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Novel Approaches of Herbal Microsponges Design, Formulation and Characterization: An Overview

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ABSTRACT
Polymeric delivery devices called microsponges are made of porous microspheres. They are small, spherical particles that resemble sponges and have a highly porous surface.They have less side effects and better patient compliance while also being very efficacious, stable, non-irritating, non-toxic, non-allergic, and non-mutagenic. Numerous advantageous aspects of microsponge technology make it a flexible medication delivery method. Microsponge Systems are built on tiny, polymer-based microspheres that can suspend or entrap a wide range of materials like drug, herbal extract etc. These microspheres may then be added to a designed product such herbal gel, cream, liquid, or powder. Since the outer surface is often porous, material can continuously flow out of the sphere. Microsponges are porous, polymeric microspheres that are mostly applied topically but have lately been applied orally.This review provides a novel approaches to design herbal microsponges, characterization, evaluation and application of herbal microsponges.

Keywords: Microsponges; Herbal Microsponges; Microspheres, Polymer based microspheres; Non-allergic

I. INTRODUCTION

The creation of innovative microsponge base drug delivery systems has received a lot of attention recently in an effort to alter and regulate the release behaviour of the medications. The therapeutic index and duration of a drug's activity can be changed by incorporating it into a carrier system. The widespread use of substances like - hydroxy acids and vitamins in topical solutions, which can induce perceivable and provable advantages - notably in ageing or photo-damaged skin, has encouraged the public interest in skin care and skin treatment products, which is on the rise. Even though they are quite helpful, these compounds can frequently cause irritation. This irritation, which is most common in those with sensitive skin, can be felt as burning, stinging, or redness.The formulators tried using one of the two techniques to address this issue after realising it existed. Although they sacrificed effectiveness in the process, they lowered the concentration of these components. In order to make the product more emollient or skin-compatible, they have also changed the vehicle. [1,2] The positive impacts of the finished product are often also diminished by this technique. The need for alternate drug delivery systems and equipment is being fueled by the growing market for novel medications, greater sensitivity to clinical results, and rising healthcare costs.The healthcare system has been significantly impacted by medication delivery methods that can precisely regulate release rates or direct pharmaceuticals to a particular bodily spot. Transdermal delivery systems (TDS), which use the skin as a portal of entry, have been created for a number of predictable and dependable methods for systemic medications. [3] Many medications that might be delivered more effectively through skin contact have seen an improvement in effectiveness and safety. TDS, however, is not a feasible delivery method for compounds whose end target is the skin. Only lately has controlled drug release onto the epidermis been successfully attempted, with the guarantee that the medication will remain mostly localised and won't reach the systemic circulation in considerable amounts.For the regulated and targeted administration of medications into the stratum corneum and deeper skin layers, not just the epidermis, no effective delivery methods have been created. Additionally, there are other issues with topical medicine administration, including ointments that are frequently unsightly, greasiness, stickiness, and other issues that frequently lead to patient noncompliance. Due to their ineffective delivery systems, these products need large quantities of active ingredients to be therapeutically effective, which might irritate and induce allergic

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responses in certain users. Other downsides of topical preparations include uncontrolled evaporation of the active component, offensive odour, and possible drug-vehicle incompatibility. The outer layers of the skin are the target of conventional topical medication compositions. Usually, when applied, these products release their active ingredients, creating a thin layer of highly concentrated active ingredient that is quickly absorbed. In order to maximise an active ingredient's time on the skin's surface or inside the epidermis while minimising its transdermal penetration into the body, a system is required. Microsponges are small spheres that may absorb skin secretions to lessen skin shine and oiliness. Spherical particles made out of groups of even smaller spheres may store four times as much skin secretions as they weigh. Extremely tiny, harmless, unbreakable spheres known as microsponge particles do not penetrate the skin.Instead, they gather in the skin's minuscule crevices and release the medicine there over time, when the skin requires it. The microsponge system can stop substances from building up too much in the dermis and epidermis. The microsponge technology has the potential to greatly lower the irritability of potent medications without compromising their potency. The next washing then removes the empty spheres. These characteristics are met by the microsponge delivery technology, which has produced a new wave of unique, very effective, and very well-tolerated products. These products often come in the traditional forms of creams, gels, or lotions and have a reasonably large amount of active chemicals.[1]

MICROSPONGES

Won created the microsponges method in 1987. [4, 5]Polymeric drug delivery devices called microsponges are made of porous microspheres. They are small, round, sponge-like particles having a sizable porous surface.[6,7]They could also improve stability, lessen negative effects, and favourably alter medication release. The numerous positive aspects of microsponge technology make it a flexible method of medication administration. [8] Microsponge Systems are built on tiny, polymer-based microspheres that can suspend or entrap a wide range of materials. These microspheres may then be added to a designed product such a gel, cream, liquid, or powder. The use of microsponge drug delivery systems can effectively boost the effectiveness of topical active ingredients while improving product stability, safety, and aesthetics.One of the largest issues facing pharmaceutical scientists has been regulating the pace of delivery of active drugs to a specific place in the human body. The term "transdermal delivery system" (TDS), which uses the skin as the portal of entry, refers to a number of predictable and dependable techniques for systemic drug administration.[9]

Since their typical pore size is 0.25µm, where bacteria cannot penetrate, microsponges are compatible with most vehicles and ingredients, stable throughout a pH range of 1 to 11, and temperature ranges up to 130°C. They are also self-sterilizing and can be economical.[10] To address issues like greasiness and stickiness associated to topical formulations, microsponges techniques are used to improve the effectiveness of medications used topically.[11,12]Microsponge drug delivery system is a polymeric system made of porous microspheres that has received patent protection. They are small, spherical particles with a sponge-like appearance, made up of a great number of interconnected voids inside of a noncollapsible. structure with a sizable porous surface that allows for the regulated release of active ingredients [13]The microsponges range in size from 5 to 300 micrometres, and a typical 25 micrometre sphere can have up to 250000 pores and an internal pore structure that is 10 feet long, giving them a total pore volume of around 1 millilitre per gramme for significant drug retention.[14]

Properties of Microsponges

When microsponges are applied to the skin, their bioactive agent gradually releases on the skin at a predetermined time mode and responds more effectively to stimuli like rubbing, temperature, and pH effect.

- Over the pH 1–11 range, these compositions are stable.
- Even at 1300 °C, it remains stable.
- Most vehicles and excipients can be used with them.
- As the bacteria cannot pass through the holes, which have an average size of 0.25 m, they are self-sterilizing.
- They may capture up to 50% or 60% of the air.
- Both are affordable and freely available.
- These particles are the right size to penetrate the skin, and the composition of microsponges allows them to absorb six times as much oil as their own weight without drying out.
- In other words, it offers prolonged release and sustained activity for up to 12 hours.
- They are more flexible in their formulation. [15]

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Benefit of Microsponges drug delivery system

Diffusion can be used to regulate the medication release from Microsponges when they are put to the skin. Microsponges deliver benefits such as better product efficacy and decreased irritation often associated with powerful therapeutic agents like benzoyl peroxide by programming the release of the active component on the target location of the skin.[16, 17] Below are a few advantages of medication delivery methods based on microsponges (Fig. 1).

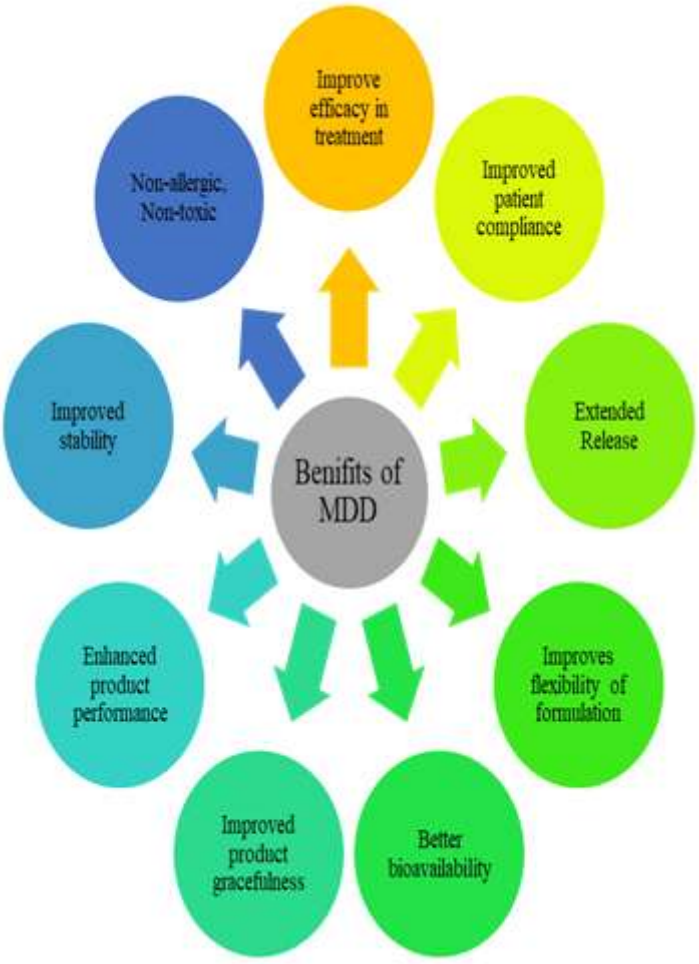

Fig. 1: Benefit of Microsponge Drug Delivery (MDD)

Approaches for Formulation of Microsponges

Liquid-Liquid suspension polymerization [18,19]

In this method of polymerization, the monomers are dissolved in a suitable solvent with the surfactant, the active component, before being supplemented with other ingredients and a suspending agent to create a suspension. Once the solvent has been removed, the spherical structure becomes porous. The polymerization may be started by introducing a catalyst or by raising the temperature. Microsponges are left with a spherical, porous shape once the solvent has been removed from the polymerization process (Fig. 2).

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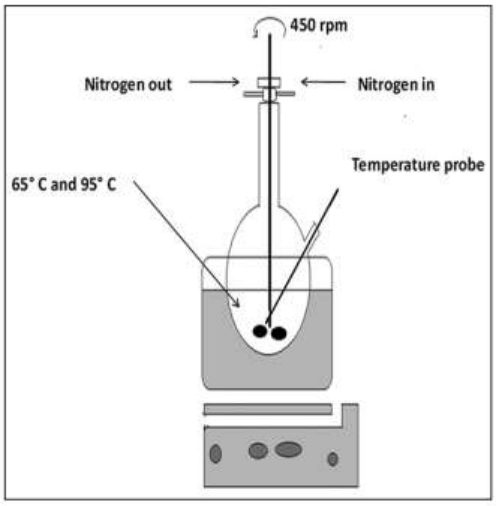

Fig. 2: Liquid-Liquid Suspension Polymerization

Quasi-emulsion solvent diffusion[20, 21]

By employing various polymer quantities and the quasi-emulsion solvent diffusion process, microsponges may be created. The polymer is dissolved in a suitable solvent to create the inner organic phase, and then the additional medication is dissolved under ultrasonication at 35 °C. This answer passed the inner phase. Pouring the inner phase into the outer phase (polyvinyl alcohol solution in water). The mixture is then filtered to remove the generated microsponges after being stirred. In an air-heated oven, the microsponges are dried at a temperature that is suitable for polymer (Fig. 3).

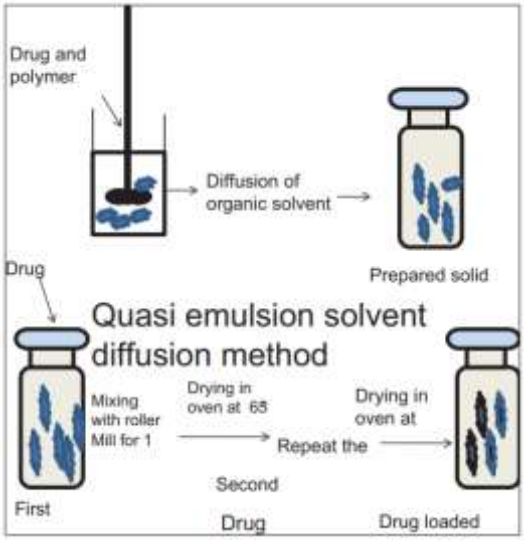

Fig. 3: Quasi-Emulsion Solvent Diffusion Methods

Drug Release Mechanism of Microsponges

There are several various ways to create the topical agent formulation using microsponges, such as a gel, cream, or lotion. The active components spread out of the globule into the vehicle during application topically to the appropriate region of the skin and reached the target location (Fig. 4). The active ingredient's rate of release from the formulation may be planned in advance; the release can be started or stimulated by a variety of release triggers, as shown in Fig. 4. [22-25]

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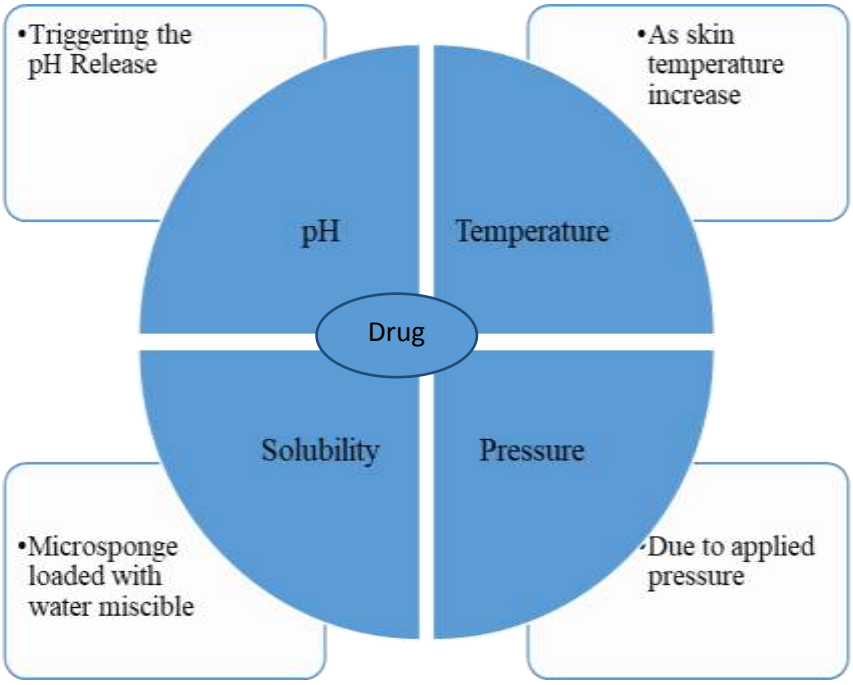

Fig. 4: Drug Release Mechanism of Microsponge

Characterization of Microsponges

Preformulation Characterization

The purpose of preformulation parameters is to pinpoint the physicochemical characteristics, melting point, and excipients that may have an impact on formulation design, manufacturing process, pharmacokinetics, and biopharmaceutical qualities. Organoleptic properties are investigated out as a chemical state, taste, odour, and colour of the medicine. [26]

Identification and drug-polymer compatibility

Differential scanning calorimetry (DSC)

DSC studies are used to verify the thermal behaviour, physical combination, and formulation of medications as well as their compatibility. For example, with heats of fusion of 83.56 J/g, 82.81 J/g, and 57.93 J/g, respectively, the thermogram of curcumin microsponges exhibits a broad endotherm at 82.83 °C, a sharp endotherm at 176.57 °C, and an exotherm at 199.933 °C. Changes have taken place, as evidenced by the shifting of endotherms, the appearance of a new exotherm, and a drop in the heat of fusion. [27]

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrometer is used to interpret the identification of functional groups found in pure drugs, physical mixtures of drugs, and polymers. For example, curcumin (CUR), ethyl cellulose (EC), and curcumin microsponge FTIR spectra. As the distinctive transmittance bands in the spectra of CUR were found to be located at 1597, 1505, 1275, and 1157 cm^{-1}, respectively, and correspond to aromatic -C-O stretching of (-OMe and -OH) and -C-O-C stretching (–OMe). At 3500 cm^{-1}, distinctive bands for conjugated ketonic -C=O and phenolic -OH vibrations were also seen. The spectra of EC, exhibit the distinctive absorption of alcoholic hydroxyl groups at 3476.71 cm^{-1}, whereas the spectra of CUR microsponges, exhibit band broadening at around 3400 cm^{-1} and characteristic bands in the range of 1597-950 cm^{-1}. [27]

Particle Size analysis of Microsponge

The microsponge's particle sizes are measured using optical microscopy, laser light diffractometry, and other suitable techniques. Rajurkar et al. used an optical microscope to examine the naproxen gel microsponge particle size and discovered that the microsponge was of uniform size. The pore size was less than 1µm, and the average particle size was 110.30 µm. Optical microscopy was used to measure the clotrimazole microsponge's particle size, which ranged from 48 to 65.2 µm with a mean particle size of 58.37 0.52 µm.were spherical, and it was discovered that the mean pore size was 8.31±0.38 m. [28]

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Analysis of morphology and surface topography of Microsponges

Microsponges must have pores in order to function, and SEM and transmission electron microscopy may be used to determine the internal and exterior morphology and surface topography of microsponges (TEM).Rajurkar et al. examined naproxen microsponge and found that they were uniformly spherical and free of drug crystals on the surface. SEM and TEM analysis of the miconazole nitrate particle size, shape, and surface morphology revealed a porous, spherical form in the m range.[29]

Analysis of pore structure

The pore width of the microsponges can affect the rate of medication release. Analysis is also done on a number of microsponges' porosity metrics, including total pore surface area, intrusion-extrusion isotherms, pore size distribution, average pore size diameters, shape and morphology of the pores, bulk, and apparent density. [30, 31]

Determination of loading efficiency and production yield

The loading efficiency (%) is calculated using the following equation:

Loading Efficiency = (Actual drug content in Microsponges)/(Theoretical Drug Content)X100

By precisely determining the beginning weight of the raw materials and the end weight of the produced microsponge, it is possible to assess the production yield of the microparticles.

Production Yield = (Practical Mass of Microsponges)/Theoretical mass (Polymer + Drug) X 100

According to Mehta et al., the manufacturing yield of the clotrimazole microsponge formulation was less than 40%, whereas the loading efficiency ranged from 80 to 95 percent.[32,33]

In vitro dissolution analysis

Microsponges' dissolving profiles are investigated using the USP XXIII dissolution equipment and a modified basket made of 5 m stainless steel mesh rotating at 150 rpm. Mehta et al. measured the drug release of clotrimazole gel from microsponges and found that 88-89%, 98.1%, and 99.4% of the medication were released after 12 hours. According to research by Mohan et al., a biphasic release of 27–36% of the medication occurred in the first hour of an in vitro dissolving study utilising a USPXXI dissolution assembly (basket type) in 900 ml of pH 7.4 saline phosphate buffer solution at 37°C–5°C and spun at 50 rpm. After 8 hours, the cumulative release from the micro sponge varied between 62% and 95%. [34]

Analysis of true density

The real density of microsponges is determined using an ultrapycnometer. [35]

Viscosity measurement

The Brookfield viscometer's measurement of viscosity. According to Mayur et al. (2013), the observed rheology of a gel formulation containing tioconazole was investigated using a Brookfield digital viscometer DV-2P-L and a spindle S96 at a speed of 20 rpm and a torque range of 60% to 100% at a temperature of 25°C10°C. When naproxen microsponge gel was evaluated using a DV-III+Rheometer and spindle No. 2 at 25°C, Rajurkar et al. [36] discovered that it had a pseudoplastic character.

Spreadability Study

By measuring the diameter of the liquid gel after one minute between two horizontal plates (2020 cm^2), the spreadability study of the gel formulation was calculated. It was discovered that the upper plate's standardised weight was 125 g. Spreadability as determined by the following formula:

Spreadability = M.L/T

Where M= wt. tied to the upper slide

L = Length of glass slides

T = Time taken to separate the slides

Acyclovir sodium topical gel's spreadability was measured in grammes per centimetre per second (g.cm/sec) and was found to be 12.5, 11.75, 11.25, and 11.17.[37]

pH determination

By utilising a digital pH metre and taking readings an average of three times, Rajurkar et al. were able to discover that the pH of the naproxen gel microsponge was 6.2±0.2. Optimized Rajshree et al., 2014 using a digital pH metre, the pH of the microsponge of the miconazole nitrate-loaded hydrogel was evaluated. The results were as needed by the formulation: pH 6.7±0.06, 6.8±0.06.[4]

Stability test

Microsponge stability tests are conducted using a variety of formulations at varying temperatures and relative humidity levels. The stability of the mupirocin microsponge was examined after 15, 30, and 45 days of storage in glass bottles and was tested at 5°C, 25°C/60% RH, and 40°C/75% RH. According to ICH criteria,

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Rajurkar et al. observed the stability research of microsponge naproxen gel after maintaining it at 40°C with 45% RH for 90 days.[4]

Applications of Microsponges

Topical Delivery

Topical medications are frequently used in dermatological problems therapy and cosmetics. However, particularly in those who are sensitive, they are linked to significant skin irritancy. This irritation has been linked to the topical treatments' active components' fast release and subsequent buildup. Microsponge Technology for distribution allows for a controlled release of the putting skin-contact active compounds. A number of microsphere-based Topical medications have undergone safety evaluations, and effectiveness in the treatment of and for aesthetic purposes with skin conditions, and are currently marketed in the US. Formulations of benzoyl peroxide are among them retinol, 5-FU, and HQ plus retinol compositions of agents used topically that use the Microsponge drug delivery little or no irritability in system technology acne patients, people with photo-damaged skin, and overlypigmentation, or AK, without sacrificing the efficacy of the agents.

Oral Delivery

Topical medications are frequently used in the cosmetic and dermatological fields. However, they have a significant skin irritancy risk, especially in people with sensitive skin. The active components of topical treatments have been linked to this irritancy via their fast release and subsequent buildup. Microspongec controlled release of the drug is made possible via delivery technologies onto the skin, active substances various microsphere-based Topical medications have been examined for their security and Effectiveness in treating and used for cosmetic purposes Currently marketed products for dermatological conditions US. Benzoyl peroxide compositions are among them HQ with retinol, 5-FU, and tretinoic acid.

Bone substitute

By combining pre-polymerized polymethylmethacrylate powder and liquid methylmethacrylate, bone-substitute compounds were created monomer with two a-tricalcium aqueous dispersions granules of a-TCP phosphate and calcium-deficient powdered hydroxyapatite (CDHA). Finished composites seemed to have pores. The finished composites' osteo-conductivity and osteo-conductivity were evaluated in-vivo by in rabbits, implantation new trabecular bone growth inside the holes where the inorganic particles were seen was positioned. The output displays a high level biocompatibility, a high rate of osteointegration, and characteristics of osteogenesis.[14]

Cardiovascular engineering using Microsponge technology

Autologous cell seeding on biodegradable materials is a laborious, intrusive method that raises the possibility of infection. It has been created a biodegradable graft material that contains collagen microsponge to allow the regeneration of autologous vascular tissue. With and without pre-cellularization, this substance was examined for its capacity to quicken in-situ cellularization using autologous endothelium and smooth muscle cells. A biodegradable scaffold called poly (lactic-coglycolic acid) was combined with collagen microsponge to create a vascular patch material. The creation of an endothelial cell monolayer, parallel alignment of smooth muscle cells, and reconstruction of the artery wall with elastin and collagen fibres were all revealed by histological findings. At six months, the patch's cellular and extracellular components had grown to levels comparable to those in native tissue.In cardiovascular surgery, this patch exhibits potential as a bioengineered material for fostering in situ cellularization and the regeneration of autologous tissue.[15]

Microponges for Biopharmaceutical Delivery

The microsponge delivery method is used in both tissue engineering and the delivery of biopharmaceuticals. Dai 2010 et al. created hybrid 3D scaffolds that combine the benefits of synthetic PLGA knitted mesh and natural type I collagen. The mechanically robust PLGA mesh functioned as a skeleton, while the collagen microsponges promoted cell seeding and tissue development. There were three groups of scaffolds: Collagen microsponge may be generated in three different ways: thinly (in the PLGA mesh's interstices), semi-thickly (on one side of the mesh), and sandwich-style (on both sides). [16]

Microsponges are intended to deliver bioactive agents efficiently at a low dose while improving stability, reducing adverse effects, and modifying drug release.[38] As stated in Table 1, the system may be used for the following applications.

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Table 1: Application of Microsponges in drug delivery[39-46]

S. No.	Applications	Advantages
1.	As Antipyretic by using Paracetamol as a Drug	Used to treat mild and moderate pain and fever
2.	As Antiprotozoal agent by using tinadazole as a drug	Treatment of parasitic infection
3.	As Analgesic by using Indomethacin as a drug	Decreased the side effects like GI irritation
4.	As Anti-acne by using Benzolyl peroxide, Erythromycin	Reduced skin irritation and sensitivity
5.	As Anti-Viral by using Acyclovir	Better activity to treat viral infection
6.	As Sunscreens	Long lasting product efficacy with better protection against sunburns.
7.	As Anti-inflammatory by using Hydrocortisone, lornoxicam, naproxen	Long lasting activity with minimized skin allergies
8.	As Anti-dandruffs by using zinc pyrithione, selenium sulfide	Extended effect
9.	As Anticholinergic by using Dicycloamine drug	Effective local action
10.	As antibacterial by using Mupirocin as drug	Enhance stability and reduce side effects
11.	As Musculoskeletal by using Ketoprofen drug	Relief pain, reduced swelling, treat arthritis

Literature review on herbal Microsponges

Here we will discuss some reviews on herbal Microsponges which is given in Table 2, as per the literature survey more development is needed in the field of herbal Microsponges.

Table 2: Literature on herbal Microsponges

S. No.	Authors	Study
1.	Dutta et al., 2022[47]	Prepared and developed a method for microsponge gel as a polyherbal formulation along with their evaluation methods for sunscreen properties.
2.	Bhatia and Saini, 2018[48]	Present study was to improve the release rate of curcumin by microsponges prepared through quasi-emulsion solvent diffusion technique using ethylcellulose and PVA as carriers.
3.	Mandra et al., 2015[49]	The present study was carried out to formulate "Herbal Microsponges" by using "Methanolic" and "Petroleum ether" extracts of "Ricinuscommunis" leaves, to explore the drug release based on the type and concentration of "Polymers" used in the formulation.
4.	Sayal er al., 2020[50]	The aim of this study was to develop the Microsponges containing Havan ash composed gel formulation for the treatment of Acne. Therefore, the topical formulation containing microsponges of Havan Ash will be formulated and evaluated.
5.	Sareen et al., 2014[51]	The present study was aimed to develop and optimize the microsponges of curcumin for colon specific drug delivery in a view to bypass the upper gastrointestinal tract (GIT) for enhanced therapeutic effect.
6.	Arya and	The work was aimed to validate the gastroretentive

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	Pathak, 2014[52]	potential of microsponges via optimization of targeted floating curcumin microsponges for improved site specific absorption for gastric cancer Modified quasi emulsion solvent diffusion method was used to formulate microsponges using 3 2 full factorial design.
7.	Chanchal et al., 2008[53]	Nutracosmetics are an emerging class of health and beauty aid products that combine the benefits of nutracosmetical ingredients with the elegance, skin feel, and delivery systems of cosmetics.
8.	Eugine et al., 2008[54]	The present study was to produce ethylcellulose microparticles containing BPO which were able to control the release of BPO to the skin and reduces the side effect of commercial BPO such as irritation and percutaneous absorption.

II. CONCLUSION

Formulators may exploit the full possibilities of these unique materials by considering innovative and creative ways to administer actives, which provide greater safety, improved stability, fewer side effects from actives, enhanced multifunctionality, and improved ingredient compatibility.Innovative development tactics and unique formulation procedures round out the picture like Microsponges drug delivery system has significant promise in both the medicinal and cosmetics fields. This approach is appealing because it provides several ways to release bioactive substances with complete efficiency, safety, better stability, and decreased adverse effects. Microsponges also have significant benefits over other formulations in terms of drug mutagenicity and irritancy, and hence have a lot of promise for producing innovative formulations for topical illness. Over Microsponges the herbal Microsponges are more significant as herbs have no side effects like the synthetic drugs. So the herbal microsponge medication delivery system has a lot of potential and is a fairly new topic that has to be studied in the future with further research.

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CONFLICT OF INTREST

Authors have no conflict of interest.

ABBREVIATIONS

TDS: Transdermal Delivery Systems, **MDD:** Microsponge Drug Delivery, **DSC:** Differential Scanning Calorimetry, **FTIR:** Fourier Transform Infrared Spectroscopy, **CUR:** Curcumin, **EC:** Ethyl Cellulose, **TEM:** Transmission Electron Microscopy, **SEM**: Scanning Electron Microscopy, **USP**: United State Pharmacopeia, **ICH**: International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use, **PLGA**: Poly Lactic-Co-Glycolic Acid, **PVA**: Polyvinyl Alcohol

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