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REVIEW ON MICROSPONGE DRUG DELIVERY SYSTEM: CURRENT STATUS AND THEIR FUTURE PROSPECTS

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ABSTRACT

Microsponges are the tiny sponge -like spherical particles with a large porous surface, particle size ranging from 5 to 300µm in size. Microsponges are designed to deliver the drug effectively at a comparatively lesser dose, enhancing the stability, modifying the drug release profile and minimizing the side effects. Preparation of the microsponges includes two techniques: Liquid–liquid suspension polymerization and Quasi-emulsion solvent diffusion method. Their characterization can be done in many ways like particle size determination, morphology and surface topography, scanning electron microscopy, Determination of loading efficiency, Determination of production yield, Determination of true density, determination of true density, compatibility study, resiliency, stability studies and safety studies. Present work focus on various application and future prospects of the microsponges.

KEYWORDS: Microsponges, polymer, Liquid–liquid suspension polymerization**,** quasi-emulsion diffusion solvent method, porous structure.

INTRODUCTION

MICROSPONGE DRUG DELIVERY SYSTEM

Microsponges are polymeric drug delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favourably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle.[1] The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy.

These Microsponge technology cause rapid evolution in drug delivery technology. new drugs cannot be delivered by conventional mean. In the present years the development of new drugs is not enough for the drug treatment. The biggest challenge up to date is to control the delivery rate of the medicaments by various modern technologies met by extensive research.[2]

Microsponges have the ability to store a large quantity of drugs, thus serve as a drug reservoir and can control the dug release in a sustained manner for longer period of time. Such properties can be exploited for their effective topical drug delivery as there is no chance of microsponge particles to penetrate the skin and cause any advertise to the underlying tissue.[3]

Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, elegance, flexibility in formulation, reduce side effects and modify drug release profile.

The Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain relatively high concentration of active ingredients. Microsponges are polymeric delivery system consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils sunscreens and anti-infective, anti-fungal and anti-inflammatory agents.[4]

Micro sponge is a polymeric sponge porous spherical particle consisting the drug. They are used for releasing the drug in a controlled manner. The size of micro sponge's ranges from 5 to 300 µm in diameter. Microsponges are stable at a pH range of 1-11 with stand a temperature upto 1300 °C Microsponges act as self-sterilizing agents because bacteria cannot penetrate into them as their pore size is 0.25 mm. A typical 25mm sphere will have approximately 2,50,000 pores. The main

objective of using microsponge delivery system is to achieve desired concentration of drug in blood or skin gradually. Microsponges are used in topically applied drugs to improve their performance. There are interstitial spaces between the pores that can entrap wide range of active ingredients.[5]

Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge Drug Delivery System can provide increased efficacy for topically actives agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner.

CHARACTERISTICS OF MICROSPONGES

1. Microsponge formulations are stable over range of PH 1 to 11.
2. Microsponge formulations are stable at the temperature up to 130 0C.
3. Microsponge formulations are compatible with most vehicles and ingredients
4. Microsponge formulations are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
5. Microsponge formulations have higher payload (50 to 60%), still free flowing and can be cost effective.[6]

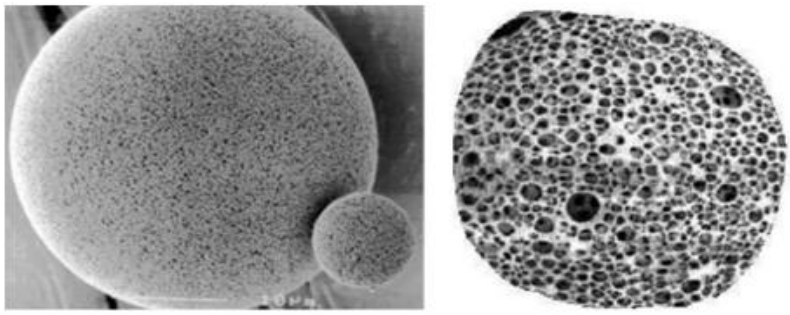

Fig No: microscopic structure of microsponge.

Advantages of Microsponges over other formulations

Microsponges provide the extended and sustained release of the medicament. It improves the compliance of the patient by decreasing the irritation. Formulations containing Microsponges are thermal, physically, and chemically stable. They decrease oiliness and greasiness on the skin by absorbing them.

Advantages over ointments

Ointments need a high concentration of API for required effective therapeutic action because of their low permeation efficiency. Because of high concentrations, it leads to side effects like irritation and allergic reactions and often it is unappealing, sticky resulting in lack of patient compliance. Moreover, they have an unpleasant odor and uncontrolled evaporation of the active ingredient. Incompatibility between the drugs and the vehicles may arise in these formulations. In comparison to ointments, microsponge delivery systems have improved permeation with minimum transdermal penetration into the body which enhance the retention time of drug within the superficial layers.[7]

Method of preparation of microsponges

Liquid–liquid suspension polymerization

Liquid–liquid suspension polymerization Typically, a solution containing monomers and active additives that are water-immiscible is created first. The number of stages involved in liquid–liquid suspension polymerization processes. This water-soluble phase is suspended in water with agitation and often comprises chemicals such as emulsifiers and dispersants. Polymerization is achieved by activating monomers with the assistance of catalysis, temperature elevation, or irradiation polymerization technique results in the formation of 1000 cages of MDS with spherical structures that are linked and resemble a bunch of grapes. After the polymerization is finished, the solid particles will be collected from the resulting suspension. After that, the particles were rinsed and dried before being used again.

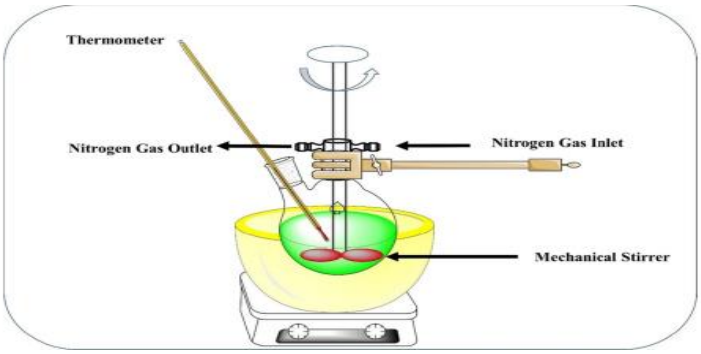

Fig No: representation of Liquid–liquid suspension polymerization method.

Quasi-emulsion solvent diffusion

The procedure described here is commonly used to make topical and oral Microsponges. The procedure involves the production of two phases, one of which is the inner organic phase, which contains the drug, and the other is the outer aqueous phase, which is then agitated and filtered before being used. The inner phase is then blended drop by drop in the outer phase with the assistance of a mechanical stirrer for 60 min. The quasi-emulsion droplets were formed as a result of continual stirring, and the solid cages of microsponge were formed as a result of further organic solvent evaporation. After that, the Microsponges were filtered and dried in the oven for 12 h. summarizes the steps required in microsponge production utilizing the approach quasi-emulsion solvent diffusion.[8]

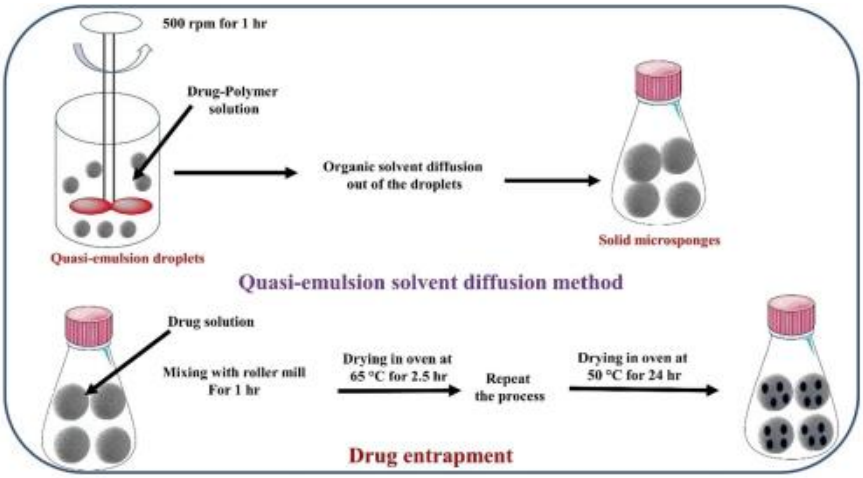

Fig No: representation of Quasi-emulsion solvent diffusion method.

To create a Microsponge delivery system for the gradual release of a useful drug, the below mentioned programmable parameters can be efficiently managed.

i. **Pressure triggered systems:** Microsponge system releases the entrapped material when pressurized/rubbed; the amount released depends upon various characteristics of the sponge. By varying the type of material and different process variables, the microsponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing microsponge showed much more softening effect. The duration of emollience was also much more for the microsponge systems.

ii. **Temperature triggered systems:** Some entrapped active ingredients can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. So it is possible to modulate the release of substances from the microsponge by modulation of temperature. For example, viscous sunscreens were found to show a higher release from microsponges when exposed to higher temperatures; thus, a sunscreen would be released from a microsponge only upon exposure to the heat from the sun.

iii. **pH triggered systems:** Triggering the pH-based release of the active can be achieved by modifying the coating on the microsponge. This has many applications in drug delivery.

iv. **Solubility triggered system:** Microsponges loaded with water-soluble ingredients like anti-perspirants and antiseptics will release the ingredient in the presence of water. Presence of an aqueous medium such as perspiration can trigger the release rate of active ingredients. Thus, release may be achieved based on the ability of the external medium to dissolve the active, the concentration gradient or the ability to swell the microspore network.[9]

PHYSICAL CHARACTERIZATION OF MICROSPONGES

1. **Particle Size Determination:** Particle size analysis of loaded and unloaded microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean particle size range. Cumulative percentage drug release from microsponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30µm can impart gritty feeling and hence particles of sizes between 10 and 25µm are preferred to use in final topical formulation.
2. **Morphology and Surface Topography of Microsponges:** For morphology and surface topography, prepared microsponges can be coated with gold-palladium under an argon atmosphere at room temperature and then the surface.
3. **Scanning electron microscopy**: The processed microsponges can be plated with palladium-gold under argon atmosphere at normal room temperature and then the surface morphology of the microsponges can be confirmed using a Scanning Electron Microscope (SEM). SEM of damaged microsponge particles can also be used to describe the ultra-structure.

4. **Determination of loading efficiency:** The loading efficiency (%) of microsponges can be calculated according to the below equation.
   Loading efficacy
   $$= \frac{\text{Actual drug content in microsponge}}{\text{Theoritical drug content}} \times 100$$
5. **Determination of production yield[10]:** The production yield of the micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.
   Production yield
   $$= \frac{\text{Practical mass of microsponge}}{\text{Theoritical mass (drug+polymer)}} \times 100$$
6. **Determination of true density:** The true density of microsponges can be measured using an ultra-pycnometer under helium gas and is calculated from a mean of repeated determinations.
7. **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).
8. **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.
9. **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.[11]

Safety studies of microsponges can be confirmed by[12]

- Allergenicity in guinea pigs
- Eye irritation studies in rabbits
- Mutagenicity in bacteria
- Oral toxicity studies in rats.
- Skin irritation studies in rabbits.

APPLICATION OF MICROSPONGES

Topical application: A topical delivery system is characterized as the material that penetrates the skin to administer a particular medication. The difficulty is using topical medication is the transportation across the barrier of the skin. Two product categories are included in topical delivery: external topicals and internal topicals.

External topicals: external topicals are applied topically to cutaneous tissues by spreading, spraying or in some other way covering the affected area.

Internal topicals: internal topicals are administered locally by applying them to the anorectal tissues, vaginally, or orally on the mucous membranes. Because topical preparations allow for medication penetration into the underling layers of skin or mucous membranes, they are typically employed for localized effects at the point of application. While some unintentional drug absorption may happen, it usually happens in little amounts and at subtherapeutic levels.[13]

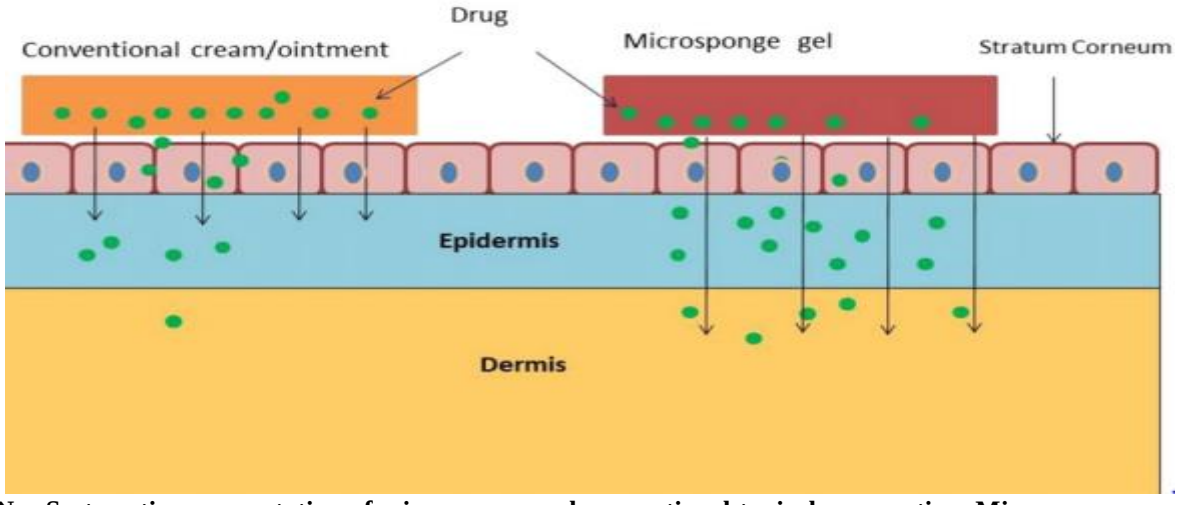

Fig No: Systematic representation of microsponge and conventional topical preparation. Microsponge provides improved permeation through stratum corneum and prolongs retention in epidermis and dermis layer.

TYPES OF TOPICAL DOSAGE FORMS

The followings are the examples for topical dosage forms.

- **DUSTING POWDER:** it is a finely divided insoluble powder containing talc, zinc oxide, or starch which are used on the skin and wounds which prevents irritation or absorbing the moisture which inhibits the bacterial growth.
- **OINTMENTS:** They are semisolid preparations intended for external application to the skin or mucous membranes. Ointments may be medicated or not. Unmediated ointments are used for the

physical effects they provide as protectants, emollients or lubricants.

- **CREAMS:** Pharmaceuticals creams are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either a W/O emulsion or an O/W emulsion or in another type of water washable base. Creams find primary applications in topical skin products. Pharmaceutical manufacturer frequently manufactures topical preparation of a drug in both cream and ointment bases to satisfy the preference of the patient and physician.
- **GEL:** They are semisolid systems consisting of dispersion of small or large molecules in an aqueous liquid vehicle rendered jelly like by the addition of a gelling agent. Topical Solutions: Topical solutions are liquid preparations, that usually are aqueous but often contain other solvents such as alcohol and polyols that contain one or more dissolved chemical substances intended for topical application to the skin.
- **TOPICAL SUSPENSIONS:** Topical suspensions are liquid preparations that contain solid particles dispersed in a liquid vehicle intended for application to the skin.
- **TOPICAL AEROSOLS**: Topical aerosols are products that are packaged under pressure. The active ingredients are released in the form of fine liquid droplets or fine powder particles upon activation of an appropriate valve system. A special dose aerosol that delivers an exact volume (dose) per each actuation.[14]

ORAL DELIVERY

In oral applications, the microsponge system has been found to enhance the solubility of poorly water-soluble drugs by trapping them within the pores of the microsponge. These pores are very small, essentially reducing the drug to microscopic particles. This results in a significant increase in the drug's surface area, which in turn accelerates the rate of solubilization.

For controlled oral delivery of ibuprofen microsponges, an acrylic polymer called Eudragit RS is employed. By adjusting the intraparticle density of the microsponges, the release of ibuprofen can be controlled.

Similarly, sustained release formulations of chlorpheniramine maleate are achieved using powder-coated microsponges. This is prepared through the dry impact blending method, facilitating oral drug delivery with controlled release properties.

BONE SUBSTITUTES

It seems like you are describing a study or experiment involving the creation of composite materials using pre-polymerized polymers of polymethyl methacrylate(PMMA),liquid methyl methacrylate monomer, aqueous dispersion of tricalcium phosphate grains, and calcium-deficient hydroxyapatite powders. These composites were observed to be porous and acted as microsponges.

Furthermore, basic fibroblast growth factor (bFGF) was incorporated into a collagen sponge sheet and sustained release of bFGF was observed in the mouse subcutaneous tissue based on the biodegradation of the sponge matrix. This sustained release exhibited local angiogenic activity, meaning it stimulated the growth of new blood vessels, and this activity varied depending on the dose of bFGF used.

This experiment suggests potential applications in tissue engineering or regenerative medicine, where the composite materials could provide structural support or act as carriers for growth factors to promote tissue regeneration.[1]

BONE AND TISSUE ENGINEERING

Pre-polymerized polymethyl methacrylate particles and liquid methyl methacrylate monomer were combined with two aqueous dispersions of tricalcium phosphate grains and powdered hydroxyapatite lacking in calcium. The finished composites functioned as microsponges and looked porous. A collagen sponge sheet containing basic fibroblast growth factor (bFGF) was maintained released in the mouse sub-cutis in accordance with the biodegradation of the sponge matrix and demonstrated dose-dependent local angiogenic activity.

RECENT DEVELOPMENTS IN MICROSPONGE DRUG DELIVERY SYSTEM

By altering the processes to create porous microbeads, nanoferrosponges, and nanosponges, several advancements were achieved. Additionally, β-CD nanosponges were created. that, unlike polymeric micro or nanosponges, can be employed for both hydrophilic and hydrophobic medicines. The oral administration of dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole, and serum albumin as a model drug was investigated for these sophisticated systems. By treating the β-CD with biphenyl carbonate, the β CD molecule was cross-linked to create these nanosponges. Additionally, several researchers noted that the nanosponges were effective gas carriers. Researchers have also found that adding a cytotoxic to a nanosponge carrier system can make the medication more potent, which raises the possibility that these carriers could be employed to target malignant cells.[15]

Due to an external magnetic trigger that causes the carriers to penetrate deeper tissue, the nanoferrosponges is a revolutionary strategy that created the self-performing carriers with improved penetration to the designated region. So causing the particle exiting a porous system to lose its magnetic substance. A method was created to create the porous micro beads as a result of the enhanced properties of porous microspheres. The monomer in this technique, known as high internal phase emulsion, or HIPE, contained an aqueous internal phase,

a cross-linking agent, and a continuous oil phase. They also noted that siRNA encapsulation was comparatively successful and that RNA stability had improved. This strategy may open up new therapeutic avenues for siRNA delivery.[2]

Medicines Investigated for the Microsponge Delivery System[2,12,16,17,18]

Numerous research provided evidence that numerous APIs have been designed in practical dose forms, the table1 listed alternative API included as microsponges in various dosage formulations for the microsponges delivery system.

Examples of microsponges with their formulations

Medications	Application	Microsponge technology
Indomethacin Paracetamol Piroxicam Femotidine Chlorpheniramine maleate Meloxicam	Inflammation Anti-pyretic, colon targeting. Rheumatoid arthritis Anti-Ulcer Hay fever Arthritis	Tablets
Benzoyl peroxide Diclofenac sodium Fluconazole Mupirocin	Inflammation inflamaton Antibacterial activity Antibacterial activity	Gels
Benzoyl Peroxide	Anti-Acne Treatment	Lotions
Hydroquinone and Retinol	Melanoma	Creams
Poly(DL-lacticco-glycolic acid)	Skin tissue engineering	Implants
Poly (lactic-co glycolic acid)	Cardiovascular surgery	Grafts
Basic fibroblast growth factor	Growth factor	Injection

RECENTLY REPORTED RESEARCH WORK IN MICROSPONGE DRUG DELIVERY SYSTEM

Sl No	AUTHOR	DRUG	METHOD	REMARKS
1	Mohanty D (2016)	Betamethasone	Quasi-emulsion Solvent diffusion method	The production yield is decreased with increasing drug ratio. The polyvinyl alcohol (PVA) concentration is increase with increasing the entrapment efficiency. The F3 formulation less drug release by increasing the drug: polymer ratio.[19]
2	Bhatia M, (2018)	Curcumin	Quasi-emulsion solvent diffusion method	The prepared microsponges have good drug content with a decreasing polymer ratio. The production yield was greatly affected by polymer ratio as well as PVA concentration. The release of all batches ranged from 65% to 89% with different polymer concentrations.[20]
3	Dinesh Mohan S, (2015)	Fluconazole	Quasi-emulsion solvent diffusion method	This study demonstrated that the use of a high amount of PVA caused a slightly increased viscosity of the dispersed phase. The drug release was found to be decreased in the range of 83% to 76% for Eudgrait L-100 because of the polymer matrix release drug after complete swelling and time required for swelling of polymer directly.[21]
4	Bansode AS, (2018)	Nystatin	Quasi-emulsion solvent diffusion method	A mixture of Ethyl cellulose and drug in dichloromethane served as the internal phase &Solution of PVA in water served as external phase. The drug release of gel loaded with nystatin increases with a decease the polymer ratio. From the results, it can be concluded that microsponge-loaded gel shows good release of the drug as compared to nystatin gel.[22]
5	Tomar MK (2022)	Clarithromycin	Quasi-emulsion solvent diffusion method	The F3 microsponge formulation exhibited a production yield of 83.75%, drug content and encapsulation efficiency of 86.04 by different concentration of polymer. F3 microsponges released 69.36% of the drug over a period of 8 hrs.

				By the combination of polymer concentration. The gel prepared using F3 microsponges was transparent, homogenous, and exhibited a pH of 6.8, Spreadability of 9.92 g/cm, and viscosity of 35370.17 centipoises. High viscosity and dispersibility values.[23]
6	Thavva VE (2019)	Terbinafine HCl	Liquid-liquid suspension polymerization	From the production yields of Terbinafine hydrochloride microsponge formulations, it was indicated that increasing the drug: polymer ratio to some extent increased the production yield. The release rate was high during the first two hours then the microsponges were able to sustain the release of THCI for more than 8 h in most formulations by combination of different PVA concentration.[24]
7	Gulati N, (2018)	Miconazole	Quasi-emulsion solvent diffusion method	It is concluded that. Out of all concentration, 300mg polymeric with drug ratio has good production yield with different concentration showed spherical porous microsponges with good entrapment efficiency 79.6% and 66.7µm particle size. The drug release profiles displayed a bi-phasic release with an initial burst effect i.e. 3.8 in 0.25 h to 26.7% in 2h followed by sustained release drug release decreases with an increase in polymer concentration.[25]
8	Pawar AP (2015)	Oxybenzone	Quasi-emulsion solvent diffusion method.	The optimized formulation possesses the particle size and entrapment showed the controlled release and was non-irritant to the rat skin. In creep recovery test it had shown highest recovery indicating elasticity. The controlled release of oxybenzone from microsponge and barrier effect of gel result in prolonged retention of the oxybenzone reduced permeation activity.[26]
9	Yadav V (2017)	Oxiconazole nitrate	Quasi-emulsion solvent diffusion method	It was found that production yield was greatly affected by drug: polymer ratio as well as by concentration of polyvinyl alcohol. It was indicated that increasing polymer concentration, increased production yield while increasing polyvinyl alcohol concentration, decreased production yield. Use of the higher amounts of PVA while preparing microsponges at a higher drug: polymer ratios caused slightly an increased viscosity of the dispersed phase.[4]
10	Syal S (2020)	Havan Ash	Quasi-emulsion solvent diffusion method	The formulation F3 has better results than other F1, F2, and F4 formulations. F3 have its appearance silver colour, consistency very good, Grittiness, homogeneity good, pH 6.3, Microsponge become highly competitive and rapidly evolving technology and more research are carrying out to optimize cost effectiveness and efficacy of the therapy.[27]
11	Rafat S, (2019)	Clobetasol Propionate	Cold method	Clobetasol propionate of microsponge containing 5, 10, and 20 mg/g of, Clobetasol propionate being low-, medium- and high-Gel, in microsponge gel, Clobetasol propionate composed of 6.5% each of Carbopol 934 and gave homogeneity, good consistency, optimum pH of7.2.[28]

SCOPE AND FUTURE PROSPECTIVES OF MICROSPONGE DELIVERY

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 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 soil samples.[29,30]

CONCLUSION

With demand for novel and highly efficient pharmaceutical and cosmetic goods, the market has significant potential for microsponge technology and the adaptability it provides. As formulators consider new and creative ways to deliver actives, The active substances in polymeric delivery systems can be anything from emollients, perfumes, essential oils, sunscreens, anti-infectives, antifungals, anti-inflammatory medications, and some antibiotics. These microspheres are porous. By selecting the right injectable polymer, the rate at which medication is released can be changed. microsponge is currently being researched to employed for regulated oral administration, the bio-erodible polymer and tissue engineering-based microsponge delivery method was first developed for topical distribution. Similar to other novel drug carriers, the release of drugs from microsponges can be controlled by adjusting the temperature, pH, and solubility of the polymer in the medium. Additionally, they might improve drug release, lesser side effects, and boost medication stability. Due to its numerous advantages, the microsponge method is a reliable way to administer medication. Furthermore, MDS has a bright future in a variety of industries thanks to its advantageous qualities including continuous release, decreased irritancy, compact size, self-sterility, and compatibility with several vehicles and components. MDS has a promising future in a range of therapeutic formulations.

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