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MICROSPONGE TECHNOLOGY: A MODERN STRATEGY FOR SUSTAINED AND SITE-SPECIFIC DRUG RELEASE

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ABSTRACT

Microsponge-based drug delivery systems represent an innovative advancement in pharmaceutical technology, utilizing porous microspheres composed of physiologically inert organic polymers to achieve controlled and targeted drug release. These systems have garnered considerable attention for their ability to enhance the therapeutic efficacy and safety profile of various active pharmaceutical ingredients. Microsponges are capable of encapsulating a broad spectrum of therapeutic agents, including anti-inflammatory, antimicrobial, anticancer, and anti-allergic compounds. Their controlled-release properties contribute to improved drug stability, minimized adverse effects, and increased patient adherence. A range of fabrication techniques—such as liquid-liquid suspension polymerization, quasi-emulsion solvent diffusion, and electro-hydrodynamic atomization—have been developed for the efficient production of microsponges. These systems have demonstrated significant potential in the treatment of multiple pathological conditions, including cancer, diabetes, and inflammatory disorders. Owing to their versatility, microsponges offer a promising platform for the development of targeted and sustained-release drug delivery strategies. This review explores the design, development, and therapeutic applications of microsponge-based delivery systems, emphasizing their role in optimizing clinical outcomes.

KEYWORDS: Microsponges, Controlled Release, Drug Delivery Systems, Porous Microspheres, Targeted Therapy, Sustained Release, Therapeutic Efficacy.

INTRODUCTION

Drug delivery technology is advancing rapidly, with numerous innovative methods being developed to enhance the efficiency and cost-effectiveness of treatment protocols (Patra, J.K., 2018). Among these advancements, microparticulate drug carriers have emerged as a significant breakthrough, offering novel systems for delivering medications (Kita, K., 2011). Multiparticulate systems are particularly valuable due to their simple design and their ability to control drug release through mechanisms such as rate control, site-specific control, or a combination of both (Singh, K., 2022).

These systems are designed to improve drug absorption by ensuring more uniform distribution across the absorption site. Various microparticulate systems, including microspheres, microbeads, microcapsules, microballoons, and microsponges, have been developed and extensively studied (Asghar, L.F., 2006, Jose, S., 2011). Microsponges, which are porous microspheres composed of physiologically inert organic polymers, play a crucial role in this domain. These microspheres, typically ranging in size from 5 to 300 μm , protect the encapsulated pharmaceutical substances (Dimitrovska, A., 2011, Srivastava, R., 2012). A particle with a diameter of 25 μm may contain approximately 2.5×10^5 pores interconnected by channels, creating an internal pore space with dimensions of about 3 μm and a volume of 1 mL/g of the particle (Nokhodchi, A., 2008).

The unique design of microsphere particles includes a highly porous surface and multiple internal cavities within a stable, non-collapsible structure (Kumar, S.S., 2013). This distinctive architecture enables the entrapment of various active pharmaceutical ingredients (APIs) while providing controlled release. Microsponges are versatile and can be incorporated into a wide range of formulations, such as tablets, gels, capsules, powders, lotions, and creams. (Osmani, R.A.M., 2015). This delivery system enhances drug entrapment and stability, offers greater flexibility in formulation, and significantly minimizes unwanted side effects (Grimes, P.E., 2004).

A key advantage of microsponges is their ability to hold large quantities of active compounds either within their core or on their surface (Abioye, A., 2016). This controlled-release mechanism improves the safety, efficacy, and aesthetic appeal of various personal care products, including over-the-counter formulations. The active ingredient within the microsphere is gradually released in multiple stages. As equilibrium is reached between the particles and the medium, a dynamic exchange allows the active ingredient to flow from the

microsponge to the surrounding medium. When the medium becomes depleted or absorbed, this exchange continues from the microsponge to the skin (Sharma, S., 2006).

This method underscores the importance of developing vehicles compatible with microsponge entrapment systems (Khramtsov, P., 2021). Microsponges are patented polymeric delivery systems capable of carrying a wide array of active compounds, including emollients, fragrances, essential oils, sunscreens, anti-infectives, antifungals, and anti-inflammatory agents (Khramtsov, P., 2021). Due to their size, microsponges cannot penetrate the skin, ensuring safety. Additionally, their small pore sizes (ranging from 0.007 to 0.2 μm) protect against bacterial contamination, as bacteria cannot infiltrate the tunnel-like structure (Saboktakin, M.,). Microsponges have become one of the most extensively studied drug delivery systems, offering several advantages over other microparticulate carriers, such as ease of manufacture, improved drug loading capacity, and precise rate control. These benefits solidify their role as a vital tool in modern drug delivery systems (Vishwakarma, P., 2019, Zhang X., 2018).

METHODS FOR PREPARING MICROSPONGES

Various methods are employed in developing microsponge-based drug delivery systems, including liquid-liquid suspension polymerization, quasi-emulsion solvent diffusion, water-in-oil-in-water (w/o/w) emulsion solvent diffusion, oil-in-oil emulsion solvent diffusion, the porogen addition method, vibrating orifice aerosol generator method, electro-hydrodynamic atomization method, and ultrasound-assisted production method (Oberholzer, I.D., 2009, Johnson, T., 2010).

Lyophilization Method

In this method, porous microspheres are created by lyophilizing microspheres previously developed in a chitosan hydrochloride solution. The rapid removal of the solvent during the process results in the formation of pores. This method is fast, simple, and effective for producing microsponges. However, it often yields microparticles that are fractured or shrunken due to the quick withdrawal of the solvent.

Addition of Porogen Method

This approach involves replacing the internal aqueous phase of a water-in-oil-in-water (w/o/w) emulsion with a porogen, such as hydrogen peroxide or sodium bicarbonate. The porogen is uniformly distributed throughout the polymeric solution to create a consistent

dispersion framework, which is then redispersed in a polyvinyl alcohol (PVA) aqueous phase. After adding an initiator, the organic solvent is removed, leaving microparticles with pores of 5–20 μm . While the structure provides uniform and connected pores, it is prone to damage.

Liquid-liquid Suspension Polymerization Technique

In this single-step process, microsponges are formed by suspension polymerization in liquid-liquid systems (Zhang, G., 2020, Hari. K., 2020). The active ingredient and monomers are dissolved in a suitable solvent and suspended in an aqueous phase containing surfactants and dispersants. Polymerization is initiated by a catalyst, temperature increase, or radiation, forming a reservoir system with surface-opening pores. The method allows for single- or two-step drug loading, depending on the sensitivity of the active ingredient to polymerization. Despite its simplicity, the technique has drawbacks, such as unreacted monomers and solvent residues, and limited drug loading capacity (Aloorkar, N., 2012).

Quasi-emulsion Solvent Diffusion Method

This widely used method involves forming a quasi-emulsion with an internal and external phase. The internal organic phase contains polymer, ethyl alcohol, and a plasticizer (e.g., triethyl citrate), while the external phase comprises distilled water and PVA. The emulsion is stirred for two hours, and the microsponges are filtered, washed, and dried. This method offers high drug loading efficiency, low solvent traces, and precise control of particle size. However, issues like monomer residue, slow reactions, and reduced efficiency for thermosensitive drugs can arise.

Water-in-oil-in-water (w/o/w) Emulsion Solvent Diffusion

This technique creates biodegradable porous microspheres using an emulsifying agent (e.g., span or polyethyleneimine) to form a water-in-oil emulsion, which is then dispersed into an external PVA aqueous phase to form a double emulsion. The method efficiently encapsulates both water-soluble and water-insoluble drugs. However, the use of water-insoluble surfactants may leave residues in the final product, which is a significant limitation.

Oil-in-Oil (o/o) Emulsion Solvent Diffusion Method

This method involves creating an oil-in-oil emulsion using a volatile organic solvent as the internal phase, instead of the water-in-oil-in-water (w/o/w) approach where water evaporates gradually during stirring. Here, dichloromethane is used as the internal phase, polylactic glycolic acid serves as the polymer, and the external phase comprises Span-85 mixed with

fixed oils (like corn or mineral oil) and dichloromethane. Microsponges are prepared by gradually adding the internal phase into the dispersion medium under constant stirring. For instance, hydroxyzine HCl-loaded Eudragit RS-100 microsponges are created using this technique, with acetone as the solvent and liquid paraffin as the continuous phase. The physicochemical characteristics of the drug and polymer determine the choice of organic solvent and outer phase. A significant advantage of this method is the absence of surfactant residues in the final product. However, challenges include the complete removal of alcohol and reliance on organic solvents.

Vibrating Orifice Aerosol Generator (VOAG) Method

The Vibrating Orifice Aerosol Generator (VOAG) technique was initially used to create lipid-bilayered mesoporous silica particles. This method relies on surfactant microdroplet evaporation-driven thermal deposition to produce porous particles. The process starts with preparing a stock solution for core particles by refluxing tetraethyl orthosilicate in a hydro-ethanolic mixture containing diluted HCl. This solution is then diluted with a surfactant-containing solvent, followed by stirring to form monodisperse droplets encased in microsponges.

Ultrasound-Assisted Production Method

This technique modifies liquid-liquid suspension polymerization by using β -cyclodextrin as a monomer and diphenyl carbonate as a cross-linking agent. The reaction mixture is subjected to heating and sonication to control particle size. After cooling, the mixture is pulverized, rinsed with distilled water, and then with ethanol to obtain cross-linked β -cyclodextrin microparticles. These microparticles exhibit efficient drug-loading capabilities and reproducible results without solvent residues. However, the process may leave behind hazardous residues from the cross-linking agents.

Electrohydrodynamic Atomization Method

This method, developed by Pancholi et al. in 2009, involves producing porous chitosan microspheres. The chitosan solution is first ultrasonicated to create bubbles. Using a syringe pump, the bubble-containing solution is passed through a steel capillary, where it undergoes electrohydrodynamic atomization. The diameter of the capillary is carefully selected to maintain bubble integrity, and the applied voltage is adjusted based on the chitosan concentration. Except for the highest concentration (which is challenging to electrospray), stable cone-jet modes are achieved with controlled flow rates and voltages. The microspheres

are cross-linked using a 4% sodium hydroxide solution. This method allows for the integration of therapeutic molecules with the monomer, but expertise is required to control the particle and pore size effectively (Takeshita, S., 2021).

The release of drugs from microsponges is influenced by multiple factors, as their physicochemical characteristics are integral to drug loading and release behaviors. Analyzing microsponges using advanced techniques such as HPLC, FTIR, DSC, PXRD, and SEM is crucial for understanding their morphological features and porosity. The interplay of these properties with drug release highlights the importance of proper characterization in microsphere design.

Unlike traditional topical formulations, which aim to enhance the solubility of active compounds in the vehicle, microsphere systems operate differently. In microsphere-based delivery, the active compound must exhibit adequate solubility in the vehicle to enable efficient drug release. This balance can be achieved by modulating the equilibrium between the microsphere polymer and the delivery medium. An alternative strategy involves formulating microspheres containing both free and trapped active ingredients, creating a pre-saturated vehicle to minimize unwanted leaching.

Table 1: Different techniques for forming microspheres.

S. No.	Technique Name	Advantages	Disadvantages	Excipients
1.	Liquid-Liquid suspension polymerization technique.	Modifications to one-step or two-step drug loading procedures are possible.	Un-reacted monomers and solvent particles may be trapped. For thermo-sensitive medicines with limited drug loading efficiency. Particles are not uniform. A two step technique is required.	Surfactant like peroxide benzo-ylt-butyl, diacetyl and lauroyl peroxides, and dispersants such as methyl and ethyl cellulose. (Hari K., 2020, Wiley, J., 2011)
2.	Quasi-emulsion solvent diffusion technique.	No trapping of monomers. Solvent traces are minimal.	Unable to load water soluble medicine. Long monomer's	Edugit RS-100, Dichloromethane, plasticizer, piroxicam, and Tri-

		High drug loading There is no exposure of the medication to the environment. Controlling the stirring can readily control the size of microsponges. Sphere structured particle.	reaction. Volatile water-soluble solvent dissolves the drug.	Ethylcitrate (TEC) (Cao, Y., 2010, Thanh, L.T., 2010).
3.	w/o/w emulsion solvent diffusion technique.	Load water-soluble medicines. Entrap proteins and peptides.	Water-insoluble surfactants are used, which can leave residues in the microsponges.	Span, polyethylene imine, stearyl amine (Moussa, M., 2002).
4.	Addition of the porogen method.	Pores are well and dispersed inter-linked.	Structure disturbed	Hydrogen peroxide and/or sodium carbonate (Zhang, W., 2019).
5.	Oil-in-oil emulsion solvent diffusion method.	Surfactant traces not found	To get rid of the residues of alcohol, need to wash it well Organic materials solvents	Methocel 10000cps, eudragit-\$100, eudragit-L100, endragit-R1.100, eudragit-RS100, acetone, Liquid paraffin.
6.	Lyophilization method.	Simple, rapid, and repeatable outcomes	Microparticles may break or shrink	Hydrogen peroxide solution 7. (30%), Polyethylene Glycol (PEG) 200, PEG-400, PEG-600, Dimethyl Formamide (DMF), Dimethyl Sulphoxide (DMSO), ethylene glycol.
7.	Ultrasound-assisted production	No solvents residues. Easily repeatable	Not quite right structure. Use of potentially hazardous cross-	Beta-cyclodextrin (BCD), Diphenyl carbonate (Takeshita, S.,

			linking agents	2021, Bohr, A., 2014)
8.	Electro hydrodynamic atomization method.	Easily repeatable results	Medication molecule will bond to the monomer. Controlling particle and pore size necessitates experience.	Hydroxypropyl Methylcellulose (HPMC) and lactose monohydrate, Span 20 (Aloorkar, N., 2012).
9.	Vibrating orifice aerosol generator method.	Targeted drug delivery	Presence of acid reflux.	Tetraethyl orthosilicate and other surfactants (Li, Q., 2022).

SEVERAL FACTORS DIRECTLY INFLUENCE THE DRUG RELEASE MECHANISM FROM MICROSPONGES, SOLUBILITY

Temperature

The viscosity of certain encapsulated substances might inhibit rapid release at normal skin temperatures. An increase in skin temperature enhances the flow rate, leading to improved drug release.

Pressure

Applying pressure or rubbing microsponges facilitates the release of active substances onto the skin. The structural strength of the microsp sponge affects the amount of release.

Solubility

Microsponges containing compounds like deodorants or antiseptics release their contents upon interaction with water. Diffusion can also drive this release, depending on the partition coefficient between the microsp sponge and the external medium (Dahiya, J., 2013, Gupta, V., 2013).

pH-Triggered Systems

In systems containing pH-sensitive compounds, the release is triggered by changes in pH. Similar to solubility-driven release, diffusion and the partition coefficient between the microsp sponge and the external system also play a role.

These factors, alongside diffusion and other stimuli like steam, friction, or temperature changes, collectively determine the drug release behavior from microsponges.

Application of Microsponge-Based Drug Delivery Systems

In recent years, the focus on targeted drug delivery has significantly increased. Microsponges, a type of polymeric delivery system consisting of porous microspheres, are being explored for their versatility. These systems can encapsulate a variety of active agents, such as emollients, fragrances, essential oils, sunscreens, anti-infectives, antifungals, and anti-inflammatory compounds. The advantages of microsponges include enhanced drug loading and release control, uniform distribution, and ease of manufacturing.

Microsponge Role in Anticancer Drug Delivery

Colon-specific drug delivery systems are designed to maximize efficacy and minimize side effects by delivering high concentrations of medication directly to the colon. Microsponges have proven beneficial for oral drug delivery, extending drug release and reducing adverse effects. For example, microsponges loaded with 5-fluorouracil (5-FU) have shown promising results in treating solid tumors. These microsponges, prepared using the oil-in-oil solvent diffusion method, demonstrated controlled drug release over five hours, compared to the 20-minute release of pure 5-FU. Studies also highlighted formulations with 0.15% retinol and 4% hydroquinone, which effectively treated post-inflammatory hyperpigmentation and melanoma. Clinical trials showed significant improvements in lesion appearance with minimal side effects, supporting the formulation's safety and efficacy. Similarly, 5-FU-loaded microsponges prepared with ethyl cellulose and Eudragit RL 30 D showed enhanced effectiveness, achieving five times the efficacy of conventional therapies.

Microsponge Use in Topical Applications

Topical medications are commonly used to treat skin conditions and are also prominent in cosmetics. However, traditional formulations may cause irritation, especially in sensitive skin. Microsponge-based systems address these issues by delivering drugs into the epidermis, ensuring localized effects with minimal systemic absorption. These systems have shown efficacy in treating conditions like acne, psoriasis, eczema, dandruff, and skin cancer. Formulations such as benzoyl peroxide, retinoic acid, and 5-FU-based microsponges provide advantages over traditional treatments, including reduced irritation, better tolerability, and oil absorption.

Microsponge Systems for Oral Drug Delivery

Microsponges have also been explored for oral drug delivery, particularly for poorly water-soluble drugs. These systems enhance solubility, absorption, and bioavailability by interacting with the intestinal mucosa. A.P. Pharma, Inc. conducted the first trial of oral microsponge-based drug delivery in the U.S., demonstrating their potential for sustained release and protection of active compounds. For instance, luteolin-loaded microsponges were developed as a gastric-floating system to combat *Helicobacter pylori*, doubling the efficacy compared to pure luteolin. Similarly, albendazole microsponges, prepared using Eudragit RS100, showed increased bioavailability and effectiveness against parasitic infections in goats, suggesting their potential for oral sustained-release therapies (Ain, S., 2013).

Microsponges as Bone Replacement Technique

Bone replacement materials were developed using pre-polymerized poly-methyl-methacrylate (PMMA) granules combined with liquid methyl methacrylate (MMA). Calcium-deficient hydroxyapatite powder and tri-calcium phosphate grain aqueous dispersions were added to the monomer. The resulting composites were porous, allowing new trabecular bone to grow within the pores, where the inorganic particles were integrated. These materials demonstrated biocompatibility, osteogenesis, and osteointegration.

Microsponge Technology in Cardiovascular Treatment

Microsponge technology has also found applications in cardiovascular treatments, particularly with cardio-selective drugs. A major challenge in cardiovascular engineering is the complex and invasive nature of seeding biodegradable hematopoietic cells, which can increase infection risks. Biodegradable collagen microsponges offer a solution by facilitating the regeneration of autologous vascular tissue. Histological studies revealed the presence of an endothelial cell monolayer, parallel smooth muscle cells, and a repaired vascular wall supported by proteolysis and collagen fibers. After six months, the cellular and extracellular components of the patch closely resembled natural tissue. These patches could also be used for in situ cellularization and the formation of allogeneic tissues during cardiovascular surgeries.

Microsponge for Sustained-Release Drug Delivery

Traditional tablets and capsules typically begin working within 30 minutes and last up to 4–7 hours, with the medication eliminated from the body within 5–7 hours in healthy individuals. Drugs like nifedipine, which have a short half-life of about 2 hours, require frequent dosing

to manage cardiovascular conditions effectively. Sustained-release microsponges containing nifedipine have been developed and incorporated into tablets, offering better clinical application and improved patient compliance. Domperidone is another drug suitable for sustained-release formulations, as it often requires long-term use and high doses. Microsponge-based prolonged-release domperidone capsules reduce side effects, enhance release kinetics, and improve therapeutic effectiveness for conditions like gastroparesis, emesis, and other disorders.

Diagnostic Agent Delivery Using Microsponges

Microsponges enhance the solubility of poorly water-soluble hydrophobic drugs through their hydrophobic cores, improving the delivery and pharmacokinetics of cancer-specific combination therapies. Subhan and Torchilin describe how microsponges self-assemble, creating dense siRNA concentrations in nanoparticles while requiring lower poly-cation levels. They also highlight polymeric siRNA forming RNA interference (RNAi) microsphere structures. Modifying polyplexes can further optimize the therapeutic potential of these microsponges.

Microsponges as Vehicles for Diabetes Treatment

Diabetes, characterized by chronic hyperglycemia, is a significant health challenge that often leads to severe complications. Microsponge-based drug delivery systems offer a promising solution to enhance diabetes treatment by addressing the need for frequent dosing and improving patient adherence. A controlled-release gastro-retentive microsphere formulation of mitiglinide calcium has shown potential to reduce dosing frequency, thereby enhancing diabetes management. Research by Meenakshi and colleagues focused on glipizide floating microsponges, which extend drug release at the absorption site, reducing fluctuations in plasma drug levels. This approach is expected to sustain lower blood glucose levels for a longer duration compared to quick-release formulations. Gastro-retentive microsponges, which remain in the upper gastrointestinal tract, are considered a novel strategy for optimizing the therapeutic effects of diabetes medications.

Anti-Allergic and Anti-Inflammatory Drug Delivery Using Microsponges

Anti-allergic drugs alleviate inflammatory conditions by targeting histamine and other inflammatory mediators at specific sites. Similarly, NSAIDs, despite their gastrointestinal side effects, provide relief from pain, inflammation, and fever. Microsphere-based delivery systems offer an advanced method for delivering anti-inflammatory and anti-allergic

medications. For instance, naproxen encapsulated in a Eudragit-based microsphere gel has demonstrated improved solubility, skin permeation, and stability. This system uses Eudragit RS-100, carbopol, and PVA in a quasi-emulsion to achieve sustained drug release. Similarly, microsphere formulations for diclofenac diethylamine and flurbiprofen have demonstrated prolonged and controlled release, enhancing therapeutic efficacy and reducing side effects. Microsphere technology thus offers multiple advantages, such as better drug stability, targeted delivery, reduced adverse effects, and formulation flexibility.

Antimicrobial Drug Delivery Using Microspheres

With the rise of multidrug-resistant (MDR) bacteria, effectively delivering antimicrobial drugs is a significant challenge. Microsphere systems address this issue by improving drug targeting and controlled release. Their ease of fabrication and ability to regulate drug release in terms of rate, location, or both make them an ideal solution. Numerous studies have explored microsphere delivery systems for antibacterial drugs, showcasing their potential to enhance therapeutic outcomes while reducing costs

SCOPE AND FUTURE PROSPECTS OF MICROSPHERE DELIVERY SYSTEMS

Microsphere delivery systems (MDS) hold immense potential in the pharmaceutical industry due to their unique features, such as extended release, reduced irritation, enhanced stability, and innovative product designs. Initially developed for topical antifungal, anti-inflammatory, and anti-dandruff drugs, MDS has evolved to include oral peptide delivery and colon-specific drug administration. The development of nanosized carriers is gaining momentum, as they offer superior surface-area-to-volume ratios and greater control over drug release compared to micron-sized particles. Cyclodextrin-based nanospheres, introduced by Francisco Trotta in 2012, exemplify the potential of nanosphere technology in revolutionizing drug delivery. Additionally, microsphere-based catalysts are being investigated for environmental applications, such as degrading contaminants in water and soil. As research progresses, microsphere and nanosphere technologies are expected to transform drug delivery and environmental remediation efforts.

CONCLUSION

Microspheres are an advanced polymeric drug delivery system comprising spherical nanoparticles. These systems consist of porous microspheres with sizes ranging from 5 to 300 micrometers, tailored based on the desired texture or feel in the final product. They are versatile and can incorporate a variety of active agents, including emollients, fragrances,

essential oils, sunscreens, anti-infectives, antifungal agents, anti-inflammatory drugs, and specific antibiotics. The microsphere system relies on polymeric materials, enabling controlled drug release by selecting suitable polymers for formulation. Consequently, the Microsphere Delivery System (MDS) represents a novel and progressive technology for efficient drug delivery, undergoing continuous research and development. Initially designed for topical applications, this technology has expanded to include controlled oral drug delivery using bioerodible polymers and tissue engineering. Drug release from microsphere carriers can be fine-tuned by modifying factors such as polymer solubility, pH, or temperature of the medium. This system also offers benefits like enhanced drug stability, minimized side effects, and optimized release profiles. Due to its advantages, including sustained release, reduced irritation, compact size, self-sterilizing nature, and compatibility with various vehicles and components, MDS holds significant potential for use in diverse therapeutic formulations.

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