Functional Applications of Microsponges in Modern Pharmaceutical Formulations

Sweety J. Patel[1], Aastha A. Bhatt[2], Dr. Neelam Patel[3], Dr. Hetal Patel[4]
[1,2,3,4]*Pharmaceutics Department, Arihant school of pharmacy and Bio-research institute, Swarrnim Startup & Innovation University, Ahmedabad, India*

Abstract **-The Microsponge Drug Delivery System (MDS) is an advanced and versatile approach designed to enhance the efficacy, safety, and stability of pharmaceutical and cosmetic formulations. Microsponges are porous, polymeric microspheres with particle sizes typically ranging from 5 to 300 µm, capable of entrapping active ingredients and releasing them in a controlled manner. This system offers several advantages over conventional dosage forms, including improved drug stability, reduced irritation, enhanced patient compliance, and prolonged drug release.**

Microsponges can be prepared using various techniques such as quasi-emulsion solvent diffusion, liquid–liquid suspension polymerization, and multiple-emulsion methods. These systems are widely applicable in topical formulations like gels, creams, and lotions, as well as emerging applications in oral and targeted drug delivery. The release of drugs from microsponges can be triggered by factors such as temperature, pH, and mechanical pressure, making them suitable for site-specific delivery.

MDS has demonstrated significant potential in treating dermatological conditions such as acne, psoriasis, infections, arthritis, and wound healing, while also being widely used in cosmetic formulations for improved product performance. Additionally, recent advancements like Nanosponges and nanoferrosponges have further expanded their application in targeted and controlled drug delivery.

Overall, microsponge technology represents a promising platform for developing novel drug delivery systems, offering controlled release, reduced side effects, and improved therapeutic outcomes across pharmaceutical and cosmetic fields.

Index Terms: **Controlled drug Release Microsponge drug delivery system, Quasi-emulsion solvent diffusion, Transdermal drug delivery system**

I. INTRODUCTION

The microsponge drug delivery system was first introduced by Won in 1987, and the initial patents were granted to Advanced Polymer Systems, Inc. Later, this company further improved the technology and developed several modified forms that were applied in pharmaceutical formulations, including prescription drugs, over-the-counter (OTC) medicines, and cosmetic products. (1)

Microsponges are tiny spherical particles with a diameter generally ranging from 5 to 300 µm. These particles possess a highly porous structure that enables them to absorb skin secretions and incorporate active pharmaceutical ingredients within their internal cavities. Due to their porous nature, microsponges are often referred to as porous polymeric microspheres. The presence of numerous internal pores allows them to effectively store and release bioactive compounds in a controlled manner. Compared with conventional topical delivery systems, microsponges provide several advantages such as being non-greasy, odorless, stable, and non-irritating, which improves patient acceptability and compliance. They are capable of delivering drugs directly to the targeted site while maintaining drug stability and minimizing potential toxicity. These systems are mainly designed for topical drug delivery, where they help increase the residence time of the drug on the skin and allow controlled release over an extended period. Microsponges are commonly prepared using techniques such as quasi-emulsion solvent diffusion and liquid–liquid suspension polymerization. (2)

Microsponges can entrap a wide range of active ingredients and can be incorporated into different dosage forms such as gels, creams, lotions, liquids, or powders. The release of active substances from the microsponge drug delivery system (MSD) may occur in response to certain triggers such as temperature changes, pH variation, pressure, or skin contact. In recent years, researchers have also explored the potential of microsponges for oral drug delivery applications. Entrapping poorly water-soluble drugs within the porous structure of microsponges has been reported to improve their solubility and dissolution rate. (3)

One of the major challenges faced by the pharmaceutical industry is the efficient delivery of active pharmaceutical ingredients (APIs) to specific target sites within the body. Therefore, the development of novel drug delivery systems, including microsponge-based formulations, has gained significant attention. By incorporating drugs into suitable carrier systems, it is possible to modify the drug release profile, improve therapeutic efficacy, and reduce adverse effects. Among the different routes of drug administration, the skin is considered a reliable and convenient pathway for delivering active substances, allowing both localized and systemic therapeutic action. [4]

The drug delivery system known as TDDS uses microsponge, which is a topical drug delivery system applied topically to the skin, either for localized or systemic therapy purposes. The transdermal drug delivery system, a novel dosage form, offers several unique advantages but also some disadvantages, including poor permeability and drug entry primarily through the systemic vascular system. The micro-sized, poly-porous particles known as microsponges are safe for biological systems and have the ability to ensnare useful substances. They also have an unusual collection of advantages. Transdermal drug delivery systems, which are usually applied topically and orally and have large applications in the medical and cosmetic fields, can improve medication stability, reduce adverse effects, increase bioavailability, and more. [5]

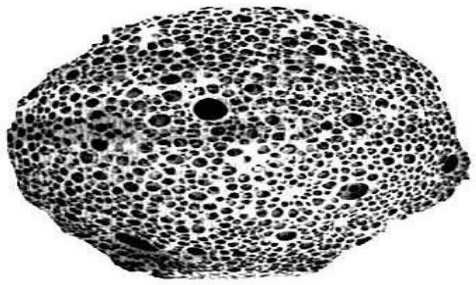


Figure 1. Structure of Microsponge

1.1 Advantages of Microsponges:

- Oil control, absorb up to six times its weight of without drying
- Improved product elegancy
- Extended release of drug
- Reduced irritation of formulas
- MDS to allow the incorporation part of immiscible products.
- Allows novel part product form
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- Extended release for continuous use up to 12 hours
- Enhanced product aesthetics to giving product more elegant feel
- Reduced of irritation, Better part of tolerance mean broader consumer acceptances
- Stability of thermal, physical and chemical are Improves
- Improves material processing e.g. liquid can be converted to powders
- Allows to incorporation of the immiscible products.
- Improves the efficacy of treatment [6]

1.2 Disadvantages of Microsponges:

- Extremely flammable.
- Presenting a risk of public safety.
- Remaining monomer residues might be toxic and harmful to human health.
- A risk to the environment [7]

1.3 Characteristics of Active Moieties that Entrapped into Microsponges:

- Active ingredients that entrapped into microsponge can then incorporated into many products such as creams, gel, powders, lotions and soaps.
- It must be completely miscible in monomer or able to be miscible with a tiny amount of a water immiscible solvent added.
- It must not react with monomers and should not make the mixture more viscous while being formulated.
- It must be nearly only slightly soluble or water immiscible.
- The microsponges' spherical structure shouldn't be collapsed.
- It must be stable when in contact with the catalyst during polymerization and under polymerization conditions.
- The vehicle's solubility of active ingredients needs to be restricted.
- Should this not be the case, the cars will exhaust the microsponges prior to the application.
- It is necessary to add a maximum of 10 to 12% weight-/weight microsponges into the vehicle to prevent cosmetic issues.
- The microsponges' polymer design and payload. [8]

1.4 Methods of Preparations:

The drug's physico-chemical characteristics dictate how the substance is loaded onto microsponges.

Single-step procedure: By this procedure, a non-polar, inert medication is loaded. This class of medication generates porogen, which has a porous structure. The porogen medication is unaffected by the polymerization process and remains stable in the presence of free radicals.

Two-step procedure: This procedure is used when the medication is sensitive to the conditions of polymerization. This approach replaces the porogen that is employed as a replacement during polymerization with an active ingredient in a low-stress test setting. [9]

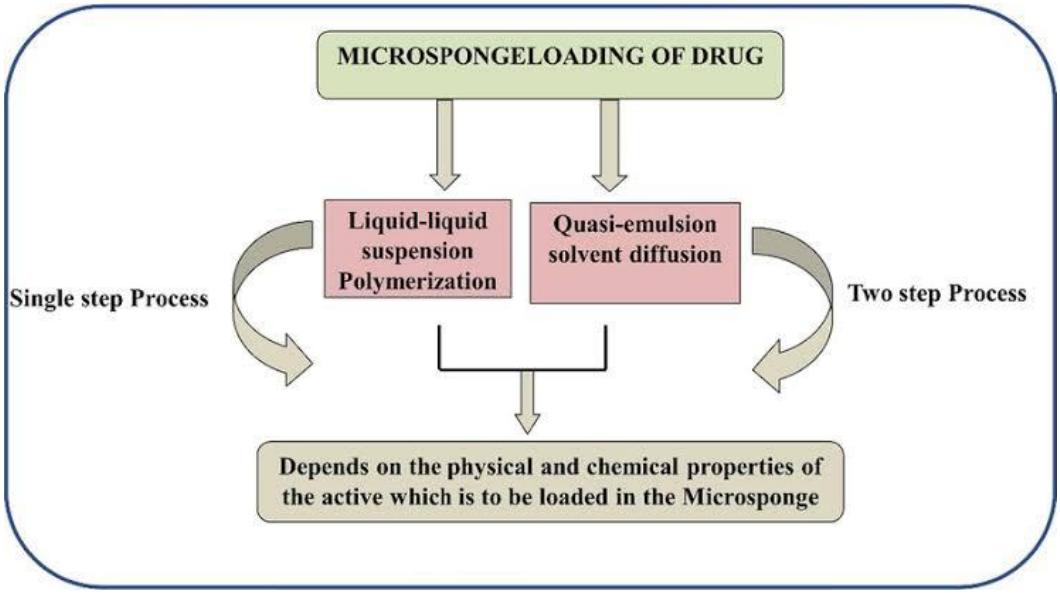


Figure 2: - Methods of Preparations

- Following are of the some preparation methods of microsponges.
  - Quasi emulsion solvent diffusion technique
  - Liquid -liquid suspension polymerization.
  - Multiple-emulsion solvent diffusion method
  - Addition of the porogen method
  - Lyophilization method
  - Vibrating orifice aerosol generator method
  - Ultrasound assisted production method

- Quasi emulsion solvent diffusion method:

The process creates two phases: the outer aqueous phase, which is filtered and agitated before usage, and the inner organic phase, which contains the medicine. After that, the inner phase is mixed drop by drop into the outer phase for 60 minutes while being stirred mechanically. Continuous stirring produced the quasi-emulsion droplets, and additional organic solvent evaporation produced the solid microsponge cages. The next stage in producing microsponges using the quasi-emulsion solvent diffusion approach was to filter the microsponges and dry them in an oven for a duration of 12 hours. [10]

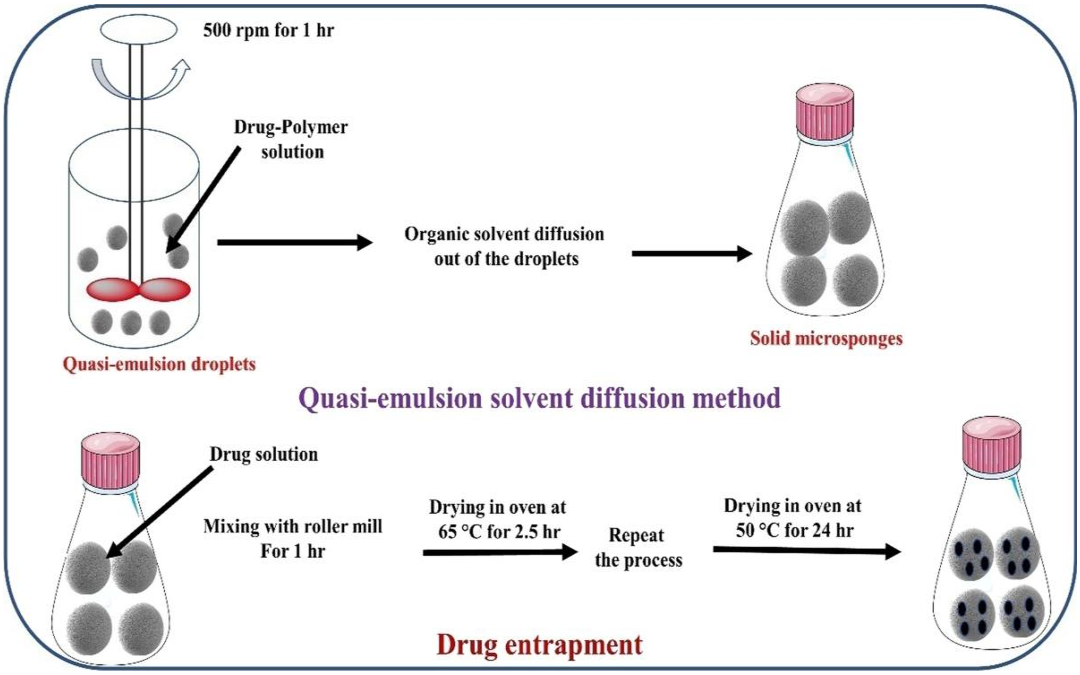


Figure 3. Quasi emulsion solvent diffusion method

❖ Liquid -liquid suspension polymerization.

Usually, a solution including water-immiscible monomers and active additives prepared beforehand. how many steps are involved in polymerization procedures involving liquid-liquid suspension. This agitation-sustained water-soluble phase is commonly composed of compounds like dispersants and emulsifiers. After the solution is created with distinct droplets of the proper size, polymerization is accomplished by activating monomers with the help of catalysis, temperature elevation, or radiation. The process of polymerization yields MDS cages with interconnected spherical structures that resemble clusters of grapes. The solid particles will be separated from the resultant suspension upon

completion of the polymerization process. The particles were then dried and washed in preparation for future use directly affect. [10]

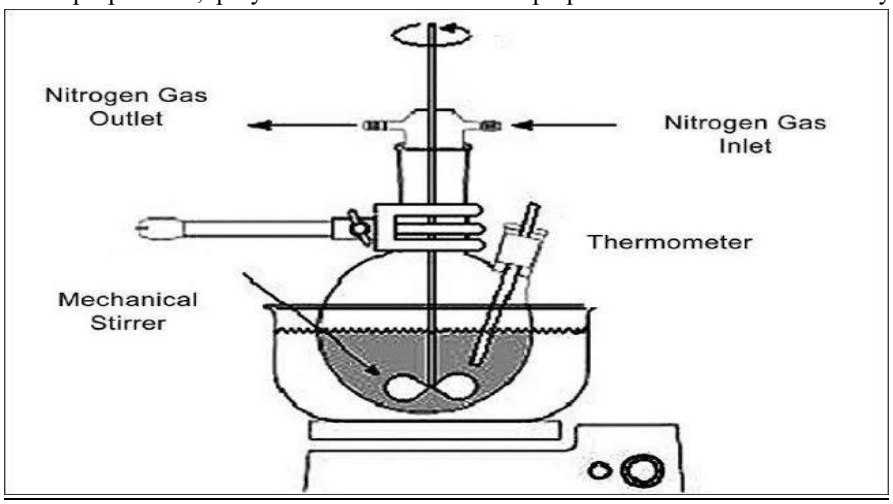


Figure 4. Liquid-liquid suspension polymerization

❖ Multiple-emulsion solvent diffusion method

The method was designed to produce biodegradable and porous microspheres. Stearyl amine was added to an aqueous inner phase, and the span was then dispersed in solution. To create a (w/o/w) double emulsion, this w/o emulsion is then dispersed once again using polyvinyl alcohol in an aqueous phase. The benefit of collecting both soluble and insoluble actives is revealed by this approach. It is also

possible to entrap thermolabile substances like proteins using this technique. [10]

- ❖ Addition of porogen method
  Porogen, like hydrogen peroxide or sodium bicarbonate, were used in place of the many emulsions in this method. This was accomplished by dispersing the porogen in a water phase that included polyvinyl alcohol after it had been dissolved in a polymeric solution to form a single-phase system. Then, in order to produce multiple emulsions, an initiator was applied. The organic solvent was then evaporated, leaving the particles behind to form MDS. [10]

- ❖ Lyophilisation method
  This method was used to transform the produced microspheres from the gelation process into porous microspheres. The microspheres were then kept for lyophilisation and incubated in a solution of chitosan hydrochloride. The rapid solvent removal in this method results in microsphere holes. The lyophilisation procedure, which produces MDS, has the drawback of generating fragmented micro particles due to the rapid solvent removal. [10]

- ❖ Ultrasound assisted production method
  This method was developed by altering the liquid-liquid suspension polymerization procedure used to generate MDS. In order to generate MDS, this method uses diphenyl carbonate as a cross-linking agent and beta-cyclodextrin monomer. The reaction mixture is heated and subjected to sonication in order to control the micro particle size. After cooling and grinding into a powder, the mixture was cleaned with distilled water and then ethanol, as shown. In terms of trapping hazardous cross-linking agent residue, this production method is likewise insufficient. [10]

- ❖ Electro hydrodynamic Atomization Method:
  By this technique, chitosan microspheres with pores were created. After sonicating the chitosan solution to produce bubbles, the resulting bubble suspension was pumped into a syringe, pumped through a steel capillary with a syringe pump, and then electro hydrodynamic atomization was applied. The capillary's diameter was selected so that every bubble in the suspension would stay within during the passage through it. The concentration of chitosan in the solution is the only factor that affects the voltage employed in the studies. Except in the cases where the maximum concentration was employed and it was difficult to electrospray, the combination of flow rate and applied voltage produced a stable cone jet mode in every instance. 4% w/v sodium hydroxide aqueous solution was used to cross-link the chitosan microspheres.

1.5 Evaluation Methodology of Microsponges:

- ➢ Particle size:
  All formulations of the microsponges is analysed for particle size by an optical microscope. The instrument was calibrated and found that factor of eyepiece micro meter was equal to 11.25 um. Sizes of 20 microsponges were calculated and after that average the particle of microsponge.
- ➢ Entrapment efficiency:
  The weighed samples of Pimecrolimus microsponges were dissolved in methanol under ultrasonication for 1 h at 30°C, the samples were filtered using a 0.2-um membrane filter and absorbance were read at 300 nm using an UV double-beam spectrophotometer after suitable dilutions with Methanol were obtained the drug content and entrapment efficiency were calculated using equation:

  Actual drug content (%) = *M*act/Mms × 100

  Entrapment efficiency (%) = *M*act/*M*the x 100

  Where, Mact is the actual drug content in weighed quantity of microsponges, Mms is the weighed quantity of powder of microsponges and Mthe is the theoretical amount of the drug in the microsponges calculated by the quantity added in the process.
- ➢ Scanning Electron Morphology (SEM):
  SEM by using of the SEM type of morphology surface topography and particle size diameter can be easily studied.
- ➢ Characterization of Pore Structure:
  The diameter and volume of the pores play a crucial role in regulating the duration and potency of the active component. The migration of microsponges' active components into the dispersion vehicle is influenced by

pore diameter as well. To investigate the relationship between pore width and volume and the rate of drug release from microsponges, mercury intrusion porosimetry can be utilized Mercury intrusion porosimetry may be used to determine the porosity parameters of microsponges, including bulk and apparent density, shape and morphology of the pores, intrusion-extrusion isotherms pore size distribution, total pore surface area, average pore diameters, and interstitial void volume percent porosity.

- Stability Studies:
  The accelerated into stability studies by carried out to according of guidelines by given of the International Council of Harmonization (ICH guidelines). The
  formulation is the tested part for stability 400 ± 2 °C/ 75 ± 5 RH, 50 ± 2 °C, 250 ± 2 °C/ 60 ±5 RH. Formulations is stored into glass vials and evaluate to after every 15, 30, 44 days for physiochemical characteristics. (11)
- In Vitro Drug Release:
  Franz diffusion cell and dialysis membrane were used for the in vitro diffusion investigation. The optimized batch was analysed using a Franz diffusion cell, which has a receiver compartment volume of 27 ml and an effective diffusion area of 1.62 cm^2. The sink condition was maintained while 1 m l of sample was extracted at regular intervals. Using a Shimadzu UV 1800, UV spectrophotometry was used to analyse the material.
- Ex vivo Permeation study
  On Franz diffusion cells, the amount of furosemide that permeated both the microsponge and the control was assessed using excised rat skin. For optimized batches, a Franz diffusion cell with a 27 ml receiver compartment volume and an effective diffusion area of 1.62 cm2 was utilized. A regular time interval was followed by the withdrawal of 1 m l of sample, and the sink condition was maintained throughout. Using a Shimadzu UV 1800, UV spectrophotometry was used to analyse the material.

II. FORMULATION CONSIDERATIONS

1. The MDS (Microsponge Drug Delivery System) can be incorporated into a wide range of topical products such as lotions, creams, soaps, and powders. While designing the vehicle for these formulations, several important factors must be considered to achieve the desired product characteristics. One of the key considerations is that the solubility of the active ingredient in the vehicle should remain low. If the drug dissolves too readily in the vehicle, it may reduce the effectiveness of the microsponge system by limiting its controlled-release function. (12)
2. To prevent cosmetic problems such as grittiness or poor texture, the concentration of MDS in the formulation should generally not exceed 10–12% w/w. In addition, the polymer structure and the amount of active ingredient loaded into the microsponges should be carefully optimized to ensure a controlled and sustained release over the intended period.
3. When developing vehicles for specific applications, the powder loading level must be appropriate but should remain within the recommended limit to maintain acceptable cosmetic properties. Furthermore, the solubility of the active compound in the vehicle must be restricted; otherwise, the polymer matrix may break down before the drug is effectively delivered to the skin. Therefore, both the polymer design and drug loading capacity should be properly adjusted to achieve the desired release profile of the active agent during the specified time. (13)

III. SAFETY CONSIDERATIONS

Microsponge delivery systems are prepared using commonly employed polymeric materials that contain only trace amounts of residual monomers. The polymers form a highly cross-linked structure, which makes the particles physiologically stable and inert. Because of this structural stability, the human body cannot easily break them down or convert them into other compounds. (14)

The relatively large size of microsponge particles prevents them from penetrating through the stratum corneum, the outermost layer of the skin. Instead, they remain on the skin surface or within the upper skin layers and act as reservoirs for the encapsulated drug. The active ingredient is then released slowly and continuously over time. This controlled release mechanism helps avoid excessive accumulation of the drug in the epidermis and may contribute to improved safety and better tolerability in topical formulations. (15)

IV. APPLICATIONS OF MICROSPONGE DELIVERY SYSTEM

4.1 Microsponge Technology in Cosmetics

Microsponge technology has important applications in oral care and cosmetic products. In oral formulations, it can be used to control the release of volatile ingredients, which helps maintain a longer-lasting feeling of freshness. These volatile compounds can be incorporated into products such as toothpaste and mouthwashes through microsponge drug delivery systems (MDS). Furthermore, MDS can also be applied in colored cosmetic products like lipsticks and blushes. The porous structure of microsponges can encapsulate pigments, which helps maintain colour stability and prolong the durability of the cosmetic formulation. This system also improves the uniform distribution of pigments and enhances the product's covering ability. As a result, cosmetics formulated with microsponge technology can provide better appearance, improved performance, and longer-lasting effects. (16)

4.2MDS-based delivery systems for drug triggering

Microsponge delivery systems are increasingly used in pharmaceutical and cosmetic formulations because they can improve drug effectiveness, enhance safety, and provide better aesthetic qualities in topical products. This technology is designed to release the active ingredient gradually over an extended period, which helps maintain therapeutic activity while minimizing the risk of side effects. (17)

Microsponge systems are mainly applied in topical formulations such as creams, gels, and lotions, particularly in over-the-counter medications and personal care products. However, their application has recently expanded to oral drug delivery as well. The porous structure of microsponges allows formulators to develop a wide range of pharmaceutical and cosmetic products with improved performance. These systems enable efficient delivery of active compounds using lower doses, enhance formulation stability, reduce undesirable reactions, and modify the drug release profile. (18)

Microsponge technology is widely used in various skincare and cosmetic products, including moisturizers, sunscreens, and specialized skin-care treatments. In topical formulations, microsponge delivery systems generally function in three different ways:

1. They act as reservoirs that provide a sustained and controlled release of the active ingredient over time.
2. They can absorb unwanted substances such as excess skin oil from the surface of the skin.
3. They serve as protective carriers that keep certain ingredients separated from direct skin contact while allowing them to act effectively on the skin surface.

Overall, microsponges are porous polymeric particles used for topical drug delivery and, more recently, for oral administration of active compounds. Their design allows efficient drug delivery with minimal dosage while improving product stability, reducing side effects, and controlling the release of therapeutic agents. (19)

4.3 MDS for topical delivery

Conventional topical drug formulations are generally believed to act mainly on the outer layers of the skin. When these preparations are applied, the active pharmaceutical ingredient is released rapidly, forming a highly concentrated layer of drug on the skin surface that is quickly absorbed. This rapid release can lead to excessive accumulation of the active substance within the epidermal and dermal layers. (21)

To overcome this limitation, the drug can be incorporated into a microsponge drug delivery system. In this system, the active ingredient is entrapped within porous microspheres that provide a controlled and gradual release of the drug. This approach helps reduce the excessive build-up of the drug in the skin and minimizes the risk of irritation while still maintaining therapeutic effectiveness.

Additionally, these drug-loaded porous microsponges can be easily incorporated into different topical dosage forms such as creams, gels, lotions, and powders, making them suitable for a wide range of pharmaceutical and cosmetic applications. (22)

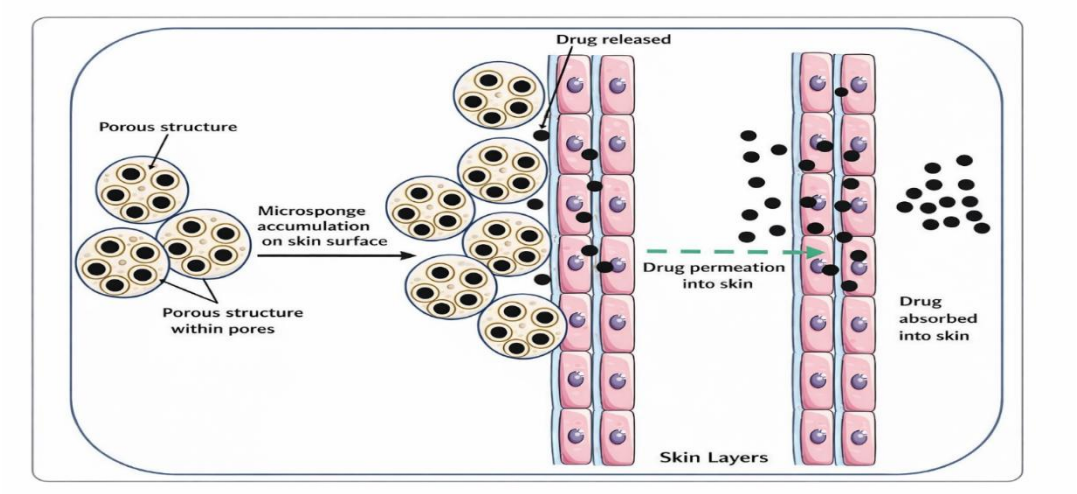


Figure 5. Mechanism of drug release from topical microsponges

4.4 MDS for oral drug delivery

The use of a microsponge delivery system (MDS) for oral drug administration is considered beneficial, particularly for drugs that have poor water solubility. The porous structure of microsponges allows these poorly soluble drugs to be entrapped within their internal cavities, which can enhance their dissolution and release characteristics. In addition, this system can help regulate the drug release behaviour in response to the pH conditions of the gastrointestinal tract. [23]

In certain formulations, microsponges may be protected with an enteric coating that prevents the drug from being released in the stomach, where the gastric environment has a highly acidic pH (about 1–3). This coating remains intact in the stomach but dissolves in the intestinal region due to the action of colonic enzymes such as glycosidase. As a result, the drug release begins after several hours, allowing the active compound to reach the lower parts of the gastrointestinal tract. When the microsponge particles reach the descending colon, they can deliver a significant portion of the encapsulated drug to the target site. Furthermore, microsponge technology enables drugs to be retained within a confined porous structure and delivered to the lower gastrointestinal tract in a controlled manner. One of the main advantages of using microsponges for colonic drug delivery is that particles smaller than about 200 µm can be readily taken up by macrophages present in colonic tissues. This property allows the drug to exert a localized therapeutic effect at the desired site. Various drug candidates have been investigated for oral delivery using microsponge systems. [24]

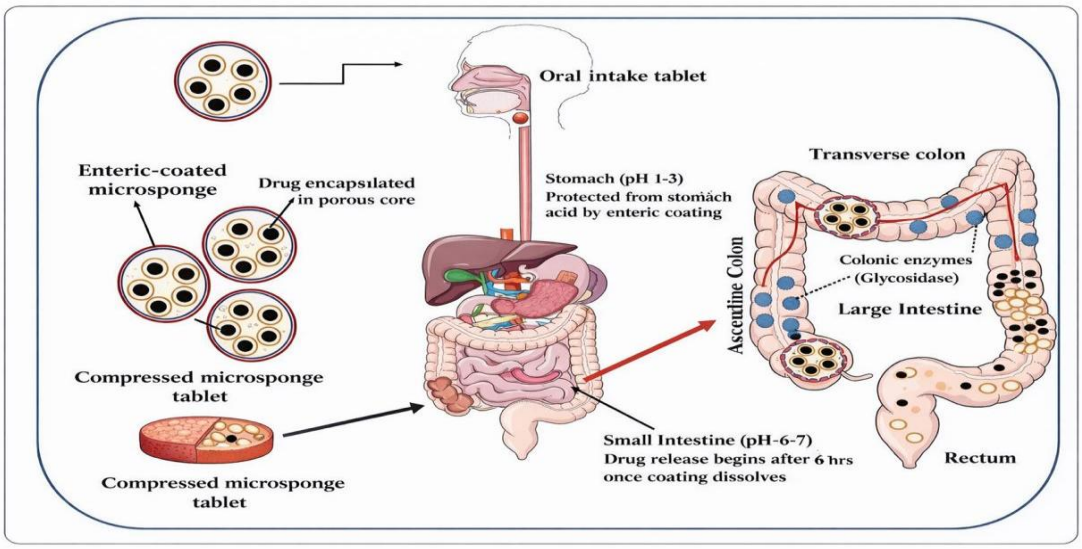


Figure 6. Drug release mechanism from microsponges an oral drug delivery system

4.5 Ocular delivery

Both water-soluble and water-insoluble drugs can be administered to the eye through topical formulations such as ointments or aqueous suspensions. However, the movement and distribution of drugs within the eye involve complex pharmacokinetic processes. After topical application, the drug penetrates the ocular tissues and may reach the anterior chamber by crossing the blood–aqueous barrier.

From the anterior chamber, the drug can move toward the trabecular meshwork and Schlemm's canal, where it is gradually eliminated through the normal turnover of aqueous humor. At the same time, a portion of the drug may pass through the blood–aqueous barrier and enter the systemic circulation. Once in the bloodstream, the drug molecules can cross the blood–retina barrier and eventually reach the posterior segment of the eye. This complex pathway highlights the challenges involved in maintaining adequate drug levels in ocular tissues after topical administration. [25]

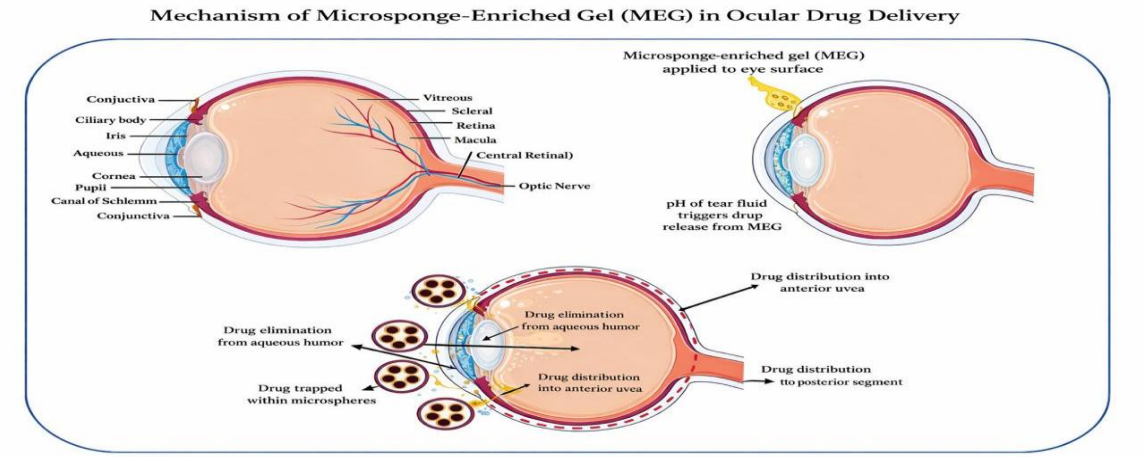


Figure 7. Mechanism of Microsponge Enriched Gel(MEG) in Ocular Drug Delivery

4.6 MDS in Cosmetics and Dermatology

The earliest patents related to microsponge technology were granted in 1987 to Advanced Polymer Systems, Inc., which subsequently applied this approach across a range of products, including cosmetics, over-the-counter (OTC) items, and prescription medications. Microsponge Drug Delivery Systems (MDS) are designed to concentrate the drug primarily on the skin surface and within the epidermal layer, thereby reducing both systemic exposure and localized skin-related side effects. Although the fundamental concept of MDS remains the same, its use in cosmetic and dermatological products differs mainly in terms of formulation considerations and regulatory requirements. Cosmetic products typically undergo faster development and reach the market more quickly, as they are subject to fewer regulatory constraints compared to dermatological drugs. Some commercially available microsponge-based cosmetic formulations. [22]

In addition, microsponge-based systems allow for targeted delivery of drugs to the skin, which helps limit excessive permeation into systemic circulation through the percutaneous route. Various dermatological formulations developed using microsponge technology and different active ingredients. [26]

4.7 MDS for bone and tissue engineering

A bone-like material was developed by combining polymethyl methacrylate powder with liquid methyl methacrylate monomer, along with tricalcium phosphate granules and calcium-deficient hydroxyapatite powders in an aqueous medium. The resulting composite exhibited a porous structure resembling microsponges and closely mimicked the appearance of natural bone. In another approach, basic fibroblast growth factor (BFGF) was loaded into a collagen sponge matrix, which gradually released the growth factor into the subcutaneous tissue of mice as the scaffold degraded. The released BFGF promoted angiogenesis in a dose-dependent manner.

Furthermore, when collagen-based microsponges containing BFGF were administered into the ischemic hind limb of mice, a marked improvement in blood circulation was observed compared to the direct administration of BFGF solution. These observations highlight the effectiveness of type I collagen as a carrier system for controlled delivery of BFGF. [28,29] Building on this concept, a biodegradable

graft incorporating collagen microsponges has been developed for cardiovascular tissue engineering, enabling regeneration of damaged tissues. Additionally, a composite patch fabricated using biodegradable polymers and collagen microsponges shows promise as an advanced material for cardiovascular repair and surgical applications. [30]

4.8 MDS in Arthritis

Microsponge-based delivery systems have been explored for improving the therapeutic performance of diclofenac in arthritis management. Diclofenac, a widely used nonsteroidal anti-inflammatory drug (NSAID), is commonly prescribed to reduce pain and inflammation in arthritis and other musculoskeletal conditions. However, its oral administration is often associated with drawbacks such as gastrointestinal irritation and extensive first-pass metabolism. To overcome these limitations, topical formulations incorporating Microsponge Drug Delivery Systems (MDS) have been developed.

In one study, Osmani and co-workers prepared diclofenac diethyl amine-loaded microsponge gels using a quasi-emulsion solvent diffusion method to achieve sustained drug release. Their formulation was evaluated against a marketed product, Voltaren Emulgel (1.16% w/w). The conventional gel released approximately 81.11% of the drug within 4 hours, whereas the microsponge-based formulation extended the release up to 8 hours, [27] demonstrating improved controlled delivery. Similarly, Hadi and colleagues developed microsponge systems containing Lornoxicam for arthritis treatment and formulated them into tablets. Their results showed prolonged drug release, with about 86% to 96% of the drug being released over a period of 12 hours, indicating the effectiveness of microsponge technology in sustaining drug delivery. [31]

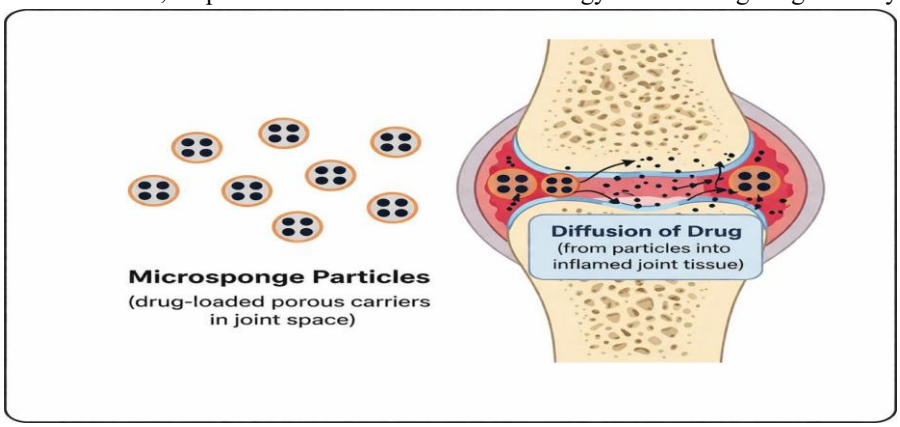


Figure 8. Microsponges in arthritis

4.9 Skin Protection using MDS

Ultraviolet (UV) radiation is known to cause skin damage such as sunburn and can also contribute to serious conditions like basal cell carcinoma and malignant melanoma, making the use of sunscreens essential for protection. To enhance the effectiveness of sunscreen formulations, Microsponge Drug Delivery Systems (MDS) have been investigated. Pawar and co-workers developed an MDS-based formulation for the delivery of oxybenzone, a commonly used broad-spectrum sunscreen agent, utilizing the quasi-emulsion solvent diffusion technique.

Conventional formulations of oxybenzone, such as creams and lotions, are often associated with adverse effects including skin irritation, dermatitis, and systemic absorption. To address these issues, the researchers optimized formulation variables like ethyl cellulose and dichloromethane using a 3^2 factorial design, and the optimized microsponges were further incorporated into a hydrogel base. The resulting formulation demonstrated a high drug entrapment efficiency of approximately 96.9 ± 0.52%.

In vitro release studies showed a controlled and sustained release pattern, and in vivo testing confirmed that the formulation was non-irritating to rat skin. Mechanical evaluation through creep recovery testing indicated good elasticity of the gel. Additionally, when compared with a marketed product, the microsponge-based gel exhibited a higher sun protection factor (SPF 25 vs SPF 20), along with reduced irritation and toxicity. The improved SPF performance may be attributed to the prolonged retention of oxybenzone in the skin due to its controlled release from the microsponge system. [32]

4.10 MDS in acne

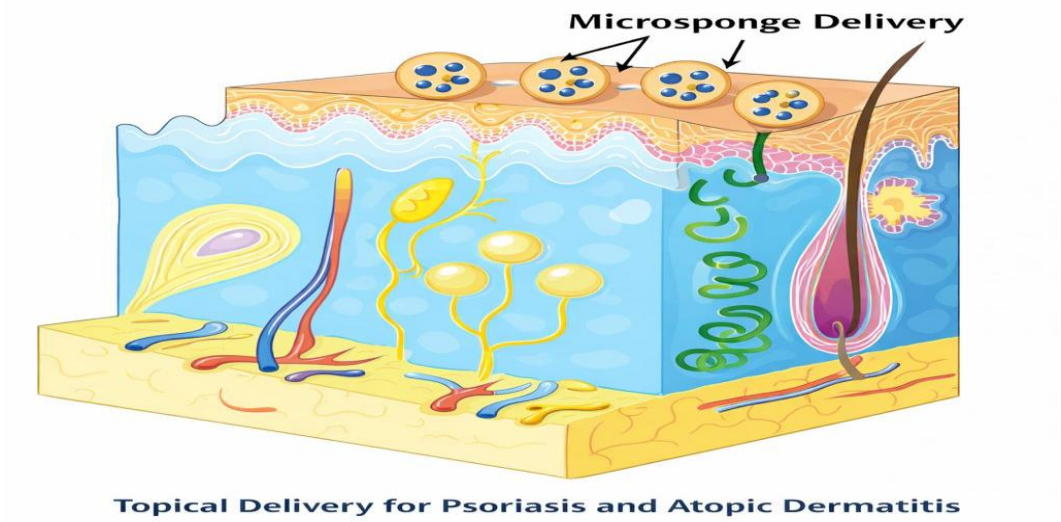
Acne is a widespread dermatological condition often associated with inflammation of the skin. Benzoyl peroxide is one of the most commonly used agents for its treatment. To improve its delivery and minimize rapid release, Jelvehgari and co-researchers developed ethyl cellulose-based Microsponge Drug Delivery Systems (MDS) for topical application. Their findings indicated an initial burst release of the drug within the first hour, followed by a more controlled and steady release over the next 7 hours. This initial rapid release was likely due to the presence of some unentrapped drug on the surface, while the subsequent sustained release reflected the gradual diffusion of the drug from the microsponge structure. (33)

In another study, Osmani and colleagues formulated a microsponge-based cream containing miconazole nitrate, an anti-acne agent, to achieve extended drug release. The microsponges were prepared using Eudragit RS-100 through a quasi-emulsion solvent diffusion technique and later incorporated into a cream base. The developed formulation demonstrated prolonged drug release, with approximately 78.28% of the drug being released over 8 hours. In contrast, a conventional cream released around 83.09% of the drug within just 4 hours, indicating that the microsponge system provided a more sustained and controlled delivery profile. (27)

4.11 MDS in psoriasis

Psoriasis is a long-term inflammatory skin condition that can significantly reduce a patient's quality of life. Microsponge Drug Delivery Systems (MDS) have been explored as a promising approach for its management. For instance, microsponges containing mometasone furoate—an anti-inflammatory and anti-pruritic agent commonly used in psoriasis—have been prepared using the emulsion solvent diffusion technique. These formulations exhibited a biphasic release pattern, characterized by an initial rapid release followed by a sustained phase. Approximately 29–36% of the drug was released within the first hour, while a total of 78–95% was released over an 8-hour period. (34)

In another approach, clobetasol propionate-loaded microsponge gels were developed to provide prolonged drug release and thereby reduce the frequency of application in psoriasis treatment. These formulations demonstrated an extended release profile lasting up to 12 hours, compared to about 2.5 hours for conventional preparations. Additionally, dithranol-loaded microsponges incorporated into dendrimer-based systems have been investigated for enhanced topical delivery, offering improved therapeutic effectiveness in the management of psoriasis. (35)



4.12 MDS in skin infections

Microsponge Drug Delivery Systems (MDS) have also been investigated for the management of eczema and atopic dermatitis, particularly in topical forms such as gels and lotions. Mupirocin, a widely used topical antibiotic for treating primary and secondary skin infections, has been incorporated into microsponge-based formulations to improve its therapeutic performance. Amrutiya and co-workers developed mupirocin-loaded microsponges using the emulsion solvent diffusion method and further

incorporated them into an emulgel base for topical application.

Evaluation studies using a cellulose dialysis membrane confirmed a controlled and sustained release profile of the drug. Skin deposition studies conducted on rat abdominal skin indicated that a significant amount of mupirocin remained localized in the skin for up to 24 hours. The optimized formulation was found to be stable and non-irritating, as demonstrated by the Draize patch test. In comparison to conventional ointments, which released the drug within approximately 4 hours, the microsponge-based gel provided an extended release lasting up to 10 hours, highlighting its advantage in prolonged drug delivery. [34]

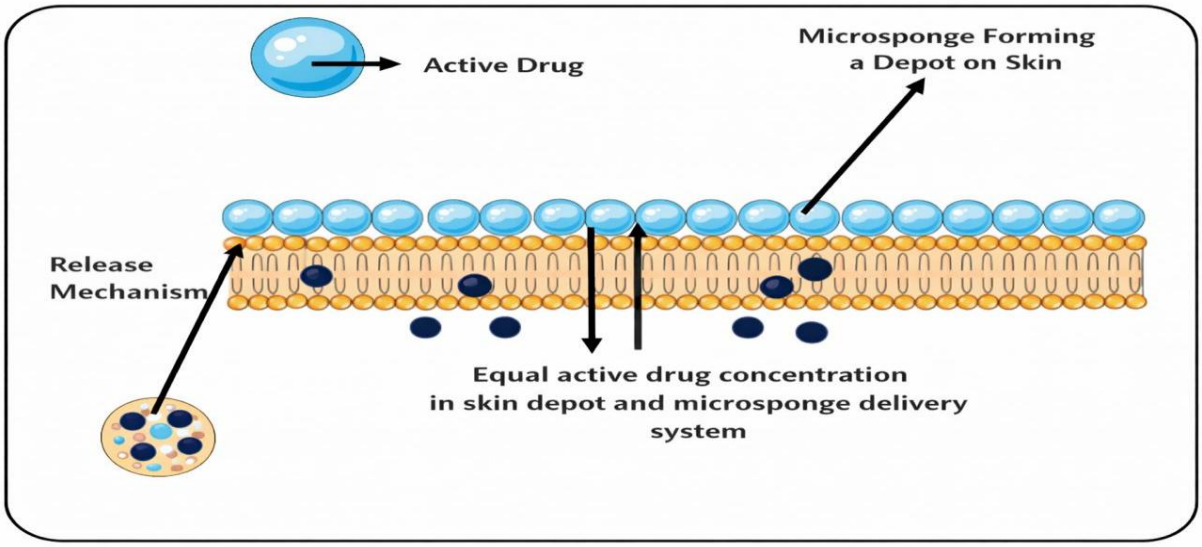


Figure 9. Microsponge drug mechanism in skin infection

4.13 Diabetic wound healing using MDS

Pandit and co-researchers developed a microsponge-based formulation containing Nebivolol and incorporated it into a gel system to maintain a moist environment during the later stages of wound healing. Nebivolol, primarily known as an antihypertensive agent, also promotes vasodilation, which can be beneficial in improving blood flow at the wound site. In the context of diabetic wounds, its action through the nitric oxide pathway helps reduce neuropathic complications and enhances endothelial function, thereby supporting tissue repair.

In vitro studies demonstrated that nearly 80% of the drug was released over an 8-hour period, indicating a sustained release profile. The incorporation of the drug into the microsponge gel effectively slowed down its release compared to conventional formulations. Additionally, the porous structure of the microsponge system contributed to improved wound healing in diabetic animal models, likely by facilitating better drug retention and maintaining a favourable healing environment. [14]

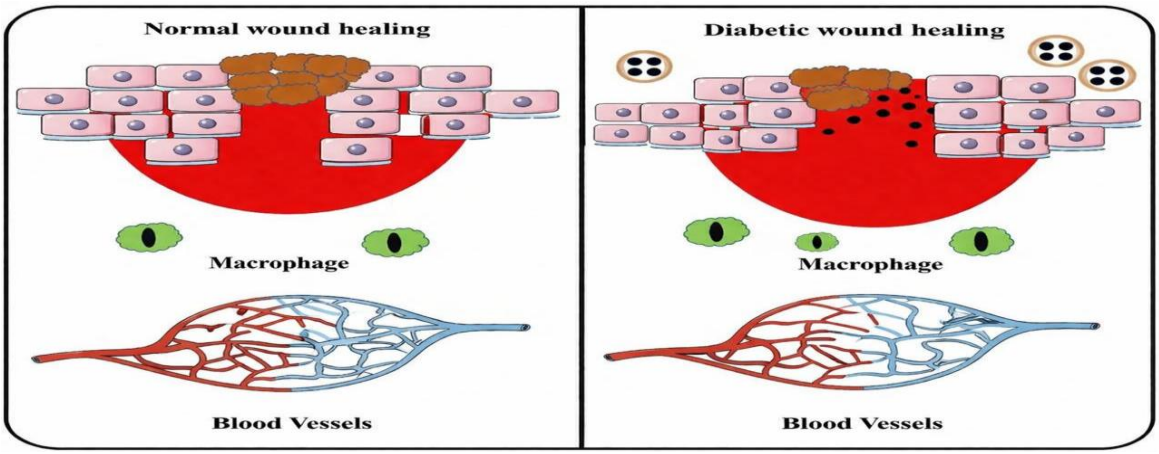


Figure 10. Microsponges in diabetic wound healing

4.14 MDS as antifungal

Terbinafine hydrochloride-loaded microsponges were formulated using the quasi-emulsion solvent diffusion method as reported by Thavva et al. The in vitro release profile of the microsponge-based gel was compared with that of a conventional drug-loaded gel. Results indicated that the plain gel released approximately 96.65% of the drug within 6 hours, whereas the microsponge formulation provided a sustained release extending up to 10 hours. This demonstrates that microsponge-based gels can prolong drug release more effectively than traditional gel systems. (36)

Similarly, Dombe et al. developed a microsponge drug delivery system (MDS) for oxiconazole nitrate using the same preparation technique, followed by incorporation into a gel base. Oxiconazole nitrate, an antifungal agent, is known for its poor water solubility and potential side effects. The prepared microsponges were spherical, well-defined, and showed a satisfactory production yield ranging from 61.44% to 80.45%, indicating the efficiency of the method. The formulation exhibited a maximum drug release of 87.77% over 8 hours, while the microsponge gel demonstrated controlled drug release for up to 12 hours. (26)

4.15 MDS in colon cancer

Microsponge drug delivery systems (MDS) have shown potential in reducing drug-related toxicity while enabling sustained release in oral formulations. Gupta and colleagues developed an MDS of 5-fluorouracil (5-FU) using Eudragit RS100 with the aim of improving therapy for colon cancer. 5-FU is widely used against various solid tumor, and its therapeutic effectiveness increases when higher concentrations are localized within tumor tissues, which may also help minimize systemic toxicity.

The formulation was prepared using an oil-in-oil emulsion solvent diffusion technique. In comparison, pure 5-FU exhibited a rapid release, completing drug liberation within approximately 20 minutes, whereas the microsponge-based system significantly prolonged the release up to around 5 hours. Additionally, studies on cell viability indicated improved performance of the MDS-loaded 5-FU compared to the free drug. These findings suggest that microsponge-based delivery of 5-FU could serve as a promising alternative to conventional oral administration in cancer treatment. (37)

4.16 Other applications

Microsponge drug delivery systems (MDS) have recently gained attention as an advanced platform capable of delivering not only conventional drugs via topical and oral routes but also biomolecules such as siRNA and fibroblast growth factors. Notably, a single RNA interference (RNAi) microsponge has the capacity to deliver hundreds of thousands of siRNA molecules into a target cell, highlighting its potential in modern therapeutic applications and pharmaceutical research. (38)

To better understand the formation and structural characteristics of RNAi microsponges, researchers applied innovative analytical techniques, including femtosecond X-ray single-shot diffraction using X-ray free-electron lasers, along with coherent diffraction imaging based on synchrotron radiation. These advanced methods provided insights into the nanoscale architecture associated with RNAi microsponge formation. The mechanism of siRNA release and transfer from the microsponge system is illustrated. (39)

V. RECENT ADVANCES IN THE MDS

Researchers and pharmaceutical companies are increasingly exploring advanced drug delivery systems that offer superior stability compared to conventional microsponge drug delivery systems (MDS). Some of these improved formulations are outlined below:

1)Nanosponges: - Nanosponges have gained attention as efficient carriers, particularly for gas delivery and targeted drug transport. When cytotoxic drugs are incorporated into these systems, their therapeutic performance can be enhanced through improved targeting of cancerous cells. These structures are commonly synthesized by cross-linking β-cyclodextrin with cross-linking agents such as biphenyl carbonate, resulting in a stable porous network. Nanosponges are versatile enough to accommodate both water-soluble and poorly soluble drugs. Various drugs, including flurbiprofen, dexamethasone, and itraconazole, have been studied using this delivery approach. (41)

2)Nanoferrosponges: -Nanoferrosponges are an emerging class of carriers that exhibit responsiveness to external magnetic fields. This property allows them to be directed toward specific sites within the body, enhancing tissue penetration. After reaching the target, the magnetic component can be removed

or neutralized, leaving behind a porous structure that facilitates controlled drug release. This targeted delivery mechanism improves drug localization and effectiveness.

3)Porous Microbeads: -Porous microbeads have been developed to provide improved characteristics compared to conventional microspheres. These systems are typically produced through polymerization and cross-linking techniques, often involving a high internal phase emulsion composed of an external oil phase, an internal aqueous phase, and a suitable cross-linking agent. They are widely used in various drug delivery routes, including topical, oral, and buccal applications. Moreover, porous microbeads have shown promising potential for siRNA delivery, as they enhance RNA stability and enable efficient encapsulation, thereby offering new possibilities for advanced therapeutic strategies. (43)

REFERENCES

[1] Sisodia, V., Tangri, S. K., & Rana, H, -Recent Trends on Microsponges: Opportunities and Challenge, *Indian Journal of Research in Pharmacy and Biotechnology*, 2023, vol.27, no.3, pp.451-467.

[2] Tyagi, S., Singh, D., Kumar, P., Saxena, C., Paul, P., & Verma, G, - Microsponges and Nanoparticles for Treatment of Topical Skin Infections: A Review Eur Microsponges and Nanoparticles for Treatment of Topical Skin Infections: A Review, *In Chem. Bull*, 2023, vol.12, no.8, pp.4599-4620.

[3] Gunasheela S, v. Chandrakala, & S. Srinivasan. -Microsponge: A n adaptable topical drug delivery system, *World Journal of Advanced Research and Reviews*, 2022, vol.15, no.1, pp.396-411.

[4] Tiwari, A., Tiwari, V., Palaria, B., Kumar, M., & Kaushik, D. - microsponges: a breakthrough tool in pharmaceutical research, *Future Journal of Pharmaceutical Sciences*, 2022, vol.8, no.1, pp.1-25.

[5] Liu, Q. -Toward Application of Microsponges in Transdermal Drug Delivery System, *MOJ Bioequivalence & Bioavailability*, 2015, vol.1 no. I, pp.7-12.

[6] Vitthal, P., & Anuradha, S. -A review on microsponges drug delivery system, *International Journal of Research and Analytical Reviews*, 2020, vol.7, no.1, pp.961-974.

[7] Manpreet Kaur, Ritu Rani, Ajeet Pal Singh, Amar Pal Singh. -Microsponge: A review, *Journal of Drug delivery and therapeutics*, 2024, vol.14, no.6, pp.294-297.

[8] Jayasawal, P., Rao, N. G. R., & Jakhmola, V. -Microsponge as Novel Drug Delivery System: A Review, *Indo Global Journal of Pharmaceutical Sciences*, 2022, vol.12, pp.21-29.

[9] Sharma, S., Sharma, A., Kaur, C., Shaheed Baba, A., & Singh Jujhar, -A. Microsponges: as a topical drug delivery system, *International Journal of Pharmaceutical Sciences and Research IJPSR*, 2020, vol.11 no.2, pp.524-534.

[10] Abhishek Tiwari, Varsha Tiwari, et.al. -Microsponges: a breakthrough tool in pharmaceutical research, *Future journal of pharmaceutical sciences*, 2022, vol.8, pp.31.

[11] Sumbria R, Gupta NB, Bhandari N, Kumar A, Mahajan S. -Microsponges: topical preparation and its applications, *World J Pharm Pharm Sci,* 2017, vol.6, no.4, pp.629–642.

[12] Chandramouli Y, Shaik Firoz B, Yasmeen R, Vikram A, Mahitha AU. -Microsponges: a novel drug delivery system for controlled delivery of topical drugs, *International J Pharm Research Application*, 2012, vol.2, no.2, pp.79–86.

[13] Kircik LH. -The microsponge delivery system reduces facial oiliness and shine during acne therapy. *J Drugs Dermatol*, 2013, vol.12, no.11, pp.1268–1270.

[14] Pandit AP, Patel SA, Bhanushali VP, Kulkarni VS, Kakad VD. -Nebivol loaded microsponge gel for healing of diabetic wound, *AAPS Pharm SciTech*, 2016, vol.18, no.3, pp. 846–854. https:// doi. org/ 10. 1208/ s12249- 016- 0574-3

[15] Mantry S, Bagchi A, Das S. -Microsponge as a novel strategy of drug delivery system, *Universe J Pharm Research*, 2015, vol.1 no.1, pp. 32–38.

[16] Vishwakarma P, Choudhary R. -MDS: a novel strategy to control the delivery rate of active agents with reduced skin irritancy, *J Drug Delivery Ther*, 2019, vol.9, no.6-s, pp.238–247.

[17] Tile MK, Pawar AY. -MDS: a novel strategy for drug delivery, *Int J Pure Application Bioscience*, 2015, vol.3, no.1, pp.224–235.

[18] Pradhan SK. -MDS as the versatile tool for drug delivery system, *Int J Res Pharm*, 2011, vol.1, no.2, pp.243–258.

[19] Kar AK, Kar B, Parya H, Kundu S, Hirawat R. -A novel approach on microsponge:

multifunctional modern dosage form, *Int J Pharm Sci Rev Res*, 2018, vol.51, no.2, pp.64–72.

[20] Kaity S, Maiti S, Ghosh AK, Pal DK, Ghosh A, Banerjee S. -MDS: a novel strategy for drug delivery system, *J Adv Pharm Technol*, 2010, vol.1 no.3, pp.284–290.https:// doi. org/ 10. 4103/ 0110- 5558. 72416

[21] Shaha V, Jain H, Krishna J, Patel P. -Microsponge drug delivery: a review, *Int J Res Pharm Sci*, 2010, vol.1, no.2, pp.212–218.

[22] Mahant S, Kumar S, Nanda S, Rao R. -MDS for dermatological applications: perspectives and challenges, *Asian J Pharm Sci*, 2020, vol.15, no.3, pp.273–291. https:// doi. org/ 10. 1016/j. ajps. 2019. 05. 004

[23] Shrivastava S, Kumar D, Dubey CK, Singh SP, Khinchi MP. -A review: microsponge- an effective drug delivery system, *Asian J Pharm Res Dev*, 2017, vol.5, no.2, pp.1–8.

[24] Srivastava R, Pathak K. -Microsponges: a futuristic approach for oral drug delivery, *Expert Opin Drug Delivery*, 2015, vol.9, no.7, pp.863–878. https:// doi. org/ 10.1517/ 17425 247. 2012. 693072

[25] Kumari A, Jain A, Hurkat P, Tiwari A, Jain SK. -Eudragit S100 coated MDS for Colon targeting of prednisolone, *Drug Dev Ind Pharm*, 2018, vol.44, no.6, pp.902–913. https:// doi. org/ 10. 1080/ 03639 045. 2017. 14200 79

[26] Barde PM, Basarkar GD. -Formulation, development and *in vitro* evaluation of Terbinafine HCl microsponge gel, *Int J Pharm Sci Rev Res*, 2015, vol.32, pp.310–314.

[27] Osmani R, Aloorkar N, Thaware B, Kulkarni P, Moin A, Hani U. -Microsponge based drug delivery system for augmented gastroparesis therapy: formulation development and evaluation, *Asian J Pharm Science*, 2015, vol.10, pp.442–445. https:// doi. org/ 10. 1016/j. ajps. 2015. 06. 003

[28] Chen G, Sato T, Ohgushi H, Ushida T, Tateishi T, Tanaka J. -Culturing of skin fibroblasts in a thin PLGA-collagen hybrid mesh, *Biomaterials,* 2005, vol.26, pp.2559–2566.

[29] Kanematsu A, Marui A, Yamamoto S, Ozeki M, Hirano Y, Yamamoto M Et al. -Type I collagen can function as a reservoir of basic fibroblast growth factor, *J Control Release*, 2004, vol.94, pp.281–292.

[30] Iwai S, Sawa Y, Ichikawa H, Taketani S, Uchimura E, Chen G Et al. -Biodegradable polymer with collagen microsponge serves as a new bioengineered cardiovascular prosthesis, *J Thorac Cardiovasc Surg*, 2004, vol.1, no.28, pp.472–479.

[31] Hadi MA, Rao NG, Rao AS. -Formulation and evaluation of minitablets- filled-pulsincap delivery of lornoxicam in the chronotherapeutic treatment of rheumatoid arthritis, *Pak J Pharm Sci*, 2015, vol.28, no.1, pp.185–193.

[32] Pawar V, Salunkhe A. -A review on MDS drug delivery system, *Int J Res Anal Rev*, 2020, vol.7, no.1, pp.961–974.

[33] Jelvehgari M, Siahi-Shadbad MR, Azarmi S, Martin GP, Nokhodchi A. -The microsponge delivery system of benzoyl peroxide: preparation, characterization and release studies, *Int J Pharm*, 2006, vol.308, no.1–2, pp.124–132.https://doi. org/ 10. 1016/j. ijpha rm. 2005. 11. 001

[34] Amrutiya N, Bajaj A, Madan M. -Development of MDS for topical delivery of mupirocin, *AAPS Pharm SciTech*, 2009, vol.10, no.2, pp.402–409. https:// doi.org/ 10. 1208/ s12249- 009- 9220-7

[35] Tripathi PK, Gorain B, Choudhury H, Srivastava A, Kesharwani P. -Dendrimer entrapped microsponge gel of dithranol for effective topical treatment, *Heliyon,* 2019, vol.5, pp.01343. https:// doi. org/ 10. 1016/j. heliy on. 2019. e01343

[36] Yadav V, Jadhav P, Dombe S, Bodhe A, Salunkhe P. -Formulation and evaluation of microsponge gel for topical delivery of antifungal drug, *Int J Appl Pharm*, 2017, vol.9, no.4, pp.30. https:// doi. org/ 10. 22159/ ijap. 2017v 9i4.17760

[37] Gupta A, Tiwari G, Tiwari R, Srivastava R. Factorial designed 5-fluorouracil-loaded MDS and calcium pectinate beads plugged in hydroxypropyl methylcellulose capsules for colorectal cancer. Int J Pharm Investi.,2015; 5(4):234–246.

[38] Han S, Kim H, Lee JB. Library siRNA-generating RNA Nanosponges for gene silencing by complementary rolling circle transcription. Sci Rep. 2017; 7(1):1–7. https:// doi. org/ 10. 1038/ s41598- 017- 10219-y

[39] Kumari A, Jain A, Hurkat P, Tiwari A, Jain SK. -Eudragit S100 coated MDS for Colon targeting of prednisolone, *Drug Dev Ind Pharm*, 2018, vol.44, no.6, pp.902–913.

https:// doi. org/ 10. 1080/ 03639 045. 2017. 14200 79

[40] Grimes PE. -A microsponge formulation of hydroquinone 4% and retinol 0.15% in the treatment of melasma and post-inflammatory hyperpigmentation, *Cutis*, 2004, vol.74, pp.362–368.

[41] Garud ST, Tiwari K. -Microsponges: a novel approach, *Asian J Pharm Sci Tech*, 2018, vol.8, no.1, pp.1–9

[42] Patel N, Chaudhary S, Chaudhary A. -Formulation development and evaluation of apremilast Nanoemulsion, *Research Journal of Pharmacy and Technology*, 2023 Jun 1, vol.16, no.6, pp.2859-66.

[43] Valluru R, Ravi G, Bose SP, Damineni S. Microsponges- a comprehensive review: success and challenges, *Indo Am J Pharm Res*, 2019, vol.9, no.7, pp.3056–3067.