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An Overview of New Methods for Designing, Formulating, and Characterising Herbal Microsponges

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ABSTRACT

Topical medicinal solutions now use microsponge technology to reduce localizes cutaneous areas responses to active drugs and prevents exposure to them systemically. Microsponges are made of macroporous beads containing an active ingredient within that are typically 10 to 25 microns in diameter. Using microsponge drug delivery, topically active drugs can be more effective while also improving product stability, safety, and aesthetic features. Drugs, herbal extracts, and other compounds can be suspended or entrapped by tiny, polymer-based microspheres found in Microsponge Systems. Then, these microspheres may be included in a produced product, like a herbal gel, cream, powder or liquid. Material can continuously flow out of the spherical since the outside surface is frequently porous. In recent years, oral use of the porous, polymeric microspheres known as microsponges has increased. This review offers innovative methods for creating herbal microsponges and discusses their characterization, assessment, and use.

KEYWORDS: Microsponges; Herbal Microsponges; Controlled release, Topical drug delivery, Polymer based microspheres; Non-allergic

INTRODUCTION:

Because it confines the therapeutic effect to the affected area and minimizes systemic side effects, topical drug distribution is a great technique for treating skin issues[1]. Improvements in efficacy and safety have been made in many drugs that could be administered more successfully through skin contact. TDS, however, is not an effective delivery method for substances whose intended final destination is the epidermis. The stratum corneum and deeper skin layers than the epidermis cannot be reached with any reliable means for controlled and localized medicine administration[3]. The outer skin layers are the target area for conventional topical medication compositions. These products typically start to release their active ingredients as soon as they're administered, forming a coating of concentrated active substance that is swiftly absorbed[4]. The use of unattractive delivery methods, such as those that are oily, sticky, or create discolorations, poses another potential challenge for topical medication delivery because it may impede patient compliance. Because the delivery system is ineffective and causes irritation and allergic reactions in significant users, for topical formulations to be medically effective, active ingredient concentrations must be high[5]. Topical formulations also have unpredictable evaporation rates of the active chemicals, which cause them to release disagreeable odors, & a high likelihood of drug-vehicle incompatibility. A technique is necessary to maximize an active agent's time on the skin's surface or inside the epidermis while minimizing its transdermal penetration into the body[6].

The issue of medicinal chemicals building up unnecessarily in the skin's dermis and epidermis can be solved by using a microsponge delivery method. Using microsponges can lessen the irritability of an effective medicine without affecting its efficacy. Various polymers, such as ethyl cellulose, Eudragit RS 100, and others are used to create microsponge. Depending on how smooth they are, microsponges can range in diameter from 5 to 300 m. With a diameter of 25 µm, there are approximately 250000 pores[7]. Clinical trial failure is caused by a number of factors, including poor ingredient solubility, poor stability due to gastric and colonic acidity, poor metabolism due to the influence of gut flora, poor absorption across the intestinal wall, poor active efflux mechanism, and first-pass metabolic effects[8, 9].

Utilizing medicinal plants, which are incredibly therapeutically beneficial, is used to treat a number of illnesses. The secondary metabolites of medicinal plants that cause physico-chemical activity in humans include alkaloids, steroids, and tannins.

Additionally, the secondary metabolites perform a number of different tasks, such as anti-inflammatory, anticonvulsant, anti-ulcer, anti-psoriatic, anti-tumor, sedative, and anti-microbial. The herbal extract can be used in the microsponge formulation utilising a variety of techniques, taking into account the quasi-emulsion solvent diffusion method. The best microsponges are created by incorporating hydrogels of plant extracts, which is how nearly all of them are made. These boost any dermatological agent's efficiency and decrease any unfavorable local effects. The microsponges allow the drug to remain in the epidermis for an extended period of time. Microsponges can provide controlled release of the medicine that is entrapped while reducing the amount of API that is deposited in the dermis and epidermis. Topical bases such as gel, ointment, emulgel, etc. can be used to manufacture microsponges. The environment may have an impact on the amount of medication release from microsponges[10].

The dermis and epidermis that make up human skin are essentially sandwiched together. Microscopically, bioengineering, and biophysical techniques have been used to thoroughly characterize the stratum corneum, which is the top layer of the epidermis. It is composed of keratinized dead corneocytes that are embedded in a network of extracellular multilamellar lipid bilayers. The barrier properties of SC are caused by the presence of extracellular lipids and impaired SC barrier function as a result of removal of the skin tape or lipid extraction, according to visualization studies in this regard because percutaneous penetration is primarily attributed to the intracellular pathway [12-14].

Due to the structure and physiology of human skin, microsponges offer increased dermatological agent efficacy and lower local adverse effects. The most important aspect of microsponges for topical application is their typical size (5-300 m) [15, 16] since they are unable to get through the stratum corneum as a result. These carriers are therefore very helpful as delivery systems for dermal applications since they allow the medication to stay on the skin's surface or epidermis for a long period of time. The active agent's transdermal penetration is reduced at the same time. This characteristic is essential in the context of topical medication delivery[18]. Additionally, because of their porous structure, microsponges enable the regulated release of the medicine that is entrapped, resulting in the least amount of the active ingredient being deposited in the dermis and epidermis[19]. Microsponges are less appropriate for topically administered direct therapy due to their particle makeup, though. For improved efficacy, they are added to topical bases like gel, emulgel, ointment, or cream. According to literature reports, loading microsponges intended for dermatological use has most frequently used gel bases[15, 20-24].

HISTORY OF MICROSPONGE

In 1987, Won invented the microsponge technology, and Advanced Polymer Systems, Inc. (Redwood City, California, US) received the initial patents. For both cosmetic and over-the-counter (OTC) and prescription pharmaceutical products, this company developed a wide variety of technique improvements[25].

Characteristics of Microsponges :[26-29]

i. Formulations for microsponges are stable from pH 1 to 11.
ii. Microsponge composition stability is unaffected by temperatures up to 130^{0}C.
iii. Most vehicles and chemicals can be used with microsponge Formulations.
iv. Due to the typical hole size of 0.25 mm, which bacteria cannot pass through so, microsponge formulations are self-sterilizing.
v. Microsponge formulations offer a higher payload (between 50 and 60 percent), are still freely flowing and may be cost-effective.

BENEFITS:

The following benefits of the Microsponge Drug Delivery System may exist:

a. The shelf life and product stability can be increased without the application of preservatives because a. bacteria cannot enter the microsponge because they are too large[30].
b. Because microsponges are highly compartmentalized, they have a large internal surface area and a high pay loading capacity[31].
c. Ingredients can have their negative qualities, such as oiliness and tackiness, as well as their unpleasant feel and odour, significantly reduced, making them appropriate for topical application to skin[32].
d. Liquids can be changed into freely flowing powder, which has advantages for material handling[32].
e. Microsponges contribute to the formulation's increased elegance[33].
f. MDS increases the effectiveness of topically applied medicines and allows for their prolonged release[34].
g. Microsponges have a wide porous surface and are made of interconnected voids within a non-collapsible structure[35].
h. Stable throughout a wide pH range of 1 to 11, and up to 130 °C temperature[36].

Microsponges provide the following advantages over traditional formulations:

Wounds, cuts, and bleeding on the epidermal layer of the skin are frequently treated with traditional medicines including lotions, gels, and ointments[37]. The skin's outermost layer absorbs the majority of conventional formulations, which are unable to reach the deeper layer. Contrarily, microsponge can penetrate and absorb into the skin's dermis layer and only needs a tiny amount of API to have therapeutic benefits, lowering the risk of adverse reactions.[10]. (Fig)

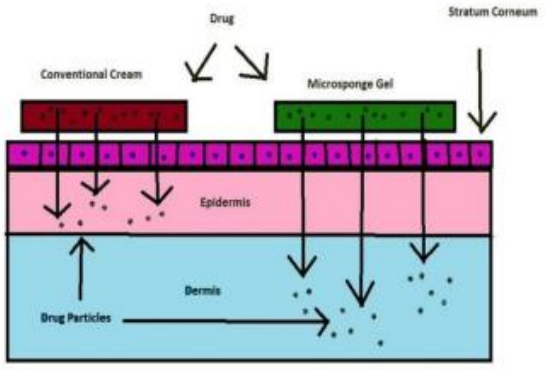

Figure-1: Difference between the conventional cream and microsponge gel

Benefits compared to liposomes and microencapsulation:

Compared to other technologies like microencapsulation and liposomes, the Microsponges have advantages. Microcapsules are unable to regulate the rate at which their contents are released because the moment the capsule's wall breaks, its contents begin to sporadically flow out. Liposomes have disadvantages such as a tiny payload, challenging production, intermittent chemical stability, and bacterial susceptibility. In contrast to the technologies stated above, the microsponge system can endure temperatures of up to 130^{0}C, pH ranges of 1 to 11, is suitable for most vehicles and materials, has a higher payload (50 to 60%), is free-flowing, and can be economically viable[38].

Benefits over ointments:

Because of their ineffective penetration, ointments require a high concentration of API for the optimum therapeutic results. Due to the high conc., it often results in unpleasant side effects, including allergic reactions and discomfort, and is unsightly and sticky, which reduces patient compliance. They also have a disagreeable smell and uncontrolled API component evaporation. The drug delivery method for microsponges is more permeable than that of ointments, allowing for less transdermal penetration into the body and longer drug retention inside the skin's top layer[39].

Limitation:

The formulation techniques involving the use of organic solvents as porogens could be hazardous to the environment because of their high flammability. Sometimes, residues of leftover monomers can absorb and pose a threat to human health[40].

Features of the Material Entrapped in the Microsponge:

Most liquid or soluble components have the potential to become caught in the particles. The following criteria must be met by actives in order for them to be captured in microsponges:

i. To prevent cosmetic issues, the active component must exhibit restricted solubility with the carrier vehicle[41].
ii. It should be either water insoluble or only very little soluble[42].
iii. The payload and polymer composition of microsponges must be optimized for the appropriate release rate over the allotted time.
iv. When in contact with the catalysts for polymerization and the conditions for polymerization, it should be stable[43].

Process for Preparing Microsponges:

Depending on the physicochemical properties of the medication to be loaded, drug loading in microsponges can be achieved in one step or two phases as described in the liquid-liquid suspension polymerization and quasi emulsion solvent diffusion methods [(44-48)].

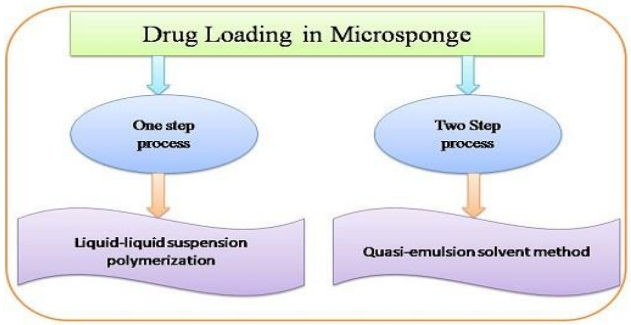

Figure-2: Microsponge Preparation Processes

1. Liquid- Liquid Suspension Polymerization[(49-51)]:

Porous microspheres are created in this liquid-liquid suspension polymerization process utilizing this technique. They are created by dissolving the monomers with the active ingredients in a suitable monomer solvent solution first, and then dispersing the resulting mixture in an aqueous phase including additives (surfactants, suspending agents, etc.). The next step is to start the polymerization by adding a catalyst, raising the temperature, or using radiation.

The different steps involved in creating microsponges are summed up as follows:

- Choosing a monomer or mixture of monomers.
- Chain monomer formation as polymerization starts.
- Ladders arise as a result of cross-linking between chain monomers.
- Microsphere agglomeration results in the formation of microsphere bunch. Spherical particles are produced by folding the monomer ladder.
- Bunches are bound together to form microsponges.

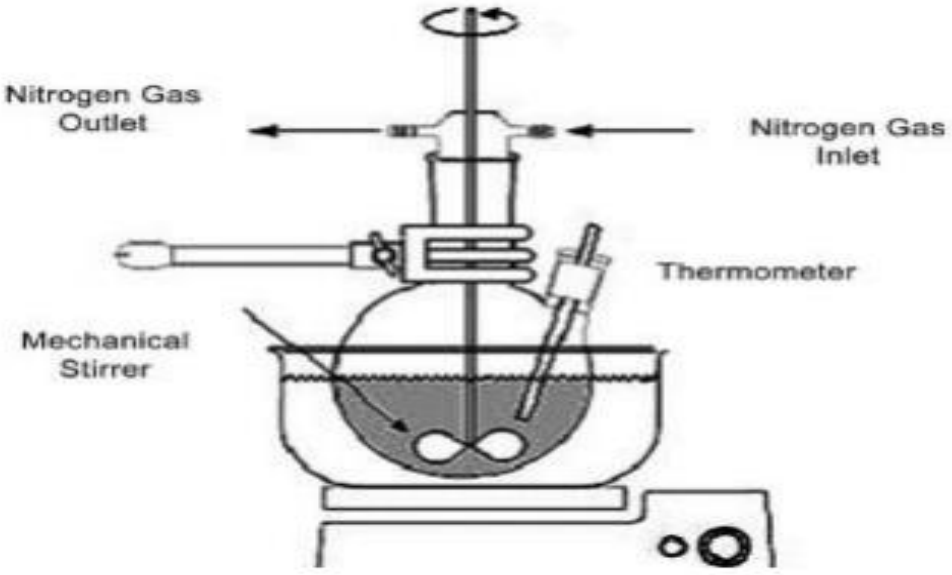

Figure-3: Liquid-liquid suspension polymerization preparation utilizing a reaction vessel.

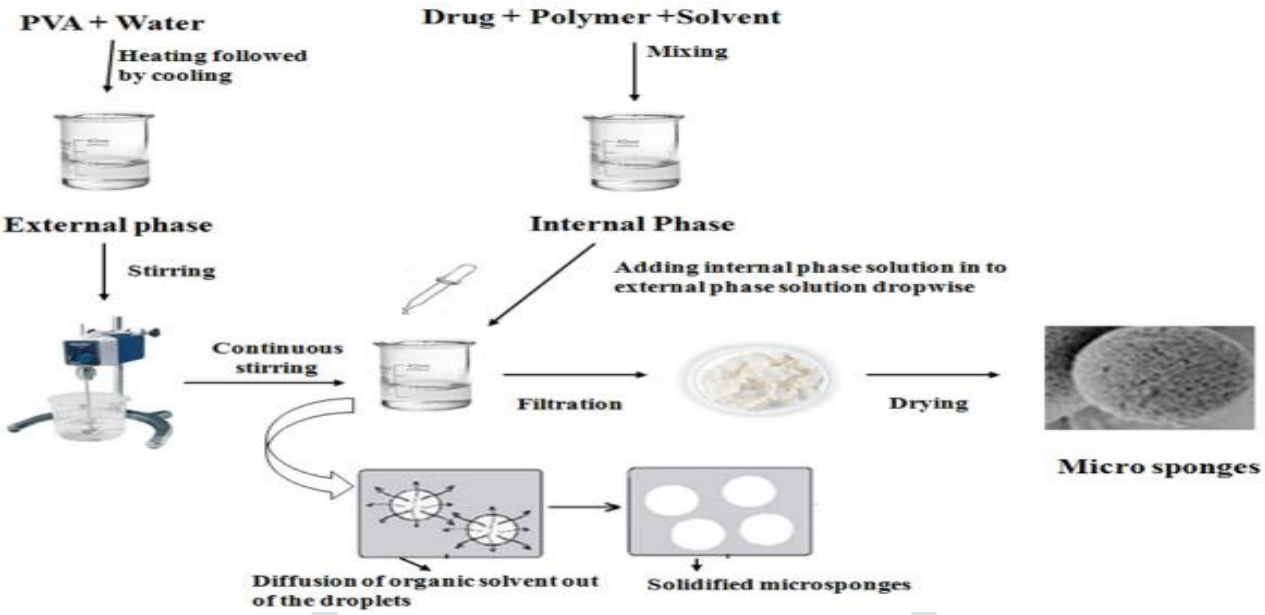

Figure-4: Quasi-emulsion solvent diffusion technique for making microsponges

2. Diffusive quasi-emulsion solvent:[52-55]

This approach uses a two-step process to create the microsponges using a quasi-emulsion solvent diffusion technique and varied polymer amounts. The inner phase was made using an ethyl alcohol solution of Eudragit RS 100. The medicine can then be dissolved in the solution by adding it and ultrasonically stirring it at 35° C. A solution of Polyvinyl alcohol in water (the outer phase) was then filled with the inner phase. In order to separate the microsponges, the liquid is filtered after stirring for 60 minutes. In order to calculate production yield (PY), the microsponges are dried for 12 hours at 40°C in an air-heated oven.

MECHANISM OF ACTION[56]:

- The vehicle is injected with the active ingredient that has been entrapped.
- Due to the open structure of the particles and the fact that the active is free to travel between the particles and the vehicle when the vehicle reaches saturation.
- After the product is applied to the skin, the active will seep into the skin and deplete the vehicles, which then become unsaturated and disrupt the balance.
- It either absorbs or dries out the medium. The stratum was then absorbed by the microsponge particles.

Drug release mechanism from Microsponges:

The following variables affect the microsponge's ability to release its active components[57]:

1. Pressure triggered systems:

Microsponges' active ingredients can be discharged onto the skin by rubbing or applying pressure[28].

2. Systems that are activated by temperature:

Some active compounds could be too viscous to spontaneously flow from microsponges on the skin at ambient temperature[58]. Therefore, changing the temperature may be used to control the substance discharge from the microsponge. Only when heat from the sun is present would a microsponge produce a sunscreen, for example, because thick sunscreens exhibit a superior release from microsponges when subjected to superior temperatures[59].

3. pH – activated devices:

Create a pH-based active release by modifying the microsponge's covering[60].

4. Solubility Activated system:

When there is water around, microsponges can emit substances that dissolve in water, such as antiperspirants and antiseptics. Active chemicals may release more quickly when an aqueous media is present, such as perspiration[61].

MICROSPONGE EVALUATION METHODOLOGY:

- **Analysis of particle size:** Utilizing optical or electron microscopes, the particle size distribution is investigated. Other relevant methods, such as laser light diffractometry, may also be used to measure the particle size of Microsponges[62].
- **Morphology and surface topography:** The surface morphology of the microsponge and photon correlation spectroscopy (PCs), scanning electron microscopy (SEM), and transmission electron spectroscopy (TEM), which are frequently employed in the microsponge coated

with gold-palladium under an argon atmosphere at room temperature, are some of the techniques used in the morphological analysis of microsponges' topography[63].

- **Loading efficiency:** How well the microsponges are loaded may be determined using the following equation:

$$\text{Loading efficiency}(\%) = \frac{Actual\ drug\ content\ in\ microsponges}{Theoretical\ content} \text{x}100$$

- **Production Yield:** The standard mass of the raw materials and the typical mass of the manufactured microsponges may both be used to calculate the output yield of the microparticles.

$$\text{Production Yield} = \frac{Practical\ Mass\ of\ Microsponges}{Theoretical\ yield\ (drug + polymer} \text{x}100$$

- **True density:** The microsponge's actual density is estimated using an ultra-pycnometer and helium gas by averaging out several observations.
- **Compatibility study:** It is possible to evaluate the compatibility of drugs and polymers using thin layer chromatography (TLC) and Fourier transform infrared spectroscopy (FT-IR) [64].
- **Release evaluation:** Diffusion can be used to track the release of microsponges or as a secondary trigger together with moisture, pH, temperature, and resistance. This releasing technique is used to enhance the attractiveness of manufactured goods[65].
- **Resiliency:** The viscoelastic qualities of the microsponges can be adjusted for creating softer bead lets depending on the necessities of the final formulation. The rate of release slows dramatically as linkage rises[66].
- **Stability study:** According to ICH guidelines, the gel formulation's durability is evaluated. Various replicates were kept in sterile, lacquered, collapsible aluminium tubes at 75±5% relative humidity and 40±2°C temperature for 30, 60, and 90 days, the gel's in vitro release profile, pH, and outer shell were all assessed[67].
- **Examining the pore structure:** The rate of medicine release may vary depending on the microsponges' pore size. Porosity characteristics for microsponges are also examined, including apparent density, mass, total pore surface area, intrusion-extrusion isotherms, pore size distribution, and average pore diameters[68, 69].

Therapeutic application of microsponges:

In the area of therapeutics, microsponges have many different uses. It can be used in many different ways, such as topical formulations, to treat various skin conditions and diseases. It has most recently also been applied to bone tissue engineering. Microsponges can be employed in cardiovascular engineering because they are items that self-sterilize.

In comparison to microsponges, nanosponges, nanoferrosponges, and porous microbeads are more advanced microsponges used to administer hydrophilic and hydrophobic medications topically and orally. These cutting-edge microsponges are intended to improve drug administration and lessen skin irritation. Nanoferrosponges, which are propelled by an external magnetic trigger, offer improved medication penetration and delivery to the targeted spot[70].

- **Diabetes wound healing with microsponges:** Nebivolol-containing microsponges were created and are now being used to treat diabetic wound healing. In diabetic wounds, the drug fundamentally works as a vasodilator and recovers endothelial function. In particular, the medication promotes a healing environment that is ideal for diabetic wounds, facilitating wound closure[71].
- **Microsponges in a fungus infection:** Utilization of microsponges anti-fungal gel formulation has been confirmed to extend medication release duration when compared to plain gel loaded with the drug. A regulated release of the medication for up to 12 hours was achieved with the formulation of oxyconazole nitrate microsponges used to treat fungal infections[64].
- **Microsponges for arthritic pain:** Diclofenac is delivered topically in cases of arthritis by the use of a microsponge. By overcoming gastrointestinal discomfort and first pass metabolism, diclofenac-containing microsponges can be used topically to increase patient compliance. Using the quasi-emulsion diffusion of solvent strategy, diclofenac diethylamine microsponges gel was produced, and it exhibited prolonged and controlled release for the medical management of arthritis[72].
- **Skin protection with microsponges:** The use of sunscreen shields our skin from UV rays, preventing sunburns and Several tumors, include malignant melanoma and basal carcinoma. In order to provide higher UV protection and SPF value, Oxybenzone microsponge sunscreen was developed[64].
- **Microsponges for acne:** Acne is a serious skin condition that can irritate the skin. Miconazole nitrate is a component of an anti-acne cream created by Rizkalla et al. To achieve sustained release, they created microsponges with Eudragit RS_100 and added it to the cream. Studies revealed that traditional formulations were exhausted within four hours and released 83.089% of the drug, but microsponges provided sustained drug release (78.28%) up to 8 hours[73].

- **Microsponges in psoriasis:** An inflammatory skin condition is called psoriasis. Psoriasis is also treated with microsponges. Clobetasol propionate was added to microsponges in a study to treat psoriasis. In contrast to the normal form, which releases the medicine over a period of 2.5 hours, they saw the drug last up to 12 hours[70].
- **Microsponges for skin infections:** Microsponges were additionally developed as creams to treat a number of skin disorders, such as eczema and atopic dermatit. A stable and non-irritating formulation was created by Amrutiya et al. by incorporating mupirocin into microsponges[74].
- **Microsponges in melanoma:** Pro-inflammatory hyperpigmentation (PIH) and melanoma were treated with hydroquinone microsponges that contained 4% hydroquinone and 0.15% retinol. The medication released slowly with minimal skin irritation, and just one patient had an adverse response to the formulation[75].
- **Microsponges for colon cancer:** A chemotherapeutic drug called 5-fluorouracil (5-FU) has been produced as a microsponges formulation for the treatment of colon cancer. By boosting the relative accumulation in cancer locations and lowering the toxicity, the formulation increased the drug's activity. In contrast to the microsponges, pure 5-FU released the drug for up to 5 hours, according to the drug release research[70].

Table 1: Some marketed Acne Vulgaris Preparations[76].

S. No.	Marketed product	Herbs used	Brand
1.	Clove and neem extract in the Vaadi Herbal Anti Acne Cream.	Tea tree oil, Clove oil, neem & orange extract	Vaadi Herbals
2.	Tea Tree & Cinnamon Anti-Acne Oil Control Face Wash by Lotus Herbals	Cinnamon, Oak, Tea tree oil,	Lotus Herbals.
3.	Biotique Bio Myristica Sustainable Face Pack Spot Corrector for Acne .	White sandalwood oil, pipali root, multani mitti powder, jaiphal powder, and turmeric root .	Biotique.
4.	Anti-Acne Face Wash by WOW Skin Science	Neem leaf extract with tea tree essential oil	WOW SKIN SCIENCE.
5.	Neem Tulsi Face Wash by Patanjali .	Aloe vera, neem, and tulsi .	Patanjali
6.	Anti-Acne and Anti-Pimple Herbal Gel from Soundarya Herbs	Neem, Aloe-vera, papaya.	Soundarya
7.	Khadi Organique Neem & Basil Acne Pimple Cream	Neem extract, lavender extract , basil extract, calendula extract, tea tree oil, turmeric , cinnamon bark extract,	Khadi Organique.
8.	Tea Tree Spot Gel Face Cream by Mamaearth For Acne	Tree of Tea	Mamaearth.
9.	Indus Valley Seaweed Tea tree Calming Acne Gel	Rose oil, grapefruit seed extract, rose water, wheatgerm oil, aloe vera, almond oil, niroli oil, and rose oil.	Indus Cosmeceuticals
10.	Himalaya Natural Acne Treatment Cream	Silk cotton oil, lentil, shalmali, nirgundi, Aloe vera .	Himalaya

An analysis of the literature on herbal Microsponges:

Here, we'll talk about some of the reviews of herbal Microsponges that are listed in Table 2 because, according to a literature study, this area still needs to improve.

Table 2: Researches on herbal microsponges

S. No.	Authors	Study
1.	Dutta et al., 2022[77]	Established a procedure for making microsponge gel, a polyherbal composition, and created procedures for assessing its sun protection abilities.
2.	Muruganantham, et al, 2022[78]	Generate, develop, and put into practice techniques for evaluating the qualities of sunscreen and utilizing microsponge gel as a polyherbal preparation.
3.	Gavali R S et al; 2022[79]	Develope and evaluate a microsponge-based gel with ocimum sanctum added for its antifungal properties.

4.	Velmurugan et al; 2021[80]	Create "Herbal Microsponges" utilizing "Ethanolic" extract of "Enicostemma axillare" leaves in order to explore the drug release dependent on the kind and concentration of "Polymers" used in the formulation.
5.	N. Kumar et al.; 2021[81]	A citronella oil microsponge infused hydrogel (HG-COMS) was developed as part of the manufactured project to provide future direction for developing a postponed release preparation.
6.	Sayal er al., 2020[82]	Febricate the Havan ash-based gel formulation for the microsponges to be used in the treatment of acne. As a result, a topical formulation using Havan Ash microsponges will be created and assessed.
7.	Bhatia and Saini, 2018[83]	Increasing the rate at which curcumin escapes from microsponges created using a quasi-emulsion diffusion of solvent technique using poly vinyl alcohol and ethyl-cellulose as carriers were the aim of the current work.
8.	Biswas et al; 2018[84]	Develop and evaluate a novel herbal remedy using Syzygium cumini seed extract in polymeric microspheres.
9.	Wadhwa G et al; 2017[85]	In order to increase stability, have an antibacterial impact, and reduce cutaneous toxicity, babchi essential oil is being encapsulated in ethyl cellulose (EC) microsponges in this study.
10	Mounika et al. 2015[86]	"Herbal Microsponges" were created using "Methanolic" and "Petroleum ether" extracts of leaves from "Ricinuscommunis" in order to investigate the drug release according to the kind and quantity of "Polymers" employed in the formulation.
11.	Sareen et al., 2014[87]	Develop and evaluate curcumin microsponges for colon-specific drug administration to avoid the upper gastrointestinal tract (GIT) for a greater therapeutic impact.
12.	Arya and Pathak, 2014[88]	The experiment aims to evaluate the gastro-retentive capacity of microsponges through the creation of targeted buoyant curcumin microsponges for increased specifically to site absorption for gastric cancer. A modified quasi-emulsion solvent diffusion method and a 3 2 complete factorial design were used to manufacture microsponges.
13.	Chanchal et al., 2008[89]	"Nutracosmetics" is a new category of health and beauty aids that combines the benefits of natural compounds with the sophistication, skin-smoothing properties, and delivery systems of cosmetics.
14.	Eugine et al., 2008[90]	The current research sought to develop ethylcellulose microparticles containing BPO that could be controlled in their release into the skin while also reducing some of the unfavorable effects of commercial BPO, such as skin irritation and percutaneous absorption.

FUTURE PROSPECTS:

Microsponges delivery system have a promising future in a variety of pharmaceutical applications in the years to come due to their distinctive qualities, such as improved product performance and elegance, extended release, reduced irritability, and improved chemical, physical, and thermal stability. Microsponge's delivery system was first created for the topical administration of medications such as anti-inflammatory, anti-acne, anti-fungal, anti-pruritics, anti-dandruff, and rubefacients. The primary challenge of the microsponge delivery system in the future will be obtaining for the enhanced core/shell delivery of the drug-loaded microsponges for oral peptide administration by modifying ratio of polymers. Today, it may also be employed for tissue engineering, biopharmaceutical delivery, and controlled administration of oral medications for colon-specific delivery. The biopharmaceutical (peptides, proteins, and DNA-based therapies) class of new medications is accelerating the development of drug delivery technologies.

CONCLUSION:

Innovative development strategies and distinctive formulation techniques complete the image. One example is the medication delivery method called Microsponges, which shows great potential in both the medical and cosmetics industries. This method is appealing because it offers a variety of safe, secure, more stable, and less detrimental effectful ways to release bioactive chemicals. In terms of drug mutagenicity and irritancy, microsponges also significantly outperform other formulations. As a result, they hold great promise for the development of novel formulations for topical sickness. Herbal Microsponges are more important than synthetic ones because they don't have any negative side effects. As a result, the herbal microsponge drug delivery system has a lot of potential and is still a relatively new subject that needs to be further researched.

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