, and cell proliferation because of these characteristics. These nanocomposite microsponges have been shown to induce rat bone marrow mesenchymal stem cells (rBMSCs) into osteogenic differentiation and greatly increase bone regeneration in rats with critical-sized calvarial lesions. Their injectability and high elasticity properties make less invasive procedures possible, and they are thus best suited for abnormal deformities like maxillary sinuses or tooth extraction sites. Microsponge scaffolds developed from platelet lysates have been investigated in terms of high-throughput fabrication and have been found to be well-suited for applications with soft tissue regenerations(25,26).

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