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Review Article

A Novel Approach on Micro Sponges Drug Delivery System: Method of Preparations, Application, and its Future Prospective

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ABSTRACT

Microsponges are porous microspheres ranging in size from 5 to 300 micrometers used in a polymeric delivery system. They have been studied for biomedical applications, including targeted medicine delivery, transdermal drug delivery, anticancer drug delivery, and bone substitutes. This research aims to conduct a detailed examination of existing trends and future prospects for a microsponge-based medicine delivery system. The current study investigates the Microsponge Delivery System's design, operation, and possible therapeutic uses (MDS). The therapeutic potential of microsponge-based formulations, as well as patent data, were thoroughly investigated. The authors discuss several efficient methods for producing microsponges, including 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 lyophilization method, the porogen addition method, the vibrating orifice aerosol generator method, the electrohydrodynamic atomization method, and the ultrasound-assisted microsponge. Microsponge may reduce undesired side effects and increase drug stability by boosting drug release. Hydrophilic and hydrophobic drugs can be loaded into a microsponge and transported to a specific target. When compared to traditional distribution methods, microsponge delivery technology offers numerous advantages. Microsponges, which are spherical, sponge-like nanoparticles with porous surfaces, can help increase drug stability. They efficiently alter drug release while also reducing adverse effects.

Keywords: Microsponge, Microsponge delivery system, Novel drug delivery system, Quasi emulsion solvent diffusion, Vibrating orifice aerosol generator, Electrohydrodynamic atomization.

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INTRODUCTION

Drug delivery technology is rapidly evolving when numerous medication delivery technologies are used to boost the effectiveness and cost-effectiveness of treatment procedures (Figure 1).[1] Microparticulate drug carriers were developed as a result of these endeavors to provide innovative drug carrier systems.[2] Multiparticulate systems are important because they are simple to build and can control drug release in various ways, such as rate control, site control, or both.[3] Multiparticulate systems are expected to improve drug absorption because they are more likely to be distributed uniformly throughout the absorption site. Microspheres, microbeads, or microcapsules, microballoons, and microsponges are some of the microparticulate systems developed and explored for this purpose.[4,5] Microsponges protect the entrapped pharmaceutical substance, which are porous microspheres with a stiff and/or pliable matrix that range in size from 5-300 m and are made of physiologically inert organic polymers.[6,7] 2.5x105 pores, which are present in a particle with a size of 25 m and are connected to the interconnecting channels by these pores, generate an inner pore space with a length of around 3 m and a volume of 1 mL/g of the particle.[8] Won and colleagues developed microsponge technology for the first time in 1987, to integrate a broad spectrum of medicinal chemicals in nanotechnology-based formulations.[9]

The microsponge-like spherical particles have a massive, porous surface, and hundreds of interior voids encased in a non-collapsible framework.[10] However, they are commonly used as a carrier strategy because their non-collapsible structures and porous surfaces can entrap various active pharmaceutical compounds and allow for controlled release. Drug-entrapped microsponge can be used to make a variety of formulations, including tablets, gels, capsules, powders, lotions, and creams.[11] This microsponge drug delivery technique provides enhanced drug entrapment and stability, allowing for greater formulation

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flexibility and a significant reduction in unwanted side effects.[12] Substantial amounts of active chemicals can be put into the center or incorporated onto the surface of these microparticles.[13] Microsponge delivery systems improve the safety, effectiveness, and visual appeal of a variety of over-the-counter and other personal care items. The benefits of the microsponge formulation are summarized in Figure 2. The active component is progressively released from the microsponge through a series of phases as it is trapped and introduced into the medium. The dynamic can readily move between the particles and the medium because to the open structure of the microsponge particles until equilibrium is reached, which normally occurs when the medium is saturated.[14] When the medium becomes partially depleted or absorbed, a dynamic flow occurs from the microsponge ingredient component into the medium and then from the medium to the skin.

This desired method of operation emphasizes the significance of creating a vehicle that can be used with microsponge entrapments.[14] Microsponges are patented polymeric delivery systems that can transport a variety of active chemicals, including emollients, fragrances, essential oils, sunscreens, anti-infectives, antifungals, and anti-inflammatory medicines. Because the microsponge particles are too big to be absorbed by the skin, they are considered harmless.[15] Notwithstanding the numerous advantages described above, there is a major risk of bacterial contamination of the trapped material; however, due to the lower hole width, bacteria with pore sizes ranging from 0.007 to 0.2m are unable to enter the microscope tunnel structure.[16]

Microsponges are also the most explored carrier particles due to their numerous advantages over other microparticulate systems, such as ease of manufacture, improved drug loading, and rate control.[17,18]

METHODS FOR PREPARING MICROSPONGES

Some of the methods used to develop microsponge-based drug delivery systems include 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, vibrating orifice aerosol generator method, electro-hydrodynamic atomization method, and ultrasound-assisted production method. Table 1 covers the various microsponge formation procedures that have been used, as well as the merits and downsides of each methodology.[19-33]

Lyophilization Method

This method was utilized to transform the microspheres into porous microspheres. At this step, the microspheres were grown in a chitosan hydrochloride solution before being lyophilized. The rapid removal of the solvent resulted in the formation of pores in the microspheres. Microsponges may be made fast, simply, and frequently with this process. This process is simple and efficient, but it produces microparticles that are fractured or shrunken because the solvent is withdrawn too quickly.

Addition of Porogen Method

In this method, the internal aqueous stage of the water-in-oil-in-water (w/o/w) emulsion was replaced with a porogen, such as hydrogen peroxide or sodium bicarbonate. The porogen was distributed throughout the polymeric solution to provide a consistent dispersion framework. This framework was then redispersed in a PVA-containing aqueous phase. The organic solvent was removed from the w/o/w emulsion after the addition of an initiator, leaving the microparticles behind. Hydrogen peroxide inclusion resulted in equally spaced and overlapping holes ranging in size from 5 to 20 m.[34] While it may be damaged, this porous architecture featured regularly distributed and linked pores.

Liquid-liquid Suspension Polymerization Technique

Microsponges are created (in a single step) via polymerization in suspension in liquid-liquid systems.[19,20] Before being stirred into the aqueous phase, the active components (non-polar medication) and monomers are first dissolved in an appropriate solvent solution of the monomers. In the aqueous phase, for instance, suspending agents such as surfactants and dispersants are often used to aid in suspension production. After creating a suspension with droplets of the right size, polymerization is begun by adding a catalyst or increasing temperature and radiation. In addition, this polymerization results in the formation of a reservoir system with surface-opening holes. In other cases, the pore network is generated during polymerization using an inert solvent that is entirely miscible with the monomer but completely immiscible with water. When the polymerization process is complete, the liquid is drained, leaving behind microsponges that serve as topical carriers for several active chemicals, including antifungals, rubefacients, anti-acne, and anti-inflammatory agents, among others. In some instances, it may be feasible to utilize a solvent to ensure that the functional compounds are integrated quickly and efficiently. If the medication is susceptible to polymerization, a two-step process is adopted; the polymerization is performed using a different porogen, and the functional molecule is subsequently substituted under mild circumstances.[35] Medication loading may be completed in one or two phases, which is one of the method's main advantages. This method has various disadvantages, including the need for two-step processes for thermodynamically sensitive drugs and a restricted drug loading capacity. Since monomers need considerable time to react with non-uniform structures, unreacted monomers and solvent traces may get trapped.[36]

Quasi-emulsion Solvent Diffusion Method

The most popular approach for designing microsponges is the quasi-emulsion solvent diffusion method. A quasi-emulsion

solvent diffusion technique with an exterior and interior phase was used to manufacture all micro-sponges.[37] The internal organic phase is made up of ethyl alcohol, polymer, and triethyl citrate/trichloromethane, which were injected at a concentration of 20% of the polymer to increase plasticity.[38] The external phase is mostly made up of distilled water and PVA. It was initially produced at 600°C before being applied to the exterior phase at ambient temperature. The liquid was continuously stirred for 2 hr after emulsification.[39] After filtering the mixture to remove the microsponges, the finished product was washed and dried for 24 hr at 400°C.[40] This method offers several advantages, such as producing spherical particles, little or no monomer trapping, low solvent traces, high drug loading, no medicine exposure to the environment, and the ability to simply alter the swirling to change the size of the micro-sponges. The possibility of trapping unreacted monomers and solvent traces, an unpredictable structure, slowly occurring monomer reactions, and a two-step process with poor drug loading efficiency for temperature-sensitive medications are some drawbacks of this technique.

Water-in-oil in Water (w/o/w) Emulsion Solvent Diffusion

This technique for producing biodegradable porous microspheres is simple. This approach separated an emulsifying agent such as span, polyethyleneimine, or spaced repetition from an organic polymeric solution utilizing an internal aqueous phase.[41] The w/o emulsion was then dispersed in an external PVA-containing aqueous process to create a double emulsion. Entanglement is a benefit of this method.[42] Several investigations have identified xanthan gum as an emulsifier that stabilizes the internal water-in-oil emulsion.[43] While this technique has the benefit of entrapping both water-soluble and water-insoluble compounds, the use of water-insoluble surfactants, which might retain residues inside the microsponges, is a major drawback.

Oil-in-oil Emulsion Solvent Diffusion Method

The oil-in-oil (o/o) emulsion was made by using a volatile organic liquid as the internal stage, instead of the w/o/w method, which involved letting the water slowly evaporate while stirring.[44] Dichloro-methane was the internal phase, polylactic glycolic acid was the polymer, and span-85, which is a mixture of fixed oil (Corn or Mineral) and dichloro-methane, was the external phase. To make the microsponges, the internal step was slowly added to the dispersion medium while stirring constantly.[45] hydroxyzine HCl-loaded Eudragit RS-100 microsponges were made using this method, with acetone as the dissolver and liquid paraffin as the continuous medium.[46] The physicochemical properties of the drug and the polymer used to make the microsponges affect the choice of an organic solvent and an outer phase.[7] No surfactant residues were found in the microsponges, which is a big plus for this method. The main problems with this method are that you must eliminate all traces of alcohol and use organic solvents.

Vibrating Orifice Aerosol Generator Method (VOAG)

The initial use of a vibrating orifice aerosol generator was producing lipid-bi-layered mesoporous silica particles (VOAG). Surfactant microdroplet evaporation-driven thermal deposition generated porous particles using the VOAG technique. Initially, a stock solution for the core particle was made by refluxing a hydro-ethanolic mixture of tetra-ethyl-orthosilicate in diluted HCl. This stock solution was diluted with a surfactant-containing solvent and stirred to generate monodisperse droplets, encased in microsponges.[47]

Ultrasound-assisted Production Method

This technique was developed to produce the nano-sponge by modifying liquid-liquid suspension polymerization to employ -cyclodextrin as a monomer and di-phenyl carbonate as a cross-linking agent. To control the range of the microparticles, the reaction mixture was heated and sonicated. The reaction mixture was allowed to cool before being pulverized to generate particles that were first rinsed with distilled water and then ethanol.[48] Cross-linked-CD permeable microparticles molar medications effectively load medications. The results are easily reproducible, and no solvent residues were found. Nevertheless, this approach has the disadvantage of trapping potentially hazardous cross-linking agent residues.[7]

Electrohydrodynamic Atomization Method

Pancholi *et al.* created porous chitosan microspheres using this approach in 2009.[49] The chitosan solution was ultrasonified to generate bubbles. A steel capillary was then perfused with the bubble solution using a syringe pump, and the suspension was electro-hydrodynamically vaporized. The diameter of the capillary was meticulously chosen to ensure that every suspension bubble stayed intact as it passed through. The sole factor in determining the voltage was the amount of chitosan present in the test solution. With the exception of the maximum concentration, which proved challenging to electrospray, the flow rate and applied voltage generated the stable cone-jet mode in each case. The chitosan microspheres were cross-linked using a 4% weight-volume solution of sodium hydroxide in water.[7] There is the potential for the therapeutic molecule to combine with the monomer. Controlling the particle and pore size of the microsponges generated by this approach also requires experience.

FACTORS AFFECTING THE RELEASE OF DRUG FROM MICROSPONGE

In the design and manufacture of these multifunctional microcarriers, the physicochemical characterization of the microsponge is a crucial step. Several complementary techniques, such as HPLC, FTIR, DSC, PXRD, and SEM, are used to study the morphological features and porosity of microsponges.[50]

Considering the physicochemical properties of any carrier play a key role in affecting drug loading and release behaviors at a specific target, scientists must analyze the numerous physicochemical components of microsponges using the right approaches, as seen in Figure 3. Yet, this concept contradicts the standard formulation principles used in topical treatments. Improving the solubility of the active medicine in the vehicle is generally recommended for these classic systems.[51] When using microsponge entrapment, it is highly recommended that the active chemicals be sufficiently soluble in the vehicle so that the vehicle can deliver the final loading dose of the substances before releasing them from the microsponge. This is possible by altering the equilibrium between the polymer and the carrier.[52] Producing the microsponge polymer with both free and trapped active ingredients, resulting in a pre-saturated vehicle, is another strategy for minimizing the unintended leaching of the active components. In addition to the partition coefficient between the polymer and the vehicle, diffusion or other stimuli, such as steam, pH, friction, or temperature, may influence the release rate.[9,53] Depicts a variety of factors that may influence the drug release from the microsponge.

Temperature

Some encapsulated active substances may be too viscous to transfer rapidly from microsponges to the skin at normal temperatures. Enhanced release is a result of the higher flow rate generated by a rise in skin temperature.

Pressure

By rubbing or applying pressure on microsponges, the active chemical may be released onto the skin. The strength of the microsponge determines the amount of release.

Solubility

Microsponges that contain untargeted substances such as antiseptics and deodorants release their contents upon contact with water. The release may also be initiated via diffusion, but the partition coefficient between the microsponges and the external system must be considered.

pH triggered systems

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USE OF DRUG DELIVERY SYSTEM RELYING ON MICROSPONGES

In recent years, there has been more interest in making medicines that can be given to specific parts of the body. Microsponges are flexible polymeric delivery systems that contain porous microspheres. They can contain a wide range of active chemicals, such as emollients, perfumes, essential oils, sunscreens, anti-infectives, anti-fungal, and anti-inflammatory agents. It also has a lot of benefits, such as better control over drug loading and rate, uniform distribution, and easy production.[54]

The Role of Microsponges in the Delivery of Anticancer Drugs

A colon-specific drug delivery system is one type of drug delivery system that aims to improve effectiveness and reduce side effects by putting high concentrations of medication in the colon.[55-57] Microsponges can also be used to give drugs by mouth so that they last longer and are less harmful. 5-fluorouracil can be used to treat many different types of solid tumors, and its ability to treat cancer can be improved by making it build up more in tumor areas. The solvent diffusion method for oil-in-oil emulsions was used to make microsponges with 5-FU. Pure 5-FU was found to get out in about 20 min, while microsponges slowly let out the drug for up to 5 hr after a quick release.[58] Table 2 is a list of more examples of microsponge delivery systems that contain anticancer drugs.[58-60] Grimes *et al.* made microsponges with 0.15% retinol and 4% hydroquinone to treat post-inflammatory hyperpigmentation and melanoma. People with hyperpigmentation were given hydroquinone for a longer time, even though it made their skin less sensitive. An open-label trial was done to see how bad pigmentation was, and the area of the lesion got a lot better and the number of sick people got a lot less. One person dropped out of the study because of a mild allergic reaction, which showed that the formulation was safe.[13] In a different study, Jain and his colleagues used the quasi-emulsion solvent diffusion technique in ethyl cellulose and Eudragit RL 30 D to make 5-Fluorouracil-loaded microsponges. They found that 5-FU 5-FU was five times as effective as usual.[58-60]

Microsponge used in the topical administration

Topical medications are often used to treat skin conditions and even in cosmetics, even though they can cause severe skin irritation, especially in people with sensitive skin.[61] The Transdermal Delivery System (TDS), which uses the epidermis as its primary site, has been used to develop a number of reliable and predictable systems for systemic medications.[62] In this method, the medicine is slowly injected into the epidermis in the hope that it will stay mostly localized, have little effect on the skin, and not have a big effect on the circulation throughout the body.[63,64] Numerous topical products with microsphere bases that have undergone testing for protection and efficacy in the treatment of dermatological disorders[65] are now available in the United States. Acne, psoriasis, dandruff, eczema, scleroderma, hair loss, skin cancer, and other terrible conditions can be treated effectively with microsponges that can be turned into creams, lubricants, and moisturizers (Table 3). Benzoyl peroxide, retinoic acid, HQ + retinol, and 5-FU-based formulations are a few examples

Table 1: A combined list of various techniques of microsponge formation with advantages and disadvantages of each technique.

Sl. No.	Techniques name	Advantages	Disadvantages	Excipients	References
1	Liquid-liquid suspension polymerization technique.	Modifications to one-step or two-step drug-loading procedures are possible.	Un-reacted monomers and solvent particles may be trapped. For thermo-sensitive medicines with limited drug loading efficiency. Particles are not uniform. A two-step technique is required.	Surfactants like peroxides, benzo- yl,t-butyl, diacetyl and lauroyl peroxides, and dispersants such as methyl and ethyl cellulose.	19,20
2	Quasi-emulsion solvent diffusion technique.	No trapping of monomers. Solvent traces are minimal. High drug loading. There is no exposure of the medication to the environment. Controlling the stirring can readily control the size of microsponges. Sphere structured particle.	Unable to load water soluble medicine. Long monomer's reaction. Volatile water-soluble solvent dissolves the drug.	Edugit RS-100, Dichloromethane, plasticizer, piroxicam, and Tri-Ethylcitrate (TEC).	21,22
3	w/o/w emulsion solvent diffusion technique.	Load water-soluble medicines. Entrap proteins and peptides.	Water-insoluble surfactants are used, which can leave residues in the microsponges.	Span, polyethylene imine, stearyl amine.	23
4	Addition of the porogen method.	Pores are well dispersed and inter- linked.	Structure disturbed.	Hydrogen peroxide and/or sodium carbonate.	24,25
5	Oil-in-oil emulsion solvent diffusion method.	Surfactant traces not found.	To get rid of the residues of alcohol, need to wash it well. Organic materials solvents.	Methocel 10000cps, eudragit-S100, eudragit-L100, eudragit-RL100, eudragit-RS100, acetone, Liquid paraffin.	26,27
6	Lyophilization method.	Simple, rapid, and repeatable outcomes.	Microparticles may break or shrink.	Hydrogen peroxide solution (30%), Polyethylene Glycol (PEG) 200, PEG-400, PEG-600, Dimethyl Formamide (DMF), Dimethyl Sulphoxide (DMSO), ethylene glycol.	7,28
7	Ultrasound-assisted production.	No solvents residues. Easily repeatable	Not quite right structure. Use of potentially hazardous cross-linking agents.	Beta-cyclodextrin (BCD), Diphenyl carbonate.	29,32
8	Vibrating orifice aerosol generator method.	Targeted drug delivery.	Presence of acid reflux.	Tetraethyl orthosilicate and other surfactants.	26
9	Electro hydrodynamic atomization method.	Easily repeatable results.	Medication molecule will bond to the monomer. Controlling particle and pore size necessitates experience.	Hydroxypropyl Methylcellulose (HPMC) and lactose monohydrate, Span 20.	33

Table 2: Microsponge drug delivery for anticancer agents.

Sl. No.	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Prednisolone	Colon target MSP tablets to treat ulcerative colitis.	Quasi- emulsion solvent diffusion.	Eudragit S 100 (ES)	Inflammatory Bowel Disease (IBD) and other colon illnesses are managed.	59
2	Meloxicam (MLX)	Erosion-based colon-targeted matrix tablet.	Quasi- emulsion solvent diffusion.	Eudragit RS 100	Developing a calcium-pectinate matrix pill for colon-targeted distribution with the potential to be used as a colorectal cancer adjuvant therapy.	60
3	5-Fluorouracil	--	Quasi-emulsion, solvent diffusion.	Ethyl cellulose and Eudragit RL 30 D	Increasing the efficiency of 5-FU.	58

of frequently used topical active substances.[66] When applied to the skin, microsponges have several advantages over traditional formulations, such as causing little or no irritation to people with acne, skin that is sensitive to light, or skin that is too dark.[67] Additionally, microscopic microspheres known as microsponges can absorb skin secretions and reduce skin oiliness Oral Drug Delivery System Microsponges: Encasing poorly water-soluble medications in a microsponge capillary system may make them more soluble and oral. The first microsponges-based oral medicine delivery trial was undertaken by A.P. Pharma, Inc. in the US. Because microsponge particles entangle with the rough intestinal mucosa, these carrier systems may increase bioavailability by speeding adsorption and dissolution.[7] A controlled oral distribution microsponge delivery device may safeguard active chemicals.[72] Colonic enzymes release them into the lower gastrointestinal tract. The microsponge medication delivery device will benefit if the method works.[76] Mohammad Jafar and colleagues created a luteolin-entrapped gastric floating microsponge for Helicobacter pylori. Luteolin-based microsponges had double the anti-Helicobacter pylori activity of pure luteolin.[77] In another investigation, oil-in-oil emulsion solvent diffusion caught albendazole on Eudragit RS100 microsponges. Albendazole microsponges showed a greater AUC than albendazole suspension against Haemonchus contortus in parasite-infected goats.[78] This shows that albendazole may be used orally as a sustained-release microsponge for parasitic worms. Table 4 lists other oral medicine microsponge formulations.[77-81]

Microsponges as a Bone Replacement Technique

Bone replacement compounds were made from pre-polymerized poly-methyl-methacrylate granules and liquid MMA. The monomer was mixed with calcium-deficient hydroxyapatite powder and tri-calcium phosphate grain aqueous dispersions. As the composites were porous, fresh trabecular bone formed in the pores where the inorganic particles were inserted. The material was biocompatible, osteogenic, and osteointegrated.[82]

Cardiovascular system treating microsponges

Cardiovascular engineering and several cardio-selective drugs also use microsponge technology (Table 5). Seeding biodegradable hematopoietic cells is a complex, invasive procedure that exposes patients to infection. Biodegradable collagen microsponge can regenerate autologous vascular tissue.[83] Histological investigation showed an endothelial cell monolayer, smooth muscle cells in parallel, and a repaired vascular wall with proteolysis and collagen fibres.[84] After six months, the patch's cellular and extracellular components matched real tissue. This patch may also be employed for *in situ* cellularization and allogeneic tissue formation in cardiovascular surgery, as illustrated in Table 5.[85-90]

Microsponge for Sustained Release Drug Delivery

Tablets and capsules take 30 min to start working and last 47 hr. The body eliminates the medication within 5-7 hr after oral administration in healthy people. Nifedipine's short half-life (t1/2, 2 hr) requires regular doses, although it may alleviate cardiovascular disorders. For clinical application and patient acceptance, sustained-release microsponges containing nifedipine were made into tablets.[91] Doperidone is another possibility for sustained-release formulation since it needs long-term therapy and substantial doses. Prolonged-release domperidone microsponge-based capsules minimize side effects and increase release kinetics and effectiveness for gastroparesis, emesis, and other illnesses.[11,92] Table 6 lists sustained-release microsponge formulations for diverse uses.[93-101]

Diagnostic agent delivery using microsponges

Microsponges solubilize poorly soluble hydrophobic medicines in a hydrophobic core to enhance cancer-specific combination medication administration and pharmacokinetics. Subhan and

Table 3: Brand/Trademark for microsponge products used in dermatology and cosmetics.

Sl. No.	Brand Name	Manufactured Name	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Clozole gel 15 g	Psyco Remedies	Fluconazole	Gels	Quassi emulsion diffusion method.	Ethyl Cellulose (EC) and Eudragit RS 100.	Anti-fungal infection treatment.	69
2	Ertaczo	Glenmark Pharmaceuticals Ltd.	Sertaconazole nitrate	Gel	Quasi-emulsion solvent diffusion method.	Eudragit RS100, polyvinyl alcohol.	Anti-fungal	70
3	Carbopol gel	Scott Paper Company.	Miconazole	Cream	Quassi emulsion solvent diffusion method.	Ethyl cellulose, Polyvinyl alcohol and dichloro-methane.	Diaper dermatitis, use a micro- sponge gel. Dermatitis, acne and other topical infections.	71
4	Brevoxyl	Unicure India Pvt. Ltd.,	Benzoyl peroxide	Gels, lotions, cream	Quasi-emulsion solvent diffusion method.	Ethyl cellulose and dichloromethane.	Reduced skin irritation and sensitization, Anti-acne.	72
5	EpiQuin Micro	SkinMedica, Inc. USA.	Hydroquinone and retinol	Gel, lotion, cream	Quassi-emulsion solvent diffusion method Liquid-Liquid Suspension Polymerization.	Polyvinyl Alcohol (PVA), ethyl alcohol.	Enhanced oxidation resistance, effectiveness, and visual appeal. Hyper pigmentation.	35
6	Carac Cream, 0.5%	Dermik Laborato- ries, Inc. USA.	5-Fluoracil	Gel, Cream, Solid parti- cles	Quassi emulsion solvent diffusion method.	Eudragit-L100 (Ed-L100) and/ or Eudragit-S100 (Ed-S100).	Lesion reduction, Actinic keratosis Treatment of colon cancer.	37
7	Salicylic Peel 20 and 30	Biophora Medical Skin Care, Ontar- io, Canada.	Salicylic acid	Gel, Oint- ment	Quasi-emulsion solvent diffusion method.	Eudragit RS100, dimethacrylate, ethyl cellulose, polystyrene and PHEMA.	Excellent exfoliation.	73
8	Line Elimina- tor Dual Retinol Facial Treatment	Avon Products, Inc. UK.	Retinol	Cream	Suspension polymerization technique.	methyl methacry-late/ glycol di- methacrylate.	Anti-Wrinkles.	73
9	Retin A Micro	Ortho-MCNeil Pharmaceutical, Inc. USA.	Tretinoin	Gel	Quasi emulsion solvent diffusion method.	-	Acne vulgaris.	72
10	Retinol 15 Night cream	Biomedical IMPORIUM, South Africa.	Retinol	Creams, gel	Liquid suspension polymerization method.	methyl methacry-late/ glycol di- methacrylate.	Anti-wrinkles Skin supplement.	73
11	Oil-free matte block SPF 20	Dermalogica, LLC, USA.	Zinc gluconate	Lotion	Quasi-emulsion solvent diffusion method.	Eudragit RS 100.	Sunscreen	50

Sl. No.	Brand Name	Manufactured Name	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
12	Melanin Microsponge	Advanced Polymer System Inc., US.	Melanin	Gel	Emulsion solvent evaporation method.	-	Hyperpigmentation disorders.	-
13	Ultra Guard	Scott Paper Company, USA.	Dimethicone	Cream, lotion	Liquid-liquid suspension polymerization.	Eudragit RS100, Dimethacrylate, Ethyl Cellulose, Polystyrene and PHEMA.	Protective for babies.	50,74,75
14	Lactrex 12% Moisturizing Cream	SDR Pharmaceuticals Pvt. Ltd., India.	Ammonium lactate.	Cream	Quassi emulsion diffusion method.	Ethyl Cellulose, Eudragit RS100, Polystyrene and PHEMA.	Moisturizes, 12% lactic acid, ammonium lactate and also contain water and glycerine.	50

Table 4: A list of the medications used in the formulation of the microsponge for oral drug administration.

Sl. No.	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Domperidone	MSP loaded capsules	Quasi-emulsion solvent diffusion.	Eudragit RS-100	Anti-emetic treatment of gastroparesis, emesis, and other stomach disorders.	11
2	Famotidine	Floating MSP	Quasi-emulsion solvent diffusion.	Polyvinyl alcohol Eudragit RS-100.	Anti-ulcer	79
3	Pantoprazole sodium	Tablet	Quasi-emulsion solvent diffusion method.	Eudragit RS 100), Polyvinyl alcohol.	For the management of Gastroesophageal Reflux Disease (GERD).	80
4	Luteolin	Gastric floating microsponge	Quasi-emulsion method.	-	For targeting *H. pylori* infections.	77
5	Albendazole	-	Oil-in-oil emulsion solvent diffusion method.	Eudragit RS100	To target parasitic worms in both humans and animals.	78
6	Lansoprazole	Delayed release MSP	Quasi-emulsion diffusion technique.	Eudragit L 100 and Eudragit S 100.	Proton pump inhibitor, used as a delivery system for acid labile drug lansoprazole to avoid its degradation in acidic media of the stomach.	81

Torchilin, explain how these micro-sponges self-assemble to create dense siRNA concentrations in nanoparticles with lower poly-cation concentrations.[102] They also report a polymeric siRNA that self-assembles into RNA interference (RNAi) microsponge structures. Polyplexes may be changed to change the therapeutic potential of microsponges.

As Vehicles for Diabetes Treatment

Chronic hyperglycemia, which may lead to life-threatening complications, makes diabetes a major health risk. Microsponge-based medication delivery may revolutionize diabetes therapy since it requires frequent dosing and 40–50% of patients have trouble following treatment regimens. A controlled-release gastro-retentive microsponge formulation of miti-glinide calcium, a new anti-diabetic, was created in research. *In vivo*, it reduces the requirement for frequent delivery, improving diabetic patients' adherence and diabetes management.[103] Meenakshi and colleagues generated floating microsponges of glipizide for an inquiry. The formulation allowed for longer drug release at the site of absorption, which may enhance diabetes

Table 5: Microsponge drug delivery systems for the treatment of cardiovascular disease.

Sl. No.	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Candesartan cilexetil	MSP	-	Eudragit RS 100, RL 100, S 100	Anti-hypertensive, Enhanced solubility and dissolution rate.	86
2	Metoprolol succinate	Colon-specific MSP tablet	Emulsion solvent evaporation method.	Ethyl cellulose, HPMC	Anti-hypertensive	87
3	Nicorandil	MSP sustained release tablet	Quasi-emulsion solvent diffusion.	Eudragit - RSPO and HPMC K100M.	Potassium channel opener. It is used to treat heart problems.	88
4	Temisartan	Tablet	Quasi-emulsion solvent diffusion.	Eudragit E or eudragit L in organic solution as the internal phase and aqueous solution of polyvinyl povidone as the external phase.	When compared to commercialized (Micardis®) tablet formulations, tablet formulations had a better release profile in all categories.	89
5	Valsartan	-	Quasi-emulsion solvent diffusion.	Ethyl cellulose, Polyvinyl alcohol.	Stability enhancement, reduce side effects.	90

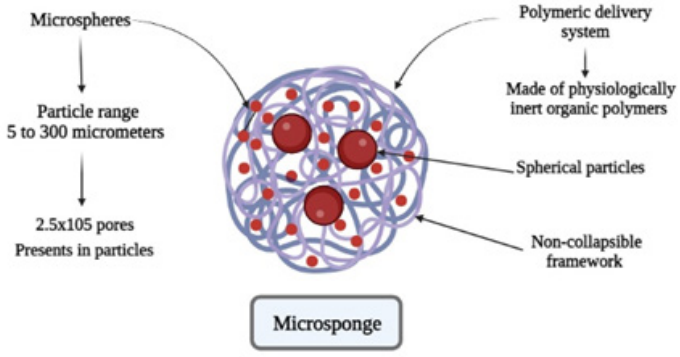

Figure 1: Ordinary diagram of microsponge.

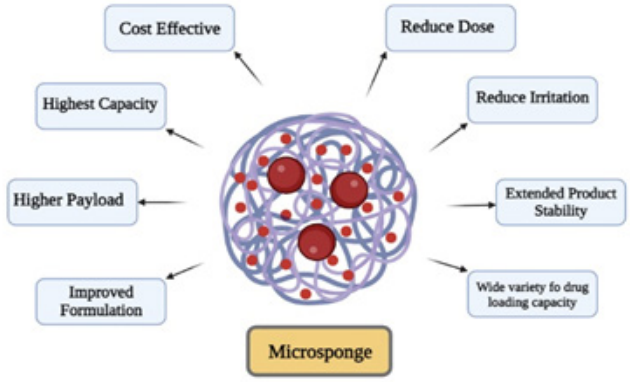

Figure 2: Advantages of Microsponge.

treatment by reducing plasma medication concentration variance. The formulation is expected to lower blood sugar levels longer than the quick-release version of glipizide and enhance diabetes circumstances for disease management (Table 7).[103-105] Floating microsponges are a unique way to make gastro-retentive diabetic medicines, which must reside in the upper GIT for optimal therapeutic action.[104]

Anti-allergic and anti-inflammatory drug delivery via microsponge

Anti-allergic drugs treat inflammatory diseases by limiting the generation and release of inflammatory mediators like histamine at the targeted location. NSAIDs alleviate pain, inflammation, and fever despite gastrointestinal side effects. Allergic areas are testing many reliable and cutting-edge medication delivery systems. Lately, topical anti-inflammatory gels containing naproxen encapsulated in a Eudragit-based microsponge delivery system have been created to solve some of the physicochemical difficulties and limits of traditional pharmaceutical formulations (e.g., poor solubility and absorption, skin permeation, stability). Naproxen microsponges were made using Eudragit RS-100, carbopol, and PVA in a quasi-emulsion.[106] Microsponge delivery technology aids many allergy problems by continually spreading drugs (Table 8). A microsponge containing diclofenac diethylamine was tested against arthritis and musculoskeletal diseases. It released medication slowly, unlike the standard formulation.[12] Flurbiprofen microsponges placed to the epidermis release bioactive compounds on a schedule and react better to friction, temperature, and pH.[107] Microsponge entrapment of medicines offers several benefits beyond managing release and drug

Table 6: Several formulations of sustained-release microsponge.

Sl. No.	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Dicyclomine	-	Quasi-emulsion solvent diffusion.	Eudragit S-100	New colon-specific medication delivery method. Polysaccharides derived from nature (pectin) for the treatment of irritable bowel syndrome.	93
2	Silver sulfadia- zine	Gel	w/o/w emulsion solvent evaporation.	Carbopol 934 and Ethyl cellulose (18–22 cps viscosi- ty grade) (EC).	Reduce applica tion frequency, reduce skin irritation, low cytotoxicity on dermal cell lines.	94
3	Levonorgestrel	-	Quasi-emulsion solvent diffusion.	Carbopol 934	Improve the bioavailability of the drug.	95
4	Indomethacin	Gel Cream	Quasi-emulsion solvent diffusion.	Eudragit RS 100	Reduces the number of doses required, improve the pharmacological action.	68
5	Paeonol	Cream	Quasi-emulsion solvent diffusion.	Ethyl cellulose-M70	Enhance paeonol permeation rate while minimizing transdermal drug penetration into the body, resulting in increased drug bioavailability.	96
6	Cinnarizine	Tablet	Quasi-emulsion solvent diffusion	Ethyl cellulose, PEG-8 caprylic,	Sustained targeted delivery system for treatment of vertigo, motion sickness, and vomiting.	97
7	Mupirocin	Emugel	Emulsion solvent diffusion method.	Ethyl cellulose and di- chloromethane as a solvent which contained PVA as an emulsifying agent.	Increased skin retention for treating skin infections.	98
8	Loratadine	Liqui-gel	Quasi-emulsion solvent diffusion.	Ethyl cellulose and PVA.	Controlled- release bioadhesive floating microsponges.	99
9	Carbamazepine	Tablet	Quasi-emulsion solvent diffusion technique.	Ethyl cellulose and Polyvinyl Alcohol (PVA).	Better encapsulation and sustained release of CBZ for oral administration.	100
10	Acetazolamide	Topical MSP *in situ* ocular gel	Liquid-liquid suspension polymerization methods. Water-in-oil-in-water (w/o/w) emulsion solvent diffusion.	Ethyl cellulose polymer.	Anti-glaucoma agent.	101

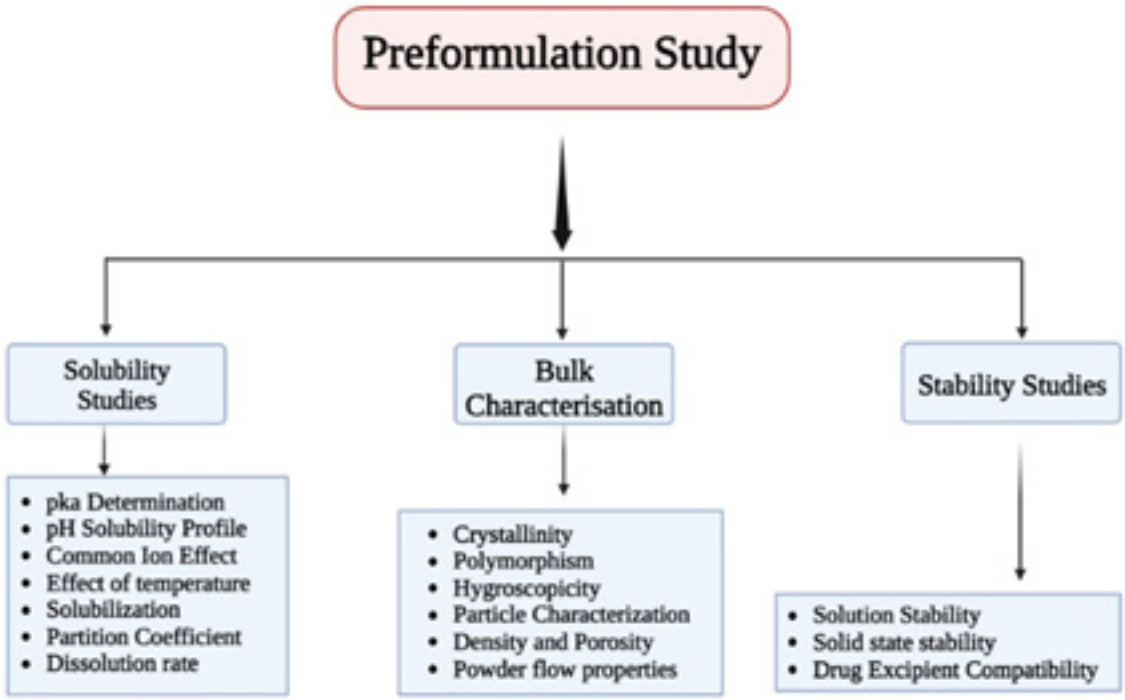

Figure 3: Physicochemical characterization of microsponges.

Table 7: The microsponge delivery technique incorporated anti-diabetic medicines.

Sl. No.	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Nateglinide	-	w/o/o double emulsion solvent diffusion.	Ethyl cellulose and hydroxy propyl methyl cellulose.	Type-2 diabetes treatment (non-insulin-dependent).	-
2	Nebivolol	Gel	Oil in oil emulsion solvent diffusion.	Eudragit RS 100 and Carbopol 934.	Diabetic rats healed wounds faster.	105
3	Mitiglinide calcium	-	Quasi-emulsion solvent diffusion method.	Eudragit RS100, ethyl cellulose, and polyvinyl alcohol.	Gastretentive MSP improves diabetes treatment by eliminating frequent dosages.	103
4	Glipizide	Floating micro- sponge	Quasi-emulsion solvent diffusion method.	Polyvinyl alcohol, triethyl citrate.	Gastro-retentive diabetes medicines.	104

loading, including less side effects, higher stability, formulation attractiveness, and formulation flexibility.[108-119]

Antimicrobial Drug Entrapment Microsponge

Most bacteria acquire multidrug resistance, making treating microbial illnesses difficult. Antibiotic delivery techniques improve effectiveness and lower costs to fight MDR. Microspheres, nanoparticles, microsponges, and liposomes may be used to better disperse active medicines.[66] The pharmaceutical industry's biggest issue is regulating active medicine distribution to a specific body area. The microsponge delivery system is easy to build and may regulate drug release through rate, location, or both.[120] Table 9 lists microsponge delivery method antibacterial medicines.[121-130]

SCOPE AND FUTURE PROSPECTIVES OF MICROSPONGE DELIVERY SYSTEMS

MDS has a promising future in the pharmaceutical industry due to its unique properties, which include enhanced product performance and refinement, extended release, less irritation, increased physical, chemical, and thermal stability, and the ability to create innovative product morphologies. MDS is designed to

Table 8: Anti-allergic and anti-inflammatory medication contained inside a microsponge delivery mechanism.

Sl. No.	Active Drug	Formulation Type	Method of Preparation	Polymer Used	Application	References
1	Hydroxyzine hydrochloride	-	Oil-in-oil emulsion solvent diffusion.	Methocel 10000 cps and in combination with Eudragit –S 100, Eudragit-L 100, EudragitRL 100 and Eudragit-RS 100.	Anti-allergic	46
2	Curcumin	MSP in oral capsule and topical drug delivery	Quasi-emulsion solvent diffusion.	Ethyl cellulose and Eudragit S 100.	Anti-inflammatory. Treatment of gastric cancer.	108
3	Celecoxib	Topical MSP gel	Quasi emulsification solvent diffusion.	Eudragit L-100, Ethyl cellulose, Polyvinyl Alcohol.	NSAID (Arthritis), Excellent trapping efficiency and regulated drug release *in vitro*.	109
4	Diclofenac sodium	Colon targeted MSP	Quasi-emulsion solvent diffusion.	Xanthan gum-facilitated ethyl cellulose microsponges p.	NSAID	110
5	Ketoprofen	MSP	Quasi-emulsion solvent diffusion.	Eudragit RS 100	NSAID (arthritis) creams cure superficial skin mycoses.	111
6	Lornoxicam	Cellulosic-microsponge gel	Quasi-emulsion solvent diffusion.	Polyvinyl alcohol (PVA), Tween80, Gelucire 48/16 and Gelucire 50/13.	NSAID (rat rheumatoid arthritis) provides rapid and persistent anti-inflammatory effects.	112-113
7	Mesalamine	Colon-specific MSP tablet	Quasi-emulsion solvent diffusion.	Eudragit RS100, Eudragit S-100 and Eudragit L100.	IBD anti-inflammatory.	114
8	Betamethasone	Controlled release gel	Quasi-emulsion solvent diffusion.	Eudragit RS 100	Skin-anti-inflammatory gel.	115
9	Flurbiprofen (FLB)	-	Quasi-emulsion solvent diffusion.	Eudragit RS 100	Colon medicine administration.	95
13	Paracetamol	MSP tablet	Quasi-emulsion solvent diffusion.	Eudragit RS 100	PCM-based colon-specific medication delivery.	116
14	Diclofenac diethylamine	Gel	Quasi-emulsion solvent diffusion.	Eudragit RS 100	Treating arthritis and musculoskeletal disorders.	12
15	Piroxicam	MSP topical gel for transdermal delivery	Quasi-emulsion solvent diffusion.	Eudragit RS100, RL100, S100	NSAID (Arthritis).	117
16	Ibuprofen	-	Quasi-emulsion solvent diffusion.	Acrylic and Eudragit RS	After compression, microsponges released a lot of tension, making them compressible.	118
17	Fenoprofen	-	Quasi-emulsion solvent diffusion.	Eudragit RS 100 and Chitosan and HPMC for tablet preparation	For colon-targeted, long-term medication.	119
18	Naproxen	Gel	Quasi-emulsion solvent diffusion.	Eudragit RS-100, carbopol, and PVA	Anti-allergic.	106

Table 9: List of anti-microbial agents entrapped in a microsponge delivery system.

Sl. No.	Active Drug	Method of Preparation	Polymer Used	Applications	References
1	Econazole nitrate	Quasi-emulsion solvent diffusion	Eudragit RS100	Anti-fungal	121
2	Ritonavir	Quasi-emulsion solvent diffusion	Eudragit® RS100 in combination with Polycaprolactone triol 300 (NPR-300) or Polycaprolactone triol 900 (NPR-900).	Antiviral agent	122
3	Mupirocin	Emulsion solvent diffu- sion	Ethyl cellulose in dichloromethane	Dermatological antibiotic. Topical administration devices for greater skin drug deposition and longer release.	98
4	Metronidazole	w/o/w emulsion solvent evaporation	Ethyl cellulose	Skin infections.	123
5	Ketoconazole	Quasi-emulsion solvent diffusion	Carbapol 940 and Eudragit RS 100	It decreased fungal gel usage on fungal-induced guinea pig skin.	124
6	Eberconazole nitrate (EB)	Quasi-emulsion solvent diffusion	Ethyl cellulose, Polyvinyl alcohol and Dichloromethane.	Topical fungal treatment may carry EB.	125
7	Tolnaftate	Quassi-emulsion solvent diffusion technique, the liquid-liquid polymeriza- tion method	Eudragit RS 100, Eudragit RL 100, Hydroxy propyl methyl cellulose (HPMC) and Carbopol 934.	Anti-fungal.	126
8	Dapsone	Quasi-emulsion solvent diffusion technique	Ethylcellulose	Spherical, homogeneous, and spongy microparticles with good encapsulation efficiency.	127
9	Flutrimazole	Quasi-emulsion solvent diffusion	Eudragit RS 100	Medication release control and topical treatment of superficial mycoses.	128
10	Clotrimazole	Quasi-emulsion solvent diffusion	Ethyl cellulose and PVA	Long-term medication release from carbopol-loaded clotrimazole microsponge.	129
11	Miconazole (MCZ)	Quasi-emulsion solvent diffusion	Eudragit RS 100	Miconazole (MCZ) vaginal candidiasis microsponges intrigue.	70
12	Babchi Essential Oil (BEO)	Quasi-emulsion solvent diffusion	Encapsulate BEO in Ethyl Cellulose (EC).	Babchi oil may cure dermatological conditions and skin irritation by reducing skin contact.	130

deliver topical antifungal, anti-inflammatory, and anti-dandruff medications. The list of granted patents for the microsponge industry, which spans the years 1985 to 2021, includes a vast array of innovations. Modifying polymer ratios is essential for the advancement of core/shell microsponge delivery systems for oral peptide administration. In addition, it can be used for tissue engineering and biopharmaceutical delivery of colon-specific pharmaceuticals. Because of the development of novel pharmaceuticals and biopharmaceuticals, drug delivery systems are advancing significantly (peptides, proteins, and DNA-based therapeutics). Micro-sized delivery systems are now obsolete, and the search for nanosized carriers is currently intensifying. Micron-sized particles have a much lower ratio of specific surface area to size and a lower capacity to alter active release than nano-sized particles. Although inorganic nanosponges have numerous applications in electronics, more research is required before they can be utilized effectively in medicine. Nanosponges will undoubtedly continue to be popular in the future.[131-134] Several articles also discuss the use of microsponge-based catalysts for the degradation of environmental contaminants in water and

Table 10: Patent databases related to medication delivery systems using microsponges

Sl. No.	Title of Patent (Description)	Inventors	Patent Number	Publication Year	References
1	Compositions and methods of manufacture of compressed powder medicaments.	Theodore H. Stanley and Brian Hague	US5855908A	1985	140
2	Weighted microsponge for immobilizing bioactive material.	Robert, *et al.*	WO1986005811A1	1986	141
3	Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen.	Won R (Palo Alto, CA)	US 4,690,825	1987	142
4	Production of microsponge.	Hiroshi Sakadou and Sueo Kida	JPS63170436A	1988	143
5	Weighted collagen microsponge for immobilizing bioactive materials.	Dean, *et al.*	US4863856	1989	68
6	Wet wipes.	Ho-ward J. Yoh	US4904524A	1990	
7	Two-step method for preparation of controlled release formulations.	Won R (Palo Alto, CA)	US 5,145,675	1992	144
8	Microsphere reservoirs for controlled release application.	Ray, *et al.*	US5725869	1996	145
9	Retinoid formulations in porous microspheres for reduced irritation and enhanced stability.	Forix, *et al.*	US5851538	1998	146
10	Percutaneous delivery system.	Tomlinson, *et al.*	US6211250	2001	147
11	Stabilized retinol for cosmetic dermatological and pharmaceutical compositions, and use thereof.	Shefer, *et al.*	US20030232091	2002	148
12	Analgetic cream comprising salicylate dispersed in silicone oil and microsponge for sustained delivery of counterirritants like menthol.	Koral Embil	WO2004014397A1	2003	149
13	Chitosan microparticles for the topical delivery of water- insoluble active agents.	Cattaneo and Maurizio	US20040247632	2004	150
14	Topical pharmaceutical and/or cosmetic dispense systems.	Koral Embil and Sergio Nacht	WO2004064803A1	2004	151
15	Drug delivery polymer with hydrochloride salt of clindamycin.	Halliday	US20080160065	2008	152
16	Nonwoven towel with microsponges.	Franklin, *et al.*	US7426776	2008	153
17	Method of removing ticks from the epidermal tissue of humans and other mammals.	Kariyon Inc.	US7604814	2009	154
18	Topical anti-acne preparations containing retinoid (tazarotene or adapalene), antibiotic (clindamycin phosphate) and/or keratolytic (microsponge benzoyl peroxide).	Fernando Ahumada Ayala	US20090318371A1	2010	155

Sl. No.	Title of Patent (Description)	Inventors	Patent Number	Publication Year	References
19	Topical administration carrier composition and therapeutic formulations comprising the same.	Celmatrix Corporation	US7749489	2011	156
20	Method of removing ticks from the skin and reducing the risk of bites.	Karykion Corporation	US8323672	2012	157
21	Nucleic acid particles, methods and use thereof.	Hammond, *et al.*	WO2014134029A1	2014	158
22	Gel composition for the treatment of common acne comprising a combination of benzoyl peroxide and adapalene and/or adapalene salt.	Galderma Research and Develop- ment	US8936800	2015	159
23	Method and apparatus for acne treatment using low-intensity light therapy.	David H. McDaniel	US9227082B2	2016	160
24	Mesalamine loaded microsponges formulation.	Dr. Rohitas Deshmukh, *et al.*	202211031794	2022	166
25	A topical gel formulation comprising microsponges of basil oil and process of preparation thereof.	Ritu Rathi, *et al.*	202211024801	2022	167
26	Microsponges drug delivery system of polyherbal drug for hepato-protective disorder.	Kishori Sunil Jagtap, *et al.*,	202221023987	2022	168

soil samples.[135-139] In 2012, Francisco Trotta *et al.* developed cyclodextrin-based nanosponges, which have been heralded as a revolutionary nanosized delivery system (Table 10).[140-159, 161-187]

CONCLUSION

Microsponges are polymeric delivery system that employ spherical nanoparticles. These systems are made up of porous microspheres varying in size from 5 to 300 micrometers, depending on the degree of flattening or after-feel needed in the final formulation. Polymeric delivery systems are made up of porous microspheres that may contain a wide range of active ingredients, including emollients, perfumes, essential oils, sunscreens, anti-infectives, antifungals, anti-inflammatory medicines, and certain antibiotics. These adaptive microsponge systems are made of polymeric materials. The pace of medicine release may be adjusted by choosing the appropriate polymer for injection. As a result, the Microsponge Delivery System (MDS) is a cutting-edge and evolving technology for regular medicine delivery that is now being studied. The microsponge delivery technology, which uses bio erodible polymers and tissue engineering, was initially created for topical distribution but is now used for controlled oral administration. Drug release from microsponge may be regulated, as with other new drug carriers, by altering the medium's polymer solubility, pH, and temperature. Moreover, they may increase medication stability, reduce unwanted effects, and change drug release in a good way. Because of its many benefits, the microsponge method is a trustworthy approach for giving medicine. Moreover, because to its beneficial properties such as continuous release, reduced irritancy, small size, self-sterility, and interoperability with many vehicles and components, MDS has a promising future in a range of therapeutic formulations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

5-FU: 5-Fluorouracil; **API:** Active Pharmaceutical ingredient; **BCD:** Beta-cyclodextrin; **BEO:** Babchi Essential Oil; **DMF:** Dimethyl Formamide; **DMSO:** Dimethyl Sulphoxide; **DSC:** Differential Scanning Calorimetry; **EC:** Ethyl Cellulose; **FTIR:** Fourier Transform Infrared Spectroscopy; **GIT:** Gastro-intestinal Tract; **HPLC:** High-pressure Liquid Chromatography; **HPMC:** Hydroxypropyl Methylcellulose; **IBD:** Inflammatory Bowel Disease; **LBL:** Layer-by-layer; **MDS:** Microsponge Delivery System; **MIC:** Minimum Inhibitory Concentration; **MLX:** Meloxicam; **MSP:** Microsponge; **NSAID:** Non-steroidal anti-inflammatory drugs; **PCM:** Paracetamol; **PEG:** Polyethylene

Glycol; **pHEMA:** Poly (2-hydroxyethyl Methacrylate); **PVA:** Polyvinyl Alcool; **PXRD:** Powder X-ray Diffraction; **RNAi:** RNA Interference; **SEM:** Scanning Electron Microscopys; **iRNA:** Small Interfering RNA; **TDS:** Transdermal Delivery System; **TEC:** Triethylcitrate; **VOAG:** Vibrating Orifice Aerosol Generator.

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