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(REVIEW ARTICLE)

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Unveiling the potential of microsponges: Enhancing oral bioavailability

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Abstract

Oral medication administration is widely recognized as the most practical and widely used method. Medications with a short half-life and easy absorption in the gastrointestinal tract are quickly removed by the bloodstream. To avoid these issues, oral controlled-release formulations have been created. There are a ton of novel formulation approaches in the realm of medication delivery systems. One new novel approach that is becoming increasingly well-liked these days is the usage of microsponges. A wide variety of active chemicals can be entrapped by the highly cross-linked, porous, polymeric structure that makes up the Microsponges Delivery System (MDS). Various polymers like ethyl cellulose, polystyrene, etc., have been utilized in forming microsponges and these active microsponges can be incorporated into formulations, such as capsules, gel, and powders, and have a broad package of benefits. The microsponges have satisfactory stability over pH values ranging from 1 to 11, they exhibit reasonable stability at temperatures as high as 130, and entrapment efficiency is great, reaching 50–60%. The preparation of microsponges involves the Quasi-emulsion solvent method, and the emulsion solvent diffusion method the release of drug through microsponges increases with increasing drug-polymer ratio and lowering polymer wall thickness. The microsponges are characterized for visual characterization, zeta potential, entrapment efficiency, and drug content. This review is focused on their advantages over other dosage forms, methods of preparation, characterization, and application of microsponges.

Keywords: Microsponges; Oral drug delivery system; Bioavailability; Polymer

1. Introduction

Microsponges are porous, non-collapsible, highly cross-linked polymeric microspheres microsponges with a particle size range of 5 to 300 µm. They can absorb a broad variety of active substances and release them gradually. Microsponges' sponge-like texture gives them special dissolving and compression characteristics. They have little negative effects and increase patient compliance. They are also very stable, non-toxic, non-allergic, non-mutagenic, and extremely effective. Microsponges made of a variety of polymers, including PHEMA, ethyl cellulose, polystyrene, and Eudragit RS100, have been used. Moreover, these active microsponges offer a wide range of advantages and can be added to formulations including capsules, gel, and powders. Microsponges have shown promise in the fields of cosmetics and pharmaceuticals. Examples of their applications include antifungal vaginal gel, enhanced arthritis therapy, burn wound treatment using silver sulfadiazine-loaded microsponge gel, gastro retentive delivery, matrix tablets, and colon-specific drug delivery systems[1].

Patented polymeric delivery systems called microsponges are made of porous microspheres that can hold a variety of active substances, including sunscreens, emollients, perfumes, essential oils, and anti-infective, anti-fungal, and anti-inflammatory compounds. Each microsphere has a huge porous surface area and is made up of numerous interconnected voids within a non-collapsible structure, much like a real sponge. Won invented the microsponge technique in 1987, and Advanced Polymer Systems was given the original patents.

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Currently, Cardinal Health, Inc. holds a license to utilize this intriguing technology for topical products. Depending on the level of smoothness or after-feel needed for the final recipe, the microsponges' diameter can range from 5 to 300 μm. A typical 25 μm sphere can have up to 250000 holes and an internal pore structure similar to 10 feet in length, meaning that even though the microsponge size may vary, the total pore volume will be approximately 1 ml/g. As a result, each microsponge develops a sizable reservoir that can hold up to its own weight's worth of active agent. These microsponge materials are made safer by the fact that the microsponge particles themselves are too big to penetrate the skin. The possibility of bacterial contamination of the materials trapped in the microsponge is another issue related to safety. Because the pore width is smaller, bacteria with a size range of 0.007 to 0.2 μm cannot enter the microsponges' tunnel structure[2].

2. Structure of microsponges

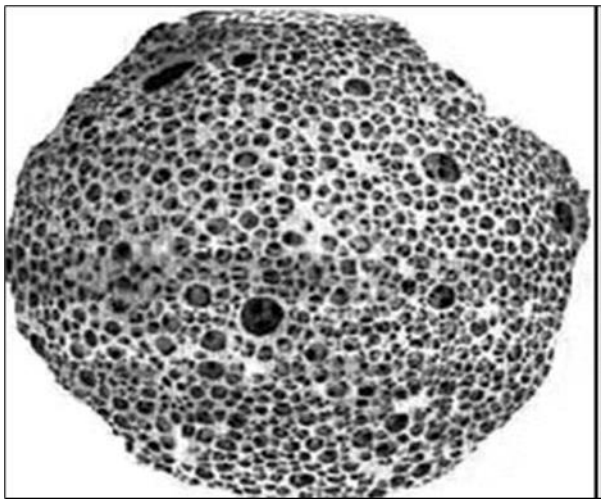

Figure 1 Highly porous structure of microsponges

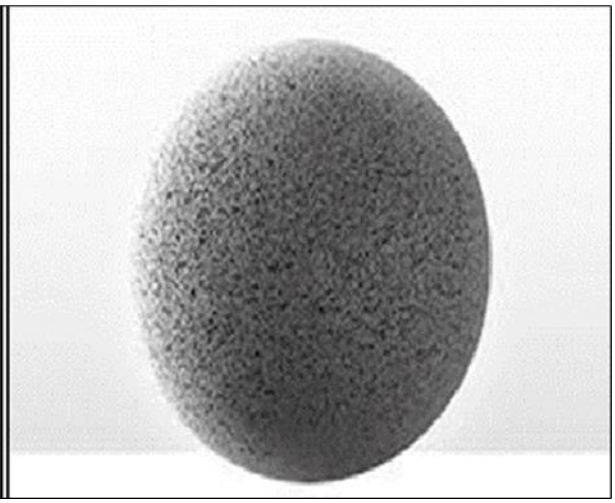

Figure 2 Structure of microsponges

Due to benefits like patient choice, cost-effectiveness, ease of large-scale manufacturing of oral dosage forms, and comfort of drug administration via the oral route, oral medication is the most often used method of drug administration. Approximately 60% of well-known small-molecule pharmaceutical drugs that are sold commercially are taken orally. According to current estimates, oral formulations account for approximately 90% of all pharmaceutical formulations sold worldwide that are meant for human consumption. Approximately 84% of the most popular pharmaceutical drugs are taken orally, and their current market worth is $35 billion, growing at a rate of 10% each year.

Patients are generally more compliant with oral formulations than with other parenteral routes like injections—intravenous, subcutaneous, and intramuscular—and with inhaling asthma medication. Moreover, medications taken orally have the ability to target specific GI tract regions for the localized treatment of pathological conditions like colorectal and stomach cancers, infections, inflammations, bowel diseases, gastro-duodenal ulcers, and gastroesophageal reflux disorders[3].

A medication can be given in a variety of ways to provide a systemic pharmacological effect. The most popular way to administer drugs is orally when the medication is eaten and mainly passes through the small intestine's barrier to enter the systemic circulation. Oral drug delivery is the most

essential route for achieving systemic effects from drug administration. It's likely that oral administration accounts for at least 90% of all medications used to cause systemic effects[4].

2.1. Advantages of microsponges over other technologies and delivery systems

- Microsponges provide more control over drug release. Generally, microspheres are unable to regulate the rate at which the active pharmaceutical ingredients (API) are released. The API inside the microsphere will be revealed as soon as the wall breaks.
- When compared to liposomes, microsponges have improved chemical stability, a larger payload, and a simpler formulation.

- Unlike ointments, microsponges can absorb skin secretions, which lessens the skin's shine and greasefulness. Because ointments are sometimes greasy, sticky, and unsightly, patients may not comply with their recommended course of treatment[5].

2.2. Advantages of microsponges delivery system

- Up to six times the weight of oil can be absorbed by microsponges without drying up.
- It offers extended release, or continuous activity for up to 12 hours.
- A more elegant product.
- Decrease irritability and increase tolerance, which improves patient compliance.
- Additionally, it can increase therapy efficacy.
- Their physical, chemical, and thermal stability is superior.
- They are non-toxic, non-allergenic, non-mutagenic, and non-irritating.
- The integration of immiscible items is permitted by MDS.
- Their formulation flexibility is superior.
- The ability to transform liquids into powders enhances the handling of materials.
- It is adaptable enough to create new product shapes.
- MDS can increase a drug's bioavailability6.

2.3. Characteristics of microsponges

- Formulations are stable within the pH range of 1 to 11.
- Formulations for microsponges remain stable up to 130°C in temperature.
- The majority of vehicles and components are suitable for microsponge compositions.
- Because microsponge formulations have an average hole size of 0.25µm, which is too small for bacteria to pass through, they are self-sterilizing.
- Microsponge compositions can be economical and have a greater payload (50–60%) while remaining free-flowing7.

2.4. Composition of microsponges

The micro-sized particles can entrap liquid or dissolvable substances. The following conditions must be met for materials to become entangled inside microsponges: the API components must have limited solubility in the vehicle. Its water-immiscibility must be restricted. To achieve the desired release rate for a given amount of time, the microsponges' design and polymer loading must be enhanced. It must be impervious to a variety of polymerization conditions and catalysts**.**

2.4.1. Polymers Used in the Microsponge Delivery System

Eudragit RS 100, Eudragit RL 100, ethyl cellulose, Carbopol 934, and polystyrene acrylic polymer are among the polymers used to make microsponges. 38, 60. Researchers have been examining Eudragit RS-100 polymer for usage in a wide range of applications due to its versatility. Eudragit RS PO not only made the medication more soluble, but it also created a solid dispersion-like structure that enabled regulated drug release. The effectiveness of polylactic acid and polylactide-co-glycolic acid in moving proteins and peptides has been studied. Floating microsponge can be made with polymers such as Eudragit RS-100, polylactide-co-glycolic acid, and Eudragit RS PO. This is because the hydrophobic nature of these polymers keeps the particles from getting wet in watery environments. To support the structural stability of the microsponge, some microsponge formulations further incorporated a plasticizer, such as triethyl citrate, for the polymers and active moiety[8].

2.5. Method of Preparation

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 addition of porogen method, electro-hydrodynamic atomization method, and ultrasound-assisted production method are some of the techniques used to develop microsponge-based drug delivery systems[9].

2.5.1. Liquid-liquid suspension polymerization method:

Liquid suspension polymerization is used to create the microsponges in a single process. This process involves dissolving the monomers in a suitable solvent together with the active medication (non-polar), which then disperses in

the aqueous phase with agitation. To aid in the production of suspension, surfactants and suspending agents are introduced in this aqueous phase. A catalyst is added to the suspension or the temperature is raised to initiate polymerization once the suspension forms with characteristic droplets of the preferred size. a reservoir-style system that, as a result of polymerization, opens at the surface through pores. To create the pore network, an inert liquid that is miscible with monomer and immiscible with water is utilized. The liquid is taken out of the microsponge once the polymerization process is finished, infused into the premade microsponges, and then filled with different active substances that serve as topical carriers. The solvent can be used to insert functional compounds more quickly and efficiently. When a medication is amenable to polymerization, a functional group can take the place of the porogen employed in the two-step process that performs polymerization[10].

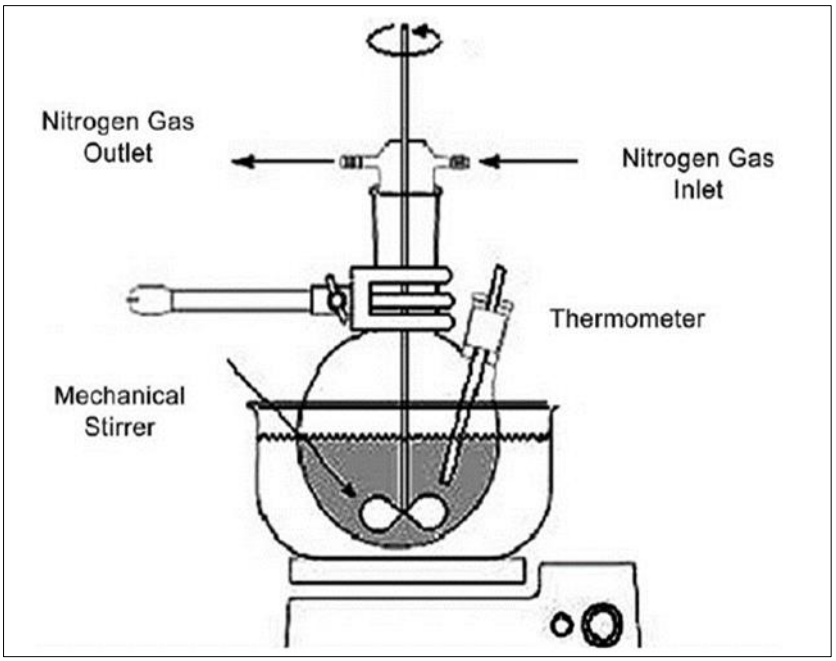

Figure 3 Liquid-liquid suspension polymerization method

2.5.2. Quasi-emulsion solvent diffusion method

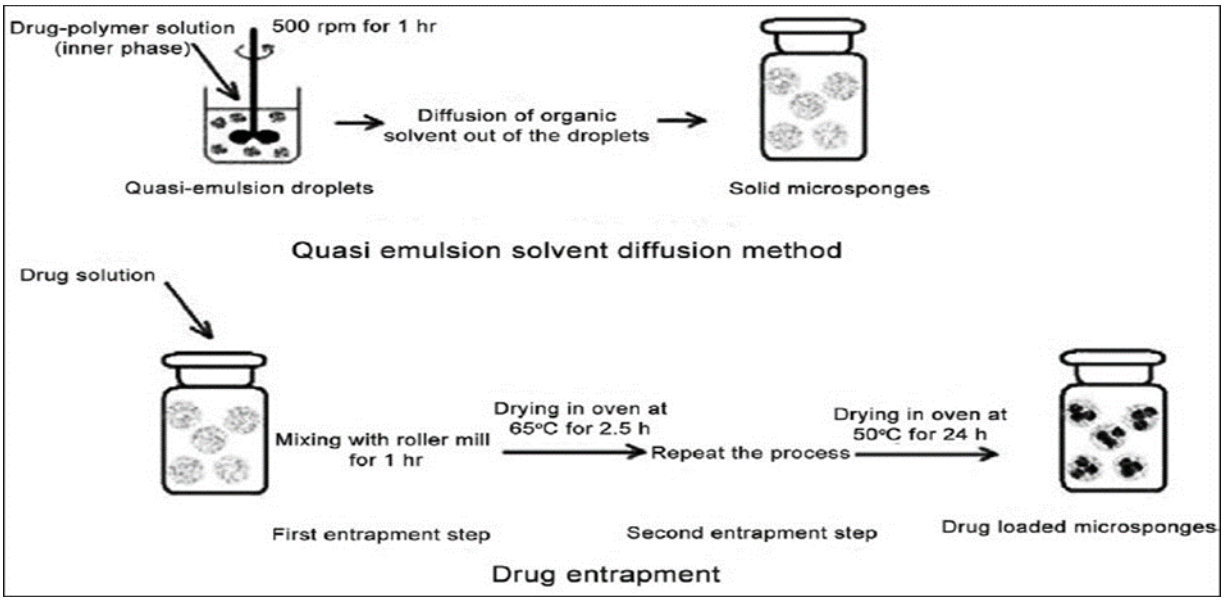

Figure 4 Quasi emulsion solvent method

The Quasi-emulsion solvent diffusion approach that is used in this two-step process allows the creation of microsponges with varying amounts of polymer. Eudragit RS 100 was dissolved in ethyl alcohol to prepare the inner phase. The medication can then be added to the solution and dissolved at 35°C using ultrasonication. The PVA solution in water (outer phase) was filled with the inner phase. After stirring for 60 minutes, the mixture is filtered to remove the micro sponges. To calculate the production yield (PY), the microsponges are dried for 12 hours at 40°C in an air-heated oven and then weighed[11].

2.5.3. Water in oil in water (w/o/w) emulsion solvent diffusion

The purpose of this innovative method is to create biodegradable porous microspheres. Using this technique, an organic polymeric solution was mixed with an internal aqueous phase that contained an emulsifying agent such as span, polyethyleneimine, or stearyl amine. To create a double emulsion, this water-in-oil emulsion was then again dispersed in an external aqueous phase containing PVA. The benefit of this approach is that it can capture medications that are either

water-soluble or water-insoluble. Moreover, thermolabile molecules like proteins can be entrapped using it. Additionally, xanthan gum was described by some authors as an emulsifier to stabilize the internal w/o emulsion.

2.5.4. Oil in oil emulsion solvent diffusion

Unlike the w/o/w approach, the oil in oil (o/o) emulsion was made with an internal phase of volatile organic liquid that was continuously stirred and allowed to progressively evaporate at a regulated rate. According to reports, the method employed a mixture of fixed oil (corn or mineral) and dichloromethane containing span 85 as the exterior phase, polylactide glycolic acid as the polymer, and dichloromethane as the internal phase solvent. To create the microsponges, the internal phase was continuously stirred and added drop by drop to the dispersion medium. This method was used to create Eudragit RS-100 microsponges loaded with hydroxyzine HCl, with liquid paraffin serving as the continuous medium and acetone serving as the dispersion solvent. The physicochemical characteristics of the organic solvent and external phase determine which one to use[12].

2.5.5. Lyophilization method

The gelation procedure was utilized to create porous microspheres, which were then transformed into microspheres using lyophilization. According to this protocol, the microspheres were lyophilized after being incubated in a chitosan hydrochloride solution. The rapid elimination of the solvent caused the microsponges to become porous. The swift and speedy solvent removal of this approach has the drawback of producing broken or shrunken microsponges[13].

2.5.6. Addition of porogen method

This method substituted a porogen-like hydrogen peroxide or sodium bicarbonate for the internal aqueous phase of the water in oil in water (w/o/w) emulsion. For this, the porogen was re-dispersed in an aqueous phase containing PVA after being dispersed in the polymeric solution to create a homogenous dispersion system. The w/o/w emulsion was then mixed with an initiator and the organic solvent was allowed to evaporate such that the microparticles were left behind. When hydrogen peroxide was added, pores with widths ranging from 5 to 20 μm were formed, distributed uniformly, and linked[14].

2.5.7. Electrohydrodynamic atomization method

In 2009, Pancholi et al. used this technique to create chitosan porous microspheres. After sonicating chitosan solution to produce bubbles, the resulting bubble suspension was withdrawn into a syringe, pumped through a steel capillary with a syringe pump, and then electrohydrodynamic atomization was applied. The capillary's diameter was selected to hold all of the suspension's bubbles as it passed through. The concentration of chitosan in the solution is the only factor that determines the voltage utilized in the studies. Every time the flow rate and applied voltage were combined, the steady cone-jet mode was produced, except in the cases where the maximum concentration was employed and it was challenging to electrospray. By using an aqueous solution containing 4% w/v sodium hydroxide, the chitosan microspheres were crosslinked[15].

3. Characterization of microsponges

- Determining particle size
- Morphology and Surface topography

- Compatibility studies
- Characterization of pore structure
- Resiliency
- Drug release kinetics
- Loading efficiency and production yield
- Stability studies

3.1. Determining the particle size

Particle size analysis of loaded and unloaded microsponges can be carried out using any appropriate technique, such as laser light diffractometry. For any formulation, the values can be stated as a mean size range. To investigate the impact of particle size on drug release, the cumulative percentage of drug released from microsponges with varying particle sizes will be plotted versus time. Particles smaller than 30μm are suggested for inclusion in the final formulation because bigger particles can provide a gritty texture**.**

3.2. Morphology and surface topography of microsponges

Prepared microsponges can be coated with gold–palladium for surface topography and morphology at room temperature in an argon environment. Scanning electron microscopy (SEM) can then be used to examine the microsponges' surface morphology. An image of a broken microsponge particle's ultrastructure can also be obtained using SEM[16].

3.3. Compatibility studies

Fourier Transform Infrared Spectroscopy (FT-IR) and thin-layer chromatography (TLC) can be used to examine a drug's compatibility with reaction adjuncts. Using differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD), one can examine how polymerization affects the drug's crystallinity (DSC). About 5 mg of samples can be precisely weighed into aluminum pans, sealed, and heated at a rate of 15 °C per minute throughout a temperature range of 25 to 430 °C in a nitrogen atmosphere for DSC[17].

3.4. Characterization of pore structure

The diameter and volume of pores play a crucial role in regulating the duration and potency of the active substance. The migration of Microsponges' active components into the medium in which they are disseminated is also influenced by pore diameter. To investigate the relationship between the pore diameter and volume and the rate of drug release from microsponges, mercury intrusion porosimetry can be utilized.

Microsponges' porosity parameters include intrusion-extrusion isotherms. Mercury intrusion porosimetry can be used to measure the pore size distribution, total pore surface area, average pore diameters, shape and morphology of the pores, bulk, and apparent density. The plotting of incremental incursion volume scan against pore diameters, which indicated pore size distributions, was done. The Washburn equation can be used to determine the pore diameter of microsponges.

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

Where D is the pore diameter (μm); γ the surface tension of mercury (485 dyn cm−1); θ is the contact angle (130); and P is the pressure (psi)[18].

3.5. Resiliency

The viscoelastic characteristics, or resilience, of microsponges, can be adjusted to yield beadlets with varying firmness or softness based on the requirements of the final formulation. The rate of release is typically slowed down by increased cross-linking.

3.6. Drug release kinetics

The kinetics of drug release from prepared microsponges were assessed using the dissolution profiles of each formulation subjected to a variety of models, including Higuchi (percentage drug released against the square root of time), Korsemeyer-Peppas (log percent drug released against the log of time), Zero order kinetics (percentage drug release against time), and First-order kinetics (log percentage drug unreleased against time)[19].

3.7. Loading efficiency and production yield

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

$$\text{Loading efficiency} = \frac{\text{Actual drug content in microsponges}}{\text{Theoritical drug content}} \times 100$$

The production yield of the microsponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained.

$$\text{Production yeild} = \frac{\text{partical mass of microsponges}}{\text{Theoritical mass (polymer + drug)}} \times 100$$

3.8. Stability studies

The stability of a given formulation to stay within its physical, chemical, microbiological, therapeutic, and toxicological parameters in a certain container or closure system is the technical definition of stability in the pharmaceutical industry. A product's capacity to maintain its physical, chemical, microbiological, therapeutic, and toxicological specifications within a certain container is known as its durability. Since it is the main obstacle to the creation of commercial preparations, the stability of the microsponge gel formulation during storage is extremely concerning.

A stability test was conducted on the developed formulation while it was stored at 4 ± 1ºC, 25 ± 2ºC, and 37 ± 5ºC with a relative humidity of 75%. Following a month, they were assessed for appearance, pH, drug content analysis, drug release profiles, rheological properties, and other factors throughout three months [20].

4. Applications of microsponges

Microsponges are thought to improve stability, reduce adverse effects, and change medication release in addition to effectively delivering a pharmaceutically active component at the lowest possible dose. Numerous moisturizers, certain rejuvenation products, and sunscreen are among the over-the-counter items that use a microsponge medication delivery method.

4.1. Microsponges for Oral delivery

The microsponge device, when used orally, has been demonstrated to accelerate the solubilization of medications that are poorly soluble in water by trapping the pharmaceuticals inside its pores. Because of the extremely small pores, the medication is effectively reduced to minute particles, and the notable increase in surface area accelerates the solubilization process. A commercial Micro sponge 5640 system was used to administer flurbiprofen in a regulated, colon-specific manner. Due to the presence of the enzyme, in vitro experiments showed that compression-coated colon-specific tablet formulations began to release the medicine during the eighth hour, which corresponds to the proximal colon arrival time. when the enzyme was added, resulting in a changed release pattern, but the drug release from the formulations produced specifically for colons that were made by pore-plugging the microsponges increased at the eighth hour[21].

2. Microsponge for Topical delivery

In both cosmetics and the management of dermatological conditions, topical agents are indispensable. However, they are linked to significant skin irritation, particularly in sensitive individuals. This irritation has been linked to the topical treatments' active components' quick release and subsequent buildup. controlled release of the active ingredients onto the skin is made possible by microsponge delivery technology. Several microsphere-based topical agents, such as benzoyl peroxide, tretinoic acid, HQ plus retinol, and 5-FU, are currently marketed in the United States and have been evaluated for safety and efficacy for cosmetic purposes as well as in the treatment of dermatological disorders. These formulations have demonstrated little to no irritancy in patients with acne, photodamaged skin, hyperpigmentation, or AK without sacrificing the agents' efficacy[22].

4.2. Microsponges for Bone and Tissue Engineering

Pre-polymerized polymethyl methacrylate powders and liquid methyl methacrylate monomers were combined with two aqueous dispersions of tricalcium phosphate grains and powdered calcium hydroxyapatite to create the compounds. The completed composites looked porous and functioned like tiny sponges.

4.3. Microsponges for biopharmaceuticals delivery

In tissue engineering as well as biopharmaceutical delivery, the microsponge delivery system (MDS) is utilized[23].

4.4. Microsponge technology in cosmetics

Oral cosmetics can benefit from the innovative application of microsponge technology, which prolongs the length of the "fresh feel" by prolonging the release of volatile compounds. Such evaporative materials are simply incorporated as MDS into dental pastes or mouthwashes. By trapping the color in the microsponge, MDS can be used to prolong the life of a variety of colored cosmetic products, such as rouge or lipsticks. MDS increases the covering power and helps to break up homogeneity. As a result, the vibrant cosmetics created with MDS will be quite exquisite.

4.5. Microsponge delivery systems for drug triggering

Microsponge delivery methods are being investigated because of the higher efficacy of medications when formed as microsponge, enhanced safety, and better aesthetic appearance of formulations used for topical treatments, over-the-counter pharmaceuticals, and personal care goods. This delivery strategy may potentially minimize side effects while preserving therapeutic efficacy by allowing the active moiety to be released gradually over time.

They are useful for many different things. Although it is mostly used for topical treatments, it has lately been used for oral medication administration. It provides a formulator with numerous options for creating pharmaceutical or cosmetic products. They are designed to improve product stability, lessen side effects, alter drug release, and distribute the active moiety efficiently with the least amount of dosage.

The microsponge delivery method with over-the-counter products includes treatments including various moisturizers, sunscreens, and specific revitalization solutions. Three methods are employed in products that are being developed or marketed for topical delivery using the microsponge system:

The MDS reservoir releases the active moieties over an extended length of time.

As a place where undesirable materials, such as extra skin oil, can be absorbed.

MDS are closed containers designed to keep ingredients away from the skin while they function on the epidermis[24].

4.6. Microsponges for anti-acne drugs:

One prevalent skin condition among young adults may be acne. Although topical medication is the primary method of treating it, the effectiveness and patient compliance of different topical antiacne bioactive molecules is impacted by adverse effects. To improve topical treatment for inflammatory diseases, some potentially innovative carriers and delivery methods, such as liposome microemulsions, solid lipid nanoparticles, and nano lipid carriers, are being investigated. Microsponges are now being developed as a cutting-edge drug delivery technology, prepared to maximize the therapeutic action profile of anti-inflammatory disease medicines. Because benzoyl peroxide (BPO) has bactericidal activity against Propionibacterium acnes, it is the first topical drug used to treat skin problems. Another medication of choice for treating acne is erythromycin, which works by lowering the skin's concentration of Propionibacterium acnes. However, the medication is unquestionably inactivated in the stomach environment and causes nausea, vomiting, and abdominal discomfort in addition to causing gastric irritation[25].

4.7. Microsponge in cardiovascular engineering

The process of creating a biodegradable material with autologous cell seeding is intricate, invasive, and fraught with infection risk. A biodegradable graft material with collagen microsponges that would allow autologous vascular tissue to regenerate has been developed as a solution to these issues. This substance was examined both with and without pre-cellularization to see if it may speed up in situ cellularization using autologous endothelium and smooth muscle cells. To create a vascular patch material, poly (lactic-co-glycolic acid) was combined with collagen microsponge, a biodegradable scaffold[26].

5. Conclusion

Microsponge technology is developing quickly and has a lot of potential uses in the pharmaceutical industry**.** By loading the active pharmaceutical ingredient into the microporous beads, the microsponge delivery technology of the controlled release system reduces side effects while improving therapeutic efficacy. By extending dosage intervals and offering a site-specific drug delivery system, microsponges can be successfully integrated into bio erodible polymer-based oral drug delivery and controlled-release drug delivery systems. This improves patient compliance. At present, sunscreens, over-the-counter skin care products, prescription medications, and cosmetics all use this technology. The use of this type of medication delivery system could improve our knowledge of how various diseases are healed.

Given its special qualities—such as longer release, decreased irritancy, compact size, self-sterilization, compatibility with most vehicles and components, and flexibility in developing innovative product forms—MDS has a bright future in a variety of pharmaceutical applications in the years to come. Consequently, MDS is a rapidly developing topic. By using this microsponge drug delivery system bioavailability can be enhanced.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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