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Microsponges: An Innovative Instrument in Pharmaceutical Research

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Abstract

A microsponge delivery system is a novel and distinctive method of administering medications organizationally. The use of microsponge medication delivery enables efficient and prompt regulation of drug administration.

Microsponge delivery system consists of porous microspheres that vary in sphere size range (5 to 300 µm). These microspheres have a significant porous frame and a small spherical form. Microneedle drug delivery systems are typically used for drug administration via the skin, although they lately show potential for drug transfer through the mouth, eyes, and injection routes. Microsponge delivery systems can readily alter the pharmacological release pattern and enhance the stability of the formulation while simultaneously reducing the adverse effects of the medicine.

The primary objective of microsponge medication delivery is to achieve the greatest peak plasma concentration in the bloodstream. The most notable characteristic of Microsponge delivery systems is their inherent ability to self-sterilize.

In conclusion, the microsponge delivery system has been extensively studied and shown to have antiallergic, antimutagenic, and nonirritating properties. This study covers the formulation, criteria for medication inclusion in microsponge delivery systems, formulation techniques, evaluation parameters, and the function of microsponge delivery systems in treating different illnesses. This study will be valuable for examining the usage of microsponge delivery systems in various diseases.

الاسفنج المايكروي: أداة مبتكرة في البحوث الصيدلانية

مصطفى رعد عبد الباقي ، فرقان محمد عبدالاله

الخلاصة

المقدمة: يعد نظام توصيل الادوية باستخدام الاسفنج المايكروي طريقة جديدة ومميزة لإعطاء الأدوية بطريقة منتظمة. إن استخدام الاسفنج المايكروي لتوصيل الدواء يتيح التنظيم الفعال والسريع لإدارة الدواء.

يتكون نظام التوصيل الاسفنج المايكروي من كريات مجهرية مسامية تختلف في نطاق حجم الكرة (5 إلى 300 ميكرومتر). تحتوي هذه الكرات المجهرية على إطار مسامي كبير وشكل كروي صغير. تُستخدم أنظمة توصيل الدواء باستخدام الإبر الدقيقة عادةً لإعطاء الدواء عبر الجلد، على الرغم من أنها أظهرت مؤخرًا إمكانية نقل الدواء عبر الفم والعينين وطرق الحقن. يتمتع نظام التوصيل الاسفنج المايكروي بالقدرة على تغيير نمط الإطلاق الدوائي بسهولة وتعزيز استقرار التركيبة، مع تقليل الآثار الضارة للدواء في نفس الوقت.

الهدف الأساسي من توصيل الأدوية باستخدام الإسفنج المايكروي هو تحقيق أعلى تركيز في البلازما في مجرى الدم. الميزة الأكثر بروزًا لنظام التوصيل الاسفنج المايكروي هي قدرتها الكامنة على التعقيم الذاتي.

في الختام، تمت دراسة نظام توصيل الاسفنج المايكروي على نطاق واسع وأظهر أنه يتمتع بخصائص مضادة للحساسية ومضادة للطفرات وغير مهيجة. تغطي هذه الدراسة التركيبة، ومعايير إدراج الدواء في نظام توصيل الاسفنج المايكروي، وتقنيات التركيب، ومعايير التقييم، ووظيفة نظام توصيل الاسفنج المايكروي في علاج الأمراض المختلفة. ستكون هذه الدراسة ذات قيمة كبيرة في المستقبل لفحص استخدام نظام توصيل الاسفنج المايكروي في أمراض مختلفة.

1. Introduction

Medication delivery systems with precise control over release rates and targeted medication distribution to particular body areas significantly influence the healthcare system. Traditional formulations of topical medications target the superficial skin layers. Consequently, upon application, they discharge their active components and provide a concentrated amount of active drug ingredient that is promptly assimilated (Cheng et al., 2023). Nevertheless, they result in an extreme buildup of substances inside the outermost layer of the skin and the layer underneath it. Hence, it is necessary to possess a system that prolongs the active component's duration on the skin's surface or inside the epidermis.

Meanwhile, the system must reduce the permeation of active ingredients through the skin and into the body (Raina et al., 2023). A novel medication delivery method known as "Microsponge" was recently identified. The Microsponge Delivery System is a proprietary polymeric system composed of porous microspheres that are extensively cross-linked. These particles are tiny, spongy spheres containing many interconnected empty spaces inside a non-collapsible framework (Biharee et al., 2023). This expansive permeable surface regulates the rates at which the active substance is released. The diameter of microsponges ranges between 5 and 300 μm, and distinctive spheres with a diameter of 25 μm may include as many as 250,000 holes. This leads to a substantial reservoir filled with the active agent up to its maximum capacity. The substance can encapsulate various active substances, including emollients, perfumes, sunscreens, essential oils, and anti-fungal, anti-infective, and anti-inflammatory compounds. It is used as a carrier system for topical application (Wani et al., 2022).

The microsponge technology was developed by Won in 1987, and the earliest patents were granted to Advanced Polymer Systems, Inc. This Company created many versions of the technique and applied them to various cosmetic, over-the-counter (OTC), and prescription pharmaceutical products. Cardinal Health, Inc. has acquired a license to use this fascinating technology to develop topical therapies (Kumar and Kumar Kataria, 2022).

2. Advantages of Microsponges Compared to Other Formulations

Microsponges provide several benefits in contrast to alternative preparations now available on the market.

2.1.Advantages Compared to Traditional Formulations

Conventional formulations of topical drugs are specifically formulated to target the outermost layers of the skin. Upon application, these products release their active components. The product offers a high concentration of active ingredients that are rapidly assimilated. This leads to an excessive buildup of components in both the epidermis and the dermis (Supe and Takudage, 2021). Microsponges can prevent this from happening. The microsponge system has the potential to effectively reduce the adverse effects of drugs, such as irritation, without compromising their effectiveness. This is achieved by gradually releasing the active component to the skin, similar to the microsponge Benzoyl peroxide preparations that demonstrate high effectiveness with low irritation (Nora Zawar. Yousif and Zeina D Salman, 2023).

2.2.Advantages in Comparison to Liposomes and Microencapsulation

Microsponges offer superior features compared to other technologies, such as microencapsulation and liposomes. Controlling the rate of actives' release is often challenging with microcapsules. The encapsulated actives will be released upon the rupture of the microcapsule wall. Liposomes are characterized by their restricted capacity, challenging formulation, limited chemical stability, and susceptibility to microbial contamination (Antonijoan et al., 2007; Biharee et al., 2023).

2.3.Advantages in Comparison to Ointments

Patient adherence to ointment is diminished due to its visually unappealing, thick, and oily consistency. Ointments have limited efficacy as drug delivery methods, hence inducing irritation and sensitization due to the need for a large quantity of active drug ingredients for optimal therapeutic outcomes. Another disadvantage of topical preparations is the unpleasant smell, unregulated evaporation of the active component, and the possibility of medications being incompatible with the vehicles used. On the other hand, the microsponge system prolongs the duration in which an active ingredient remains either inside the epidermis or on the skin surface (Rahman et al., 2022).

3. The Benefits of the Microsponge Medication Delivery Method Can Be Summarized as Follows (Shailaja and Ashok, 2022; Tiwari et al., 2022)

1. It provides uninterrupted activity and sustained release for 12 hours.
2. Improves the overall functionality and effectiveness of the product.
3. Reduces discomfort and enhances patient adherence.
4. Enhances the product's elegance.
5. It can be integrated into many compositions.
6. Exhibits excellent thermal, physical, and chemical stability.
7. This substance does not cause irritation, mutations, toxicity, or allergies.
8. Permits the incorporation of immiscible substances.
9. Transforms liquids into solid particles to enhance the management of substances.
10. Enhances the absorption and availability of drugs.
11. Enhances therapeutic efficacy.
12. It can absorb skin secretions up to 6 times its weight without changing its outward appearance, reducing skin oiliness.

4. Required Characteristics for Microsponge Drug Delivery Systems

(Borawake et al., 2021; Choudhary and Akhtar, 2022)**:**

1. Exhibit a pH range of 1 to 11 with consistent stability.
2. Exhibit thermal stability up to 130°C.
3. These products possess self-sterilization capabilities due to their pore size of 0.25µm, which effectively blocks the entry of germs. Consequently, there is no need to add any preservatives to these products.
4. Possess a substantial loading capacity, often ranged 50% - 60%.
5. This product has excellent fluidity and is cost-effective.
6. Provide excellent compatibility with various vehicles and substances.

5. Properties of Materials Suitable for Encapsulation in Microsponges (Mandal et al., 2024; Yehia et al., 2022)

The microsponge technology allows for the encapsulation of active chemicals, enabling their incorporation into various products like powders, creams, lotions, gels, and soaps.

Material intended for entrapment in microsponges must meet certain conditions, including:

1. It should have low water miscibility or limited solubility.
2. It must exhibit inertness towards monomers.
3. The formulation mustn't increase mixture viscosity.
4. It must not induce the collapse of the spherical architecture of the microsponges.

5. The substance should have complete miscibility with the monomer. It should also have the ability to enhance its miscibility by adding a tiny quantity of an immiscible solvent, such as water.
6. Resistant to polymerization of catalysts and circumstances.
7. The materials confined in the vehicle must have limited solubility to prevent issues in cosmetic preparations. If solubility is not limited, the cars may absorb micro sponges before the application.
8. The optimization of microsponge capacity and polymer design is necessary to achieve the required release rate over a specific period.

6. Techniques for the Production of Microsponges

The microsponge drug delivery device may be manufactured using two methods. The procedure may be either a single-step liquid-liquid suspension polymerization or a two-step procedure of the quasi-emulsion solvent diffusion approach. The choice between the two methods depends on the medicine's physico-chemical characteristics that must be loaded.

6.1.Liquid-Liquid Suspension Polymerization

The microsponges are produced using a one-step process called liquid-liquid suspension polymerization, as illustrated in Fig.1. This approach involves dissolving the monomers, together with the active medication (which is non-polar), in a suitable solvent for the monomer. The resulting mixture is then dispersed in an aqueous phase with simultaneous agitation. To create a suspension, suspending agents and surfactants are introduced into the aqueous phase. The suspension is made by forming droplets of a specific size, which are then subjected to polymerization by adding a catalyst or raising the temperature. A polymerization-induced reservoir system that opens at the surface via pores. A non-reactive liquid that does not mix with water but mixes with the monomer is used to create a network of pores. Once polymerization is finished, the liquid is filtered from the microsponge and infused into a premade microsponge. Afterward, different active substances are incorporated into the microsponge, serving as topical application carriers. Solvents might be used to facilitate the prompt and effective incorporation of functional compounds. Two-step methods are employed, and polymerization is conducted using porogen, which the functional group replaces if the medicine is sensitive to polymerization (Jyoti and Kumar, 2018; Shukla and Niranjan, 2022).

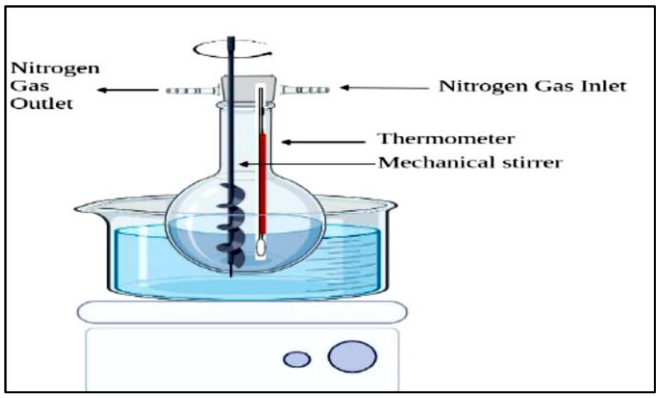

Figure 1: Liquid-Liquid Suspension Polymerization Method for Microsponge Preparation (Mantry Et Al., 2022)

6.2. Microsponges May be Formed Using a Quasi-Emulsion Solvent Diffusion Procedure Involving

Several polymers. Two stages are involved in this process: an inner phase and an exterior phase. Eudragit type RS 100, located within the inner phase, was liquified in ethyl alcohol. Then, the drug is incorporated into the solution and dissolved using ultrasonication at a temperature of 35°C. The PVA solution is combined with water in the outer phase. An inner phase was then transferred into the outer phase and stirred for 60 minutes. After the stirring operation, the solution was filtered to separate the microsponge. The microsponges are then dehydrated in a high-temperature oven at 40°C for 12 hours, after which their weight is determined as described in Fig.2. (Pokharel et al., 2023).

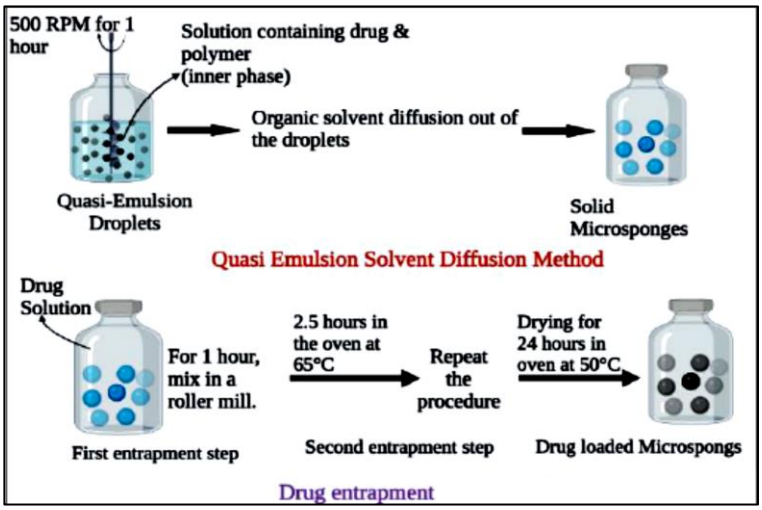

Figure 2: Quasi-Emulsion Solvent Diffusion Method for Microsponge Preparation (Wani et al., 2022)

7. Assessment of Microsponge

Particle size determination: the upper limit for the particle size of microsponge spheres is 30 µm, but the typical range falls between 10-25 µm. The particle size of the microsponge is determined using laser light diffraction or a similar technique, whether it is loaded or empty. Larger particles, measuring 30 µm in diameter, result in a gritty texture. Therefore, utilizing smaller particles, measuring 10-25 µm in diameter, in topical formulations is preferable.

1. Morphological examination of microsponges (Surface topography) to depict the microsponge's internal structure and scanning electron microscopy (SEM) may be used to examine a shattered microsponge particle.
2. The actual density of microsponges may be measured by using an ultra-pycnometer with helium gas and computing the mean of many observations.
3. Compatibility testing may be performed using several methods, including thin layer chromatography (TLC), powder X-ray diffraction (XRD), Fourier Transform infrared spectroscopy (FT-IR), and Differential Scanning Colorimetry (DSC).
4. The composition of the polymer and monomer in the microsponge may influence the drug's partition coefficient inside the microsponge system. Consequently, this directly impacts the rate at which the medicine is released from the carrier.

5. A porosity study may be conducted to analyze the pore structure and assess the dimensions of nanocavities formed in molecular dynamics simulations. A mercury intrusion porosimetry device may determine the pore structure, diameter, and volume.
6. The resiliency of microsponges may be analyzed and improved by examining how they release substances over time based on their cross-linking characteristics.
7. Evaluation of stability: the stability examinations comply with the standards established by the International Council of Harmonization (ICH).
8. Studies on dissolving were conducted in a controlled laboratory setting. The process of in vitro dissolution may be performed using the USP XXIII method. This involves using a dissolving assembly that contains 900 mL of saline phosphate buffer solution with a certain pH. The solution is heated to a temperature of 375 °C and spun at a predetermined rotation rate per minute.
9. Study of the release and deposition of drugs from microspheres. The Franz cell oriented with static diffusion is often used to facilitate the release of medication from the semisolid dosage form. This technique involves subjecting the outside layer of the skin, known as the epidermis, to a suitable temperature. In contrast, the inner layer of the skin, known as the dermis, is exposed to the receptor part of the solution, while the receptor compartment is filled with 20 mL buffer media. The buffer medium should be agitated at 600 rotations per minute and kept at 32 ±0.5 °C. Subsequently, the skin was immersed in the diffusion medium for 1 hour before the test sample was applied. A certain quantity of the sample is placed in the donor compartment. Diffusion cells evaluate the amount of medication applied externally and then analyze it at specific intervals. Afterward, the skin is meticulously detached, and the drug-affected region of the skin is purified with distilled water (Pethappachetty et al., 2022; Shirodkar and Pissurlenkar, 2022)[A1] [u2].

8. Applications of Microsponge

8.1.Microsponge Technology Has Applications in The Field of Cosmetics

Microsponge technology in oral cosmetics is particularly fascinating since it allows for the controlled release of volatile compounds, prolonging the sensation of freshness. Microsponges or volatile chemicals may be readily included in dental pastes or mouthwashes. Microsponge can prolong the lifespan of various colored cosmetic products, such as rouge or lipsticks, by capturing and retaining the color inside the microsponge. Microsponge facilitates the breakdown of homogeneity and enhances the coverage capacity. Therefore, the cosmetics created with microsponge will be gorgeous (Dutta et al., 2022).

8.2.Drug Delivery Systems Using Microsponges For Controlled Release

Microsponge delivery methods are being investigated because of the enhanced efficacy of medications, higher safety, and improved aesthetic appearance of formulae used in topical treatments, OTC pharmaceuticals, and personal care products. This delivery strategy is specifically developed to gradually release active moiety over a prolonged period, minimizing adverse effects while retaining therapeutic effectiveness. They have several applications. Primarily, it is used for topical applications, but it has also been lately exploited for administering drugs orally. It provides a formulator with many options for creating pharmaceutical or cosmetic products. These products are designed to effectively distribute the active ingredient with little dose, enhancing product stability, minimizing side effects, and adjusting medication release (Patil et al., 2022).

To provide treatments, the microsponge delivery method combines over-the-counter goods, such as various moisturizers, sunscreens, and particular rejuvenating things. Microsponge, as a delivery tool, can be used for topical administration in three different manners in items that are now being developed or are already available in social pharmacies:

1. The reservoir of the microsponge sphere releases active moieties over an extended period.
2. To serve as a receptacle for absorbing undesirable substances, such as surplus skin oils.

3. Microsponge spheres are enclosed containers that effectively isolate the components from direct contact with the skin, allowing them to operate on the surface.

Microporous drug delivery systems are used for topical application and recreational administration of bioactive substances. Microsponge aims to optimize medication delivery by minimizing the required dosage, enhancing product stability, minimizing side effects, and modifying drug release (Khattab and Nattouf, 2022).

8.3.Utilization of Microsponge for Transdermal Administration

Traditional topical medication formulations are believed to affect the superficial layers of the skin primarily. When applied to the skin, these conventional products release their pharmacologically active medication, forming a highly concentrated film of pharmacologically active drug that is quickly absorbed. To prevent the accumulation of excessive active components within the epidermis and dermis layers of skin, it is possible to use a microsponge drug delivery tool to package the medication. Microsponge technology may significantly reduce medication irritation while still preserving its efficacy. The porous structured microsponge can also be formulated into various topical dosage forms, including gels, creams, lotions, and ointments (Patole et al., 2023).

8.4.Oral Drug Delivery Using Microsponges

Although the oral route offers convenience and security, it is not universally acceptable for all delivered medications. This includes medications with a brief half-life that is rapidly excreted from the body, medicines metabolized by the acidic conditions of the stomach or bile produced in the intestine, or medications that need delivery to the colon to treat certain medical disorders (Sen et al., 2023). Consequently, this resulted in the development of methods for controlling the dispensation of the drug. Microsponges were created as pharmaceuticals, providing notable advantages compared to other delivery methods, such as nanoparticles, microspheres, and liposomes. Microsponges possess a porous configuration that enables effective colon targeting in conjunction with their extended delay period. This is accomplished by protecting the medicine from the acidic environment of the stomach, and the release of bile in the small intestine, and the drug is only released when the pH level in the colon is attained (Gade et al., 2022; Sammour et al., 2023).

8.5.Ocular Microsponge Drug Delivery

Pharmaceuticals that dissolve in water may be used as ointments or suspensions applied directly to the skin. On the other hand, drugs that do not dissolve in water can also be used externally as ointments or suspensions in water. Pharmacokinetics pertains to the complex mechanism via which drugs are absorbed and distributed throughout the eye. Subsequently, the medicine is transported into the front part of the eye by crossing the barrier between the blood and the fluid in the eye. The medicine is conveyed from the anterior segment of the eye to the Schlemm's canal and trabecular meshwork, where the replenishment of the intraocular fluid eliminates it. The medicine is eliminated from the aqueous humor and enters the systemic circulation by crossing the blood-aqueous barrier. Ultimately, a pharmaceutical component circulating in the body traverses the blood-retina barrier and arrives in the eye's posterior chamber (Dhyani and Kumar, 2022).

8.6.Cutaneous Administration of Medication Via Microsponge

The microsponge medicine delivery technology functions as a foundation for many topical formulations. The microsponge consists of polymers that can bind or retain a substantial quantity of medicine. This is attributed to its porous structure, with a pore count of around 250,000 pores per milliliter/gram. This leads to its superior capacity to transport drugs compared to alternative drug delivery systems, particularly in topical formulations, since it prolongs the duration of drug presence in the dermis or epidermis region. This facilitates reducing its lengthy use, frequency, absorption into the bloodstream, and its adverse effects on the skin, such as eczema, hypersensitivity, and rash. An alternative method to mitigate these adverse reactions is using a suitable, physiologically inert polymer that eludes recognition by the body as an external entity. The polymers

must possess non-irritation, non-mutagenicity, non-allergenicity, and non-toxicity (Dhyani and Kumar, 2024).

8.7.Microsponge Is Used in The Field of Tissue and Bone Engineering.

The admixture of liquid methyl methacrylate monomer, polymethyl methacrylate powder, tricalcium phosphate grains, and calcium-deficient hydroxyapatite powders in water led to the creation of bone-like substances that closely resembled natural bone. The final composites displayed holes and had a resemblance to microsponges. Upon the breakdown of the collagen sponge sheet, the essential fibroblast growth factor (bFGF) was released into the subcutaneous tissue of the mouse animal (Ma et al., 2022). The bFGF exhibited localized angiogenic activity in a manner that was dependent on the dosage. Collagen microsponges containing bFGF were injected into a blood-deprived animal's hind leg. This resulted in a substantial augmentation in blood circulation, a feat that could not have been accomplished by administering the bFGF bolus. The findings illustrate the importance of using type I collagen as a source of bFGF. A novel biodegradable graft material, including collagen microsponges, has been created for cardiovascular tissue grafting, aiming to enhance tissue regeneration. A novel patch, consisting of a biodegradable polymer and collagen microsponge, has been made to mend the circulatory system. This patch can function as an innovative surgical material (Bhattacharjee et al., 2014).

9. Factors Must Be Taken into Account While Formulating A Microsponge Product

(Bhattacharjee et al., 2014; Jayasawal et al., 2022; Zhang et al., 2021)

1. The microsponge drug delivery system can dispense medications in many forms, such as lotions, creams, soaps, and powders. Several factors are considered to get the desired product characteristics throughout the vehicle development process. The solubility of the active substances in the vehicle should be reduced to a minimum. Failure to meet this requirement will decrease the vehicle's microsponge drug delivery activity and reduce cosmetic problems; the automobile should not include more than 10-12% w/w of microsponge medicine delivery system. The polymer designs and payloads for the active microsponge system must be adjusted to achieve the desired release rate throughout the defined duration. When constructing vehicles for a given use, it is essential to consider certain factors to achieve the desired product features.
2. To prevent cosmetic problems, the amount of powder loaded into the automobile must be enough but not exceed 10-12%. To preserve the integrity of the polymer, limiting the solubility of the active ingredient in the vehicle is necessary, thereby preventing the skin from degrading before delivery. To achieve the desired gradual release of the active component within the specified timeframe, it is essential to accurately determine the polymer composition and loading quantities.

10. Factors Related to Ensuring Safety

Microsponge systems comprise commonly used polymers containing minimal amounts of prominent monomers. Furthermore, their cross-linking makes them biologically inactive since the body cannot break them down or replicate them into other molecules.

These macroscopic particles are of significant size and may penetrate the outermost layer of the skin due to their dimensions. They are located under the epidermis and release their substance gradually over time. This release pattern helps reduce the buildup of active substances on the skin's surface, which may improve the safety of topical treatments (Aguero et al., 2021; Gusai et al., 2021).

11. Recent Developments in Microsponge Formulation

Technological advancements have been achieved by modifying procedures used to produce nanosponges and porous micro pellets. An example is the manufacturing of nanosponges using Cyclodextrin (CD) to deliver

drugs. These sophisticated drug delivery systems are used for administering several medications, including flurbiprofen, dexamethasone, doxorubicin hydrochloride, and itraconazole (Ghourab et al., 2020; Kaur et al., 2015). The β-CD molecule is cross-linked by a reaction with biphenyl carbonate, creating nanosponges as a sophisticated formulation. Scientists have noted that including a cytotoxic component in the formulation as a carrier, system may enhance the effectiveness of the medicine. Cancer targeting and gas delivery systems were also approaches that can be utilized using microsponge (Jain et al., 2020).

The latest advancement in the field focuses on the creation and laboratory analysis of betamethasone microsponges incorporated into a gel for topical applications to reduce inflammation. The use of the Quasi-emulsion technique achieves this. A recent study has developed a microsponge formulation that contains controlled-release risperidone, which is used for treating schizophrenia and schizoaffective disorders (Rahman et al., 2022).

Microsponges were effectively synthesized using the quasi-emulsion solvent diffusion technique, employing Eudragit Rs 100 and PVA with distilled water and the liquid-liquid suspension polymerization method. These substances possess the capacity for increased stability, better ability to be formulated in various ways, and decreased occurrence of adverse reactions while preserving their effectiveness in treating medical conditions (Choudhary and Akhtar, 2022; Jayasawal et al., 2022; Wani et al., 2022).

12. Conclusive Results

The market for microsponge technology has great potential due to the need for innovative and highly effective medicinal and cosmetic products. The microsponge delivery technology has excellent potential for the accurate and controlled release of an encapsulated active chemical. This approach has the advantage of reducing the adverse effects of pharmaceuticals while ensuring treatment effectiveness. Furthermore, it demonstrated significant improvements in the stability of the formulation, as well as an increase in the refinement and flexibility of the formulation. Multiple investigations have shown they are also considered harmless, non-allergenic, and non-mutagenic. This drug delivery method is primarily used in over-the-counter (OTC) skincare products, prescription drugs, cosmetics, and sunscreens. Owing to its multiple applications in pharmaceutical administration, this technology demonstrates tremendous promise and is projected to undergo intense attention in the following years via many research programs.

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