

Review on Microsponges in Novel Drug Delivery Systems

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ABSTRACT: Microsponges are a cutting-edge drug delivery system that revolutionizes pharmaceutical distribution by allowing for accurate and prolonged medication release. Tiny, porous, polymer-based spheres that are appropriate for oral and topical use can encapsulate a variety of active ingredients, including both water-soluble and water-insoluble ones. Microsponges offer several advantages, such as better product performance, extended release, lower irritation, and greater sophistication. They can be customized to deliver medications at particular rates, which can enhance patient adherence and lessen side effects. This paper provides a comprehensive overview of microsphere technology, covering its properties, production techniques, assessment, and release mechanisms. It also emphasizes the advantages and uses of microsponges in drug delivery, such as their possibilities for gastro-retention drug delivery systems. Microsponges' versatility has prompted their investigation in a range of areas, such as topical and oral medication administration. Additionally, further progress in this area of research and development might lead to innovative drug delivery systems that enhance treatment results.

KEYWORDS: Topical administration, polymer-based spheres, active substance encapsulation.

INTRODUCTION

While many traditional drug delivery systems frequently require large quantities of bioactive agents because of their limited efficacy, there is a growing emphasis on creating novel systems that allow for targeted and controlled drug release. Microsponges are unique, highly cross-linked, sponge-like polymer-based carriers that can accommodate a wide range of therapeutic compounds (1-3). These

microspheres are primarily used for prolonged topical delivery, but they have also been used orally lately. Microsponges are designed to modify medication release over time, efficiently deliver a pharmaceutically active ingredient at the lowest possible dose, and minimize negative effects while enhancing stability, elegance, and flexibility in formulation. The microsphere technology can help prevent an excessive accumulation of

ingredients within the skin layers. These items, which have a relatively high content of bioactive substances, are typically marketed to consumers in traditional formats like lotions, gels, or creams. Polymeric microsponges are delivery systems composed of porous, sponge-like particles capable of encapsulating and releasing active ingredients, including u.v filters, moisturizers, fragrances, volatile plant based oils, and anti-infective, anti-fungal, and anti-inflammatory compounds. Traditional topical dosage forms such as creams, lotions, ointments, and powders have generated concerns regarding the mechanism of drug diffusion or release from the carrier into the skin. Additionally, topical formulations commonly have low bioavailability because they are quickly wiped off the skin and inefficiently release their active ingredients. Non-hydrophilic ointments and medicinal powders for topical use have a short skin residence time and are also fatty, oily, and uncomfortable for patients (4-6). Gels are semisolid systems in which the dispersion medium's mobility is restricted by either solvated macromolecules of the dispersed phase or an interlacing three-dimensional particle network. Increased viscosity caused by interlacing and internal friction leads to the semisolid condition.

Porous microspheres were the foundation of the first polymeric delivery system for microsponges. Microsponge technology was initially created for the contemporary drug delivery system. Microsponges are large, active agent-filled beads with a macroporous structure that typically measures between 11 and 26 microns in diameter. These porous polymeric microspheres, known as "microsponges," were commonly used for standard delayed administration. Microsponges are porous microspheres with interconnected pores and particle sizes ranging from 4 to 300 μm . These are spherical uniform polymer particles. Microspheres are designed to enhance stability, minimize side effects, alter the drug release pattern, and guarantee effective delivery of the pharmaceutical active component at the lowest possible dosage (5-7).



Figure 1. Microsponge

EVOLUTION OF MICROSPONGE TECHNOLOGY:

Won developed microsphere technology in 1987, and Advanced Polymer Systems, Inc. was awarded the first patents. The method was greatly improved by the business, resulting in numerous variations for prescription, over-the-counter (OTC), and cosmetic pharmaceutical uses.

In early, 1960-70's the microspheres early research into porous and particulate material and then they laid this groundwork for further developments.

In 1980's the development expansion into non-pharmaceutical fields and then the porous like material re used in industrial uses.

In 2010's Integration with novel advancements like nano technology and bio technology

CHARACTERISTICS:

Actives needing to fulfil the following conditions in order to be ensnared into MSPs:

- It must be completely miscible in the monomer or able to become miscible with a little addition of a solvent that is immiscible in water.
- It needs to be either barely soluble or water immiscible. It ought presumably be unaffected by monomers.

- To minimise cosmetic issues, the solubility of actives in the vehicle must be controlled, with no more than 10 to 12% w/w MSPs included into the vehicle. If not, the car will run out of MSPs before the application. MSPs' spherical structure shouldn't disintegrate.
- For a specific duration, the polymer design and payload of the MSPs for the active need to be optimised to achieve the necessary release rate. It must remain stable when in contact with the catalyst and polymerization conditions.

BENEFITS OF MICROSPONGE:

1. Increased product performance is the result.
2. Prolonged release.
3. Decrease irritability and, as a result, increase optimal affected person compliance.
4. Improved elegance of the result.
5. Authorises the development of new consequences.
6. Improves therapeutic efficacy.
7. Treat or manage affliction more swiftly.
8. Improve management of situations.
9. Improve pharmacokinetics of equivalent medicines.

10. Improved reliability for achieving new results.
11. Benefits include increased physical, chemical, and thermal strength.
12. The ability to combine non-miscible materials.
13. Improves fabric technology; for example, fluids can be converted to powders.

LIMITATIONS OF MICROSPONGES:

- Microsponges are expensive
- Large scale production of microsponges may affect consistency and challenging.
- Not all bioactive ingredients are suitable for encapsulation in microsphere systems.
- Microsphere preparation can sometimes cause irritation or adverse reactions, particularly in topical applications.
- Controlled release profile in microsponges is difficult.
- For getting the production approval from government is difficult.
- They are non-biodegradable.

IDEAL CHARACTERISTICS OF MATERIALS:

- It should be fully soluble in the monomer or rendered soluble with a minimal quantity of a water-insoluble solvent.

- It should be insoluble in water or at most mildly soluble.
- It can react with other excipients in the formulation because it must remain non-reactive to monomers.
- To maintain cosmetic stability, the active ingredients in the vehicle should have a solubility limit of 10 to 12% w/w microsponges; otherwise, the vehicle will deplete the microsponges before application.
- Microsponges should maintain their spherical configuration.
- The polymer structure and active content within the microsponges should be optimized to achieve controlled release over a specified duration.
- It must be stable while in contact with the polymerization catalyst and under polymerization conditions.

PREPARATION OF MICROSPONGES:

Microsponges can be loaded with drugs either through a single step or two step method, Techniques such as suspension polymerization in liquid media and quasi emulsion-based solvent diffusion are commonly utilized. These methods depend on the drug's physical and chemical characteristics (10-13). If the drug is normally an inert, non-polar substance, it will form a porous structure

known as a "porogen." Porogen drug, which neither inhibits nor activates polymerization and is resistant to free radicals, is entrapped in a one- step method.

1. Polymerization (Liquid-liquid suspension polymerization)

2. Quasi-emulsion Solvent Diffusion.

1. Polymerization

Porous microspheres are created through suspension polymerization in a liquid environment. The monomer and active component are dissolved in a suitable solvent in this procedure before being added to an aqueous phase that contains surfactants, suspending agents, and other

auxiliaries. A catalyst, heat, or radiation are used to start polymerization. Typically, styrene or methyl methacrylate polymerizes in a round-bottom flask. The monomer is first used to dissolve a non-polar medication, and then an aqueous phase—typically including surfactants and dispersants to aid in suspension—is introduced. Polymerization is then triggered by catalysis or higher temperatures once distinct droplets of the appropriate size have formed. A two-step method is used when the medication is susceptible to polymerization conditions. Polymerization first occurs with a substitute porogen, which is then changed with the functional material under gentle experimental circumstances. .

The steps of preparing microspheres:

Active ingredients and monomers are dissolved in suitable solvent



Polymerization begins with the formation of chain monomer



Monomer ladder is formed due to cross –linkage between the chain monomer



The polymerization process continues as the formation of a spherical structure



And then solvent evaporates and leads to formation of spherical porous microsponges

The steps involved in Quasi Emulsion solvent Diffusion method:

Polymers like Ethyl cellulose, Eudragit RSPO was dissolved in Di-chloromethane(Inner phase)



Then these polymers and drug is added in DCM and dissolved in Ultrasonication at 35c



The inner phase is poured into the PVA solution in water (outer phase)



And continuously stirring for 1 hr at 570rpm and then filtered



Dried in the oven at 40c and micro sponges are formed

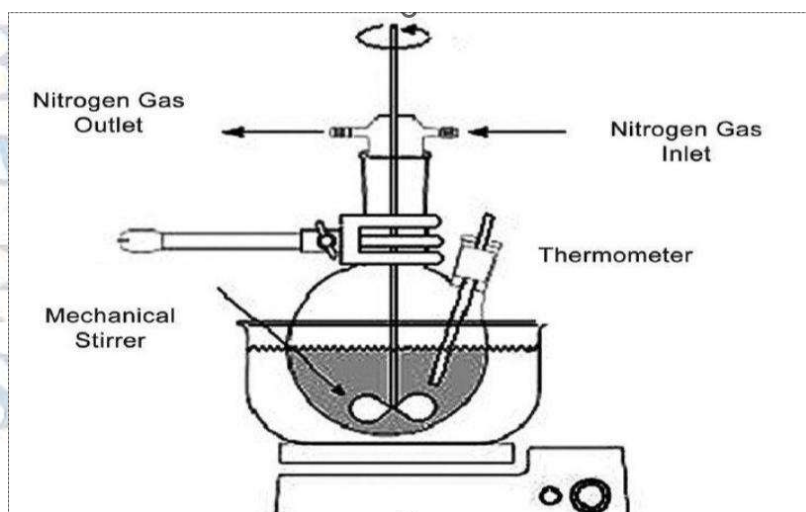


Figure 1. Microsphere preparation by liquid-liquid suspension polymerization

QUASI-EMULSION SOLVENT DIFFUSION:

A widely used application of this technique is the creation of microsponges. An internal phase comprising polymers like Eudragit S 100 mixed in dichloromethane

(an organic solvent) makes up the quasi-emulsion solvent diffusion method, which contains two phases. Subsequently, medications dissolve in polymer solution

with the aid of the ultrasonication procedure. Stirring distilled water and polyvinyl alcohol continuously for a sufficient amount of time mixture was utilized to formulate the external phase. The internal phase then mixed for three hours after pouring into the exterior phase. The next step is to filter the microsponges. Finally, the microsponges are cleansed and dried using an air-heated oven maintained at 40 °C for 12 hours.

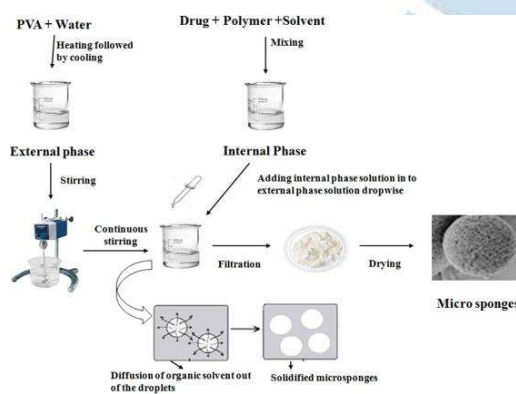


Figure 2. Fabrication of microsponges through Quasi-emulsion solvent diffusion method

SEM ANALYSIS OF MICROSPONGE

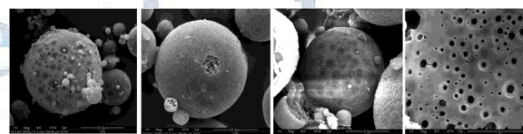


Figure 3. Microsponges under field emission scanning electron microscopy

EVALUATION OF MICROSPONGE:

1. Particle size determination
2. Scanning electron microscope study
3. Determination of loading efficiency and production yield
4. Production yield
5. Determination of true density
6. Compatibility studies
7. Polymer/monomer composition

1. Particle Size Determination:

Laser light diffraction or other suitable analytical techniques are used to measure the particle size of both loaded and unloaded microsponges, enabling specification for any formulation and size range. In order to study how particle size affects drug release, the in vitro release profiles of microsponges with different particle sizes are plotted against time. Final topical formulations are preferably in the 10 to 25 micron range since

particles bigger than 30 microns might have a gritty sensation.

2. Scanning Electron Microscope Study:

The surface morphology and topography of microsponges that have been gold-palladium coated at room temperature in an argon atmosphere can be analyzed using scanning electron microscopy (SEM). The ultrastructure of a broken microsphere particle can be analyzed using SEM (14-16).

3. Determination Of Loading Efficiency And Production Yield:

The loading efficiency (%) of the microsponges can be calculated according to the following equation

$$\text{Loading efficiency} = \frac{\text{Actual Drug Content in Microsphere}}{\text{Theoretical Drug Content}} \times 100$$

4. Production Yield:

The production yield of the microparticles will be determined by precisely measuring the initial weight of the raw materials and the final weight of the microsphere produced.

Production Yield (PY) =

$\frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Mass}} \times 100$

Theoretical Mass
(drug + polymer)

5. Determination Of True Density

The true density of Microsponges can be assessed by averaging numerous measurements taken with an ultrapycnometer and helium gas.

6. Compatibility Studies:

The compatibility of a medication with reaction adjuncts can be investigated using thin layer chromatography (TLC) and Fourier Transform Infrared spectroscopy (FT-IR). The impact of polymerization on the drug's crystallinity can be evaluated using differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD).

7. Polymer/Monomer Composition:

The factors that influence drug release from microspheres include polymer composition, drug load, and microsphere

size. The partition coefficient of the medication between the microsphere system and the vehicle can be influenced by the polymer makeup of the MDS, which can, in turn, have a direct effect on the rate at which the trapped drug is released. Plotting the cumulative percentage of drug release against time is an effective technique for examining drug release from microsphere systems with different polymer compositions.

VARIOUS DRUGS USED IN MICROSPONGE

- Adapalene (Anti-acne)
- Fluconazole (Anti-fungal)
- Ibuprofen (NSAID)
- Indomethacin (NSAID)
- Lornoxicam (NSAID)
- Curcumin (Anti-inflammatory)
- Febuxostat (Anti-gout)
- Flurbiprofen (NSAID)

APPLICATIONS OF MICROSPONGES

- The formulation active ingredients offers a sustained release mechanism
- It ensures an extended and enhanced level of activity over time.
- It effectively prolongs its benefits while minimizing irritancy, greasiness, and odour.
- It maintains high efficacy while significantly decreasing dermal irritation and hypersensitivity.
- Long lasting activity with less skin allergic responses and making it more comfortable to use
- The controlled release of the active ingredients is achieved by microsp sponge system utilizing the Quasi emulsion solvent diffusion method.
- This unique microsponges formulation is designed to deliver medication continuously over a longer period of time, making it especially useful for patients receiving arthritis treatment.
- The microsp sponge release system ensures that the formulation delivers the drug in a controlled and consistent manner (17-19).

NOVEL APPROACH FOR FORMULATION OF MICROSPONGES

Category	Examples of Original Use → New Use	Therapeutic Areas Benefiting	Trend / Key Insight
Neurology & Psychiatry Expansion	Antidepressants → neuropathic pain (Amitriptyline); Ketamine → treatment-resistant depression; Minocycline → ALS/Parkinson's; Topiramate → migraine/binge eating	CNS disorders, chronic pain, mental illness	CNS drugs are most frequently repositioned, often driven by unmet needs

Oncology Repurposing	Thalidomide → multiple myeloma; Rapamycin → cancer; Doxycycline → anti-tumor effects; Ruxolitinib → GVHD	Cancer, immune-related diseases	Anti-inflammatory/metabolic drugs show new anti-cancer roles
Cardio-Metabolic & Systemic Uses	Tadalafil → BPH; Ivabradine → angina; Colchicine → cardiovascular inflammation; Metformin → aging/cancer prevention	Cardiology, metabolic disease, aging	Known metabolic drugs find roles in longevity and vascular disease
Anti-infectives & Others Reassigned	Galantamine → Alzheimer's; Amantadine → Parkinson's/TBI; Bexarotene → Alzheimer's; Naltrexone low-dose → autoimmune diseases	Neurodegeneration, autoimmune disease	Old drugs revived for chronic immune & neurodegenerative conditions

LIST OF POLYMERS USED IN THE PREPARATION OF MICROSPONGES

SL NO	POLYMERS NAME
1	Ethyl cellulose

2	Eudragit RSPO
3	Eudragit EPO
4	Eudragit RS100
5	Eudragit RL 100
6	HPMC E15
7	Sodium alginate
8	PHEMA
9	Polystyrene
10	Corbopol940

PATENT FILED ON MICROPSONGES

SL.NO	PATENT NUMBER	PATENT NAME
1	CN107469141B	A medical dressing containing microsp sponge and preparation method thereof.
2	JP6688386B2	Hyaluronic acid microsp sponge and method for producing the same.

3	KR101900387B1	Microsponges having controlled solubility and improved redissolution property.
4	US5100783	Weighted microsphere for immobilizing bioactive material
5	1275955	Weighted microsphere
6	US5292512	"Process for producing a high density, low porosity aluminum alloy.
7	0217917	Weighted microsphere for immobilizing bioactive material
8	4092381	Methods of fabricating microsphere deuterated hydrocarbon polymer targets which emit neutrons when irradiated by high energy beams
9	US4690825	Increased density, high impact resistance polymeric compositions and articles

10	US7426776B2	Nonwoven towel with microsponges
11	US4997753	Weighted collagen microsp sponge for immobilizing bio-active material
12	WO/1986/005811	Weighted microsp sponge for immobilizing bioactive material

MECHANISM OF RELEASE

The microsponges can be utilised as controlled drug delivery systems through various drug release

mechanisms (Table 1), allowing for the programmable release of bioactive ingredients from the microsponges (20-25).

Mechanism of drug release

S.No	Release System	Mechanism
1	Pressure triggered release	Microsponges are gripped or rubbed by the device to extract the fluid. Microsponge tolerance determines the release volume.
2	Temperature-triggered release	Temperature may also have an effect on how quickly the active ingredients are released from microsponges. Certain compressed materials naturally migrate from the microsp sponge to the surface when they reach room temperature because they become extremely viscous. For instance, the viscous sunscreens are unable

		to completely exit the microsphere. As they are exposed to sunlight or an increase in skin temperature, their activity intensifies., the viscosity reduces and the flow rate rises as a result.
3	pH-triggered release	The microsponges' surface can be altered in this way, allowing the release of active chemicals to change according to pH. In order to create pH- microsponges, Conventional microsponges are coated with an enteric polymer that enables pH-sensitive activation. The USP spindle dissolution tool is employed in pH-related research. Release rises from 0% to 80% in the event that the pH falls between three and eight. Therefore, the drug's release time may be prolonged by altering the pH.
4	Solubility-triggered release	Microsponges containing water-miscible substances like antiseptics, deodorants, and antiperspirants can activate the active pharmaceutical ingredient (API) in an aqueous medium, depending on the external medium's capacity to absorb the API and its concentration gradients. Diffusion will also cause liberation by changing the partition coefficient of the elements between the microsphere and the external environment..

FUTURE ASPECTS OF MICROPSONGES

Tissue engineering: Vascular tissue engineering offers numerous chances to improve patient health and progress therapies (26-28). Conventional techniques for vascular reconstruction, such as employing expanded polytetrafluoroethylene (ePTFE) or Dacron, work well for large arteries like the aorta and iliac arteries. However, these materials often encounter issues with smaller arteries because the body tends to recognize them as foreign, which can lead to complications like thrombosis (blood clot formation). To overcome these challenges, tissue engineers are creating innovative scaffold designs. Scaffolds provide a supportive framework for new tissue growth by allowing cells to adhere and multiply. In vascular tissue engineering, these scaffolds are engineered to replicate the natural extracellular matrix of blood vessels, facilitating effective cell growth and tissue development.

RNAi: A natural cellular defense against RNA viruses and aberrant gene expression is RNA interference (RNAi). The enzyme Dicer breaks down double-stranded RNA (dsRNA) into small interfering RNAs (siRNAs), which are composed of 20–24 nucleotides. The RNA-induced silencing complex (RISC), which is comprised of

these siRNAs, is guided to complementary virus or target mRNA by one strand. The target mRNA is subsequently cleaved by the RISC complex, which results in its destruction and the suppression of gene expression.

Administrative Barrier: The substance cannot be administered orally because it does not permeate the intestinal epithelium effectively to enter the bloodstream.

Dose Delivery: Ensuring that an adequate dose is delivered without requiring frequent administration.

Immune Response and Safety: The carrier in the delivery mechanism shouldn't cause an immunological reaction in order to avoid early removal. A microsphere system employing rolling circle transcription of a DNA template was chosen as an efficient delivery method in order to accomplish this (29,30).

CONCLUSION

In conclusion, microsponges are a unique and versatile drug delivery system with numerous advantages. Due to their capacity to encapsulate various active ingredients, facilitate controlled and targeted release, and improve the efficacy and safety of treatments, they are highly prized for pharmaceutical use. Microsponges can enhance therapeutic outcomes, minimize adverse effects, and increase patient compliance. Ongoing research and innovation in this area may lead to the creation of advanced drug delivery systems tailored to specific medical needs. Due to their adaptability, microsponges are being studied for use in topical, oral, and gastro-retentive drug delivery systems. In summary, this technology shows a lot of potential for improving patient care and progressing drug delivery.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

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