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MICROSPONGES: AN INNOVATIVE TECHNIQUE FOR BIOMEDICAL RESEARCH

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ABSTRACT A microsponge delivery system (MDS) is a cutting-edge and distinctive method of structured drug delivery. Controlled drug delivery is now possible with the use of microsponge technology. MDS consists of porous microspheres with a substantially porous structure and a very small spherical shape, ranging in size from 5 to 300 microns. MDS is typically used to administer medications through topical channels, but new research has demonstrated the promise of this technique for parenteral, oral, and ocular drug delivery. While reducing the drug's side effects, MDS can readily change the pharmaceutical release shape and enhance formulation stability. Reaching the highest peak plasma concentration in the blood is the main goal of microsponge medication delivery. The most notable quality of MDS is their ability to self-sterilize. MDS is employed in countless studies as an anti-allergic, anti-mutagenic, and non-irritant. This review discusses formulation, eligibility requirements for medications to be included in MDS, formulation processes, evaluation criteria, and the function of MDS in the treatment of various illnesses. In the future, while researching MDS in other illnesses, this review will be quite helpful.

KEYWORDS : Drug delivery, microsponge, topical applications, recent advances, marketed formulation, Future Perspectives

INTRODUCTION:

Drug delivery to certain locations throughout the body is the main goal of drug release strategies. Patient compliance has a significant impact on the health care system and thus improves the effectiveness of pharmacological treatment. Delivering APIs to particular target locations of the body has proven to be a significant challenge, as the pharmaceutical industry has learned(1).

Micro-colloidal drug delivery systems, those are recently been used for research purposes are liposomes, liposomes, micelles and microemulsions have some drawbacks that are overcome by microsponge drug delivery systems. The main difficulties of liposomes are the scale-up problems, high viscosity, and tendency to disintegrate upon injection (resulting in vivo instability and abandoned drug release)(2). micelles become unstable because of their poor ability to dissolve oils (e.g. alkanes). Another drawback is using surfactants is their potential for harmful effects (3). Microemulsions have high surfactant content and their possible toxicity is the main drawback. Concern exists over the impact of environmental conditions on the solubility of drugs.

Microsponge colloidal carriers, a promising replacement for the abovementioned delivery methods, have just come into existence. The reason for this, according to reports, is that microsponges not only combine the advantages of the earlier systems but also get over their drawbacks. These spherical, porous, and strongly cross-linked small particles are known as colloidal carriers(4). The main disadvantage of transdermal administration is that a common drug delivery system is not very soluble in water, which creates a number of challenges when developing conventional dosage forms.

The evaporation of the medication, the carriers' disagreeable scents, and their ugly appearance, which can cause greasiness and stickiness and therefore affect patient compliance, are additional significant challenges with topical pharmaceutical delivery(5). Microsponge delivery system (MDS) is able to overcome these disadvantages. They claim to be able to change the medication's release profile and deliver the drug in the most effective manner at the smallest practicable dose, increasing stability.

The ability of MDS to absorb fluids leads to less oily skin. When the skin requires the medicine contained in the MDS, they gather to some extent in the skin's minuscule cracks and crannies and release it. The size of the MDS microspheres (diameter: 5-300 m) may change depending on how smooth the skin is(6).

The shape of the microsponge is spherical which is mentioned in the figure. 1. The porosity structure of microsponges also allows for controlled release of the medicine that is entrapped, resulting in limited accumulation of the active component in the dermis and epidermis(7). According to findings in the literature, loading microsponges intended for use on the skin has the most frequently used gel bases(8,9).

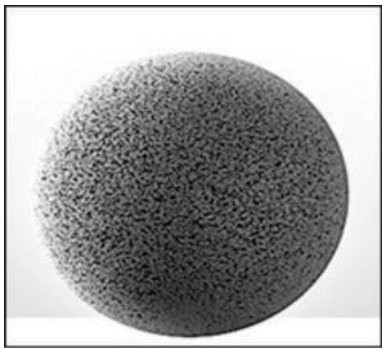

Figure.1. Microscopic structure of Microsponge

Microsponges Chemical MakeUp:

A microsponge "cage" forms as a result of the various polymers utilised to make microsponges for topical application. According to the literature that has been published, the polymers that have been investigated to date include polymethacrylates, as well known as Eudragit polymers (Eudragit RS100, Eudragit RSPO, and Eudragit S100), polylactide-co-glycolic acid, polylactic acid, polydivinyl benzene, polyhydroxy butyrate, and ethyl cellulose(10).

Table 1. Polymers and active ingredients used to make micro sponges

DRUG	POLYMER	DRUG-POLYMER RATIO	REFERENCE
Benzyl peroxide	Ethylcellulose	1:1, 1:3, 1:5, 1:7, 1:9, 1:11, 1:13	(11)
Clobestol Propionate	Eudragit RS 100	1:1, 1:2,1:3	(12)
Prednisolon	Eudragit S100	1:3, 1:6	(13)
Acyclovir sodium	Ethylcellulose	1:2, 1:3	(14)Diclofenac diethylamine Eudragit RS 1001:1, 1:2, 1:3, 1:4, 1:5, 1:6 (15)TerbinafineEudragit RSPO1:1.8, 1:4, 1:1 (16)

Application of microsponges:

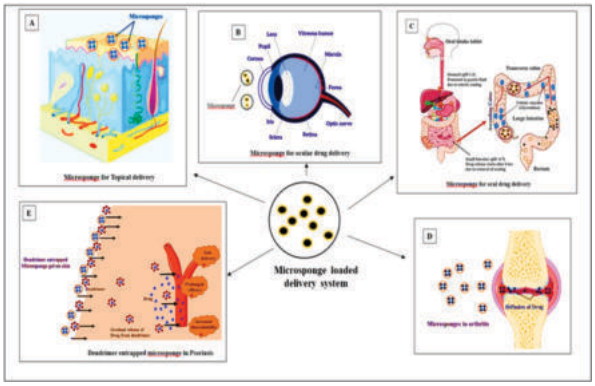

Figure. 2. (A) delivery of microsponge formulation In topical, (B) microsponge for delivery of ocular disease (C) oral delivery of microsponge formulation and release mechanism (D) microsponge delivery for rheumatoid arthritis (E) Dendrimer entrapped microsponges in Psoriasis

Table 2. Drug candidates explored for microsponge drug delivery

SI. No.	Drug Candidates	Preparation type	Applications	Formulation type	References
1.	Benzyl Peroxide	emulsion solvent diffusion	Anti-acne	Cream, gel	(17)
2.	Diclofenac sodium	Double emulsification technique	Dermal infection	gel	(18)
3.	Terbinafine Hydrochloride	Quasi-emulsion solvent diffusion	Antifungal	gel	(19)
4.	Voriconazole	Quasi-emulsion solvent diffusion	Antifungal	Gel	(20)
5.	Eberconazole nitrate	Quasi-emulsion solvent diffusion	Antifungal	gel	(21)
6.	Nebivolol	Oil-in-oil emulsion solvent diffusion	Diabetic wound	gel	(22)
7	Nitrendipine	Quasi-emulsion solvent diffusion	_	_	(23)
8.	Nystatin	Quasi-emulsion solvent diffusion	Antifungal	Gel	(24)
9.	Mupirocin	Emulsion solvent diffusion	Primary and secondary skin infection	Gel	(25)

Microsponges for Oral disease:

The use of MDS for oral drug administration is ideal because this technology can speed up the release of medications with low water solubility by trapping these substances in the pore system of the microsponge. It controls the pH of the microsponge used to administer oral medications. Due to the enteric coating, the medication is not supplied to the mouth when the microsponge is taken out of the mouth and is instead protected by stomach juice (pH 1-3). Due to the action of colonic enzymes (glycosidases), the coating dissolves in the gut, and after 6 hours, the medication starts to spread. The majority of the medications are transported by MDS as they pass through the big intestine's descending colon and the mechanism is described in pictorial form in figure 2. C. (26).

By employing ethylcellulose and PVA as carriers, Bhatia et al. hoped to increase the release of curcumin from microsponges made using a QE solvent diffusion approach. In order to assess the manufactured microsponges' potential for topical and oral medication delivery, carbopol gel was put onto a firm gelatin capsule shell before being sealed. According to tests on release rates, pure curcumin put in capsules only demonstrated an 11.7% release in an 8-hour testing, compared to microsponges, which released 93.2% of their curcumin when placed inside hard gelatin capsule shells. A further evaluation of the microsponges loaded with carbopol gel for ex vivo drug deposition tests revealed that 77.5% of the curcumin was released in under 24 hours(27). The composition of microsponges was optimised by Adalla et al. for better CBZ encapsulation and prolonged release for oral delivery. To assess the oral bioavailability in comparison to unprocessed CBZ, the best formulation was given orally to albino rabbits. The results of the instrumental examination showed that the microsponges contained CBZ in an amorphous or molecularly dispersed form. In proportion to the rise in polymer content, the microsponges' size and entrapment effectiveness increased. Reduction in CBZ release was related to this. CBZ oral absorption was improved by the ideal formulation(28).

Microsponges for ocular disease:

Acetazolamide, an antiglaucoma medication, was developed as microsponges in situ gel for ocular drug administration in the study by Elfaham et al. with the goal of improving therapeutic efficacy and reducing the systemic side effects of oral acetazolamide and it is represented in figure 2. B. The physicochemical characteristics of the in-situ gels, including pH, gelling capacity, gelation time, and rheological characteristics, as well as in vivo experiments, were assessed. The rabbit's eye didn't become irritated by it. These findings demonstrated the potential for acetazolamide microsponges in situ gel for ocular administration(29).

Microsponges for Cosmetics and Dermatology:

The capacity of microsponges to absorb skin secretions, such as perspiration and oil, is one of its most significant characteristics. Due to its extremely absorbent nature, many microsponge-loaded deodorants, antiperspirants, and sunscreens are commercially available. Additionally, skin targeting with MDS is an option for preventing excessive medication absorption into the percutaneous blood circulation. This function may be helpful for treating skin diseases like skin cancer, acne, alopecia, sunburn, hyperhidrosis, and wrinkles.

For Anti-acne drugs

In young adults, acne is a typical skin condition. Despite the fact that topical therapy is the primary method of treatment, the effectiveness and compliance of patients are impacted by the side effects of different topical antiacne bioactive molecules. The use of microsponges as a cutting-edge drug delivery technology that can enhance the action of anti-acne medications has been suggested.

Through the creation of a microsponge-based gel, Jakhar et al. examined ways to overcome the drawbacks of dapsone, such as skin sensitivity, dryness, and discolouration. The findings showed that dapsone-loaded microsponges were successfully manufactured, had good encapsulation efficiency (84.68 ±5.73%), were in the micro-size range (88.06 ±2.97 **µm** to 315.87± 1.99 **µm**), and had cumulative drug release of 52.52± 0.2%. Spongy microparticles that were round, homogeneous, and visible under field emission scanning electron microscopy. The created micro formulation shown good effectiveness and enhanced stability against the selected acne-causing bacteria. The results obtained support the idea that using a dapsone-loaded microsponge gel as an acne treatment can be successful(30).

For Psoriasis:

Psoriasis is a multisystem inflammatory condition of the skin or joints that can be persistent and even multisystemic. It is often characterised by keratinocyte hyper-proliferation and abnormal differentiation(31). Dithranol is a key topical treatment for psoriasis, but it also has undesirable side effects, including staining, burning, irritation, and necrotizing effects on both diseased and healthy cells. Tripathi et al. examined at the potential of poly(amido) amine (PAMAM) dendrimers in the topical application of dithranol through a new microsponge based gel to address these side effects and it is shown in figure.5. E. The quasi-emulsion solvent diffusion method is used to make it. The formulation's percentage yield was discovered to be 66.28%, while encapsulation efficiency ranged from 71.33% to

49.21% and average particle size was found to be between 28 ±1.12 µm and 130 ± 1.01 µm. The modified microsponge formulation was observed to be stable and non-irritating when applied topically to the animals. As a result, it may be concluded that the PAMAM-entrapped dithranol microsponge formulation can provide extended release and efficacy without creating toxicities to the skin, and can therefore be effectively projected in the treatment of psoriasis(32).

For Atopic Dermitis:

Hydroxyzine hydrochloride is used as an antihistaminic medication for atopic dermatitis. While administered orally, this medication's most frequent side effects are blurred vision, lightheadedness, and anticholinergic reactions. For the regulated administration of a topically active substance, a special delivery system i.e, microsponge delivery system has been reported. It is demonstrated by Zaki Rizkalla et al. to be able to lessen negative effects while lowering percutaneous absorption. Oil in oil emulsion solvent diffusion was used to create the drug's Eudragit RS100-based microsponges, with liquid paraffin serving as the continuous medium and acetone as the dispersing solvent. To stop flocculation and create free-flowing microsponges, magnesium stearate was added to the dispersion phase of the mixture. Due to their capacity to absorb water and their ability to disintegrate, pore inducers like sucrose and PGS were utilised to speed up the rate at which drugs were released. We were able to create microsponges with porosities between 60 and 70% and an encapsulation efficiency of over 98%. Using rabbits that had been histamine-sensitized, the pharmacodynamic impact of the selected formulation was studied. To determine when inflammatory tissues had healed, histopathological examinations were also conducted(33).

Microsponge delivery system for Colon Cancer:

Due to first-pass metabolism, oral 5-fluorouracil (5-FU) bioavailability is known to be variable. Othman et al. endeavoured to develop enteric-coated tablets with 5-FU-loaded microsponges (MS) as a novel colon cancer treatment. MS was made as a controlled release system for 5-FU and evaluated for the effectiveness of the drug encapsulation and surface morphology. In addition, pectin and hydroxypropyl methylcellulose (HPMC) were combined, and their flow as a tablet coat encasing the 5-FU-MS core tablets was observed. Additionally, the behaviour of drug release in vitro was examined in various pH environments, and the in vivo mobility of 5-FU-MS-containing manufactured tablets across the GI system was observed using X-ray imaging. The particle size ranged from 53.11 to 41.03 to 118.12 to 48.21 nm, while the encapsulation efficiency ranged from 71.80 to 1.62% to 101.3 to 2.60%. The in vivo X-ray investigation of human volunteers has demonstrated that the tablets eventually reached the colon without causing any disruption in the upper GI system. The developed carrier formulation is regarded as a revolutionary method of 100% targeted delivery of 5-FU to the colon tumour, free of drug release into the upper gastrointestinal tract or first-pass metabolism (34).

Microsponge delivery system for Rheumatoid Arthritis:

The characteristic of rheumatoid arthritis (RA) is significant bone and joint destruction brought on by an augmented autoimmune response at the articular sites(35). It has been researched to treat arthritis using a microsponge to administer Tolmetin sodium. NSAIDs, or non-steroidal anti-inflammatory drugs, include tolmetin sodium (TLM) (NSAIDs). According to pharmacokinetic studies, the currently available TLM dosage forms have a fairly protracted start to the action because of the delayed absorption from the gastrointestinal tract (GIT). In order to increase pre-gastric absorption and increase the bioavailability of TLM fast-dissolving tablets (TLM-FDT), Elsayed et al. set out to develop a combination. The Box-Behnken experimental design was used to create the TLM-FDTs, which are super-disintegrants made of crospovidone (CP) and croscarmellose sodium (CCS), and sublimators made of camphor. Later, the in vivo anti-inflammatory performance of the improved TLM-FDTs formulation was assessed. In addition to having quick disintegration and dissolving behaviour, TLM-FDTs also exhibit good friability, disintegration time, drug release, and wetting time.

As shown by noticeably decreased paw thickness in rats after carrageenan-induced rat paw oedema, a significant improvement in medication absorption and dependable anti-inflammatory activity were also noted. TLM-FDTs are a potential drug delivery method that could improve TLM bioavailability and be utilised to treat rheumatoid arthritis(36). In order to cure arthritis, Hadi et al. created MDS with lornoxicam as the active ingredient and combined them into tablets. They discovered that the medicine was released over a lengthy period of time, ranging from 86% to 96% to 12 hours(37). Figure 2. D. shown microsponge delivery in Rheumatoid arthritis.

Marketed formulation:

Now the cosmetics industry is used worldwide in the market. Some of the marketed formulations which are formulated based on the microsponge delivery system are mentioned in Table.3.

Table 3. List of marketed products for microsponge-based drug delivery systems

SI.No.	Product name	Active moiety	Manufacturer	Applications	References
1.	Ultra-guard	Dimethicone	Scott Paper Company	Protective for babies and hypoallergenic	(38–40)
2.	Carac cream	Fluorouracil	Dermik Laboratories, Inc. USA	Actinic keratoses	(40)
3.	Salicylic peel 20 & 30	Salicylic acid	Biophora medical Skin Care, Ontario, Canada	Excellent exfoliation	(40)
4.	Epiquin micro	Hydroquinone and retinol	SkinMedica Inc.	Hyperpigmentation	(39)
5.	Retin-A-micro	Tretinoin	Biomedic Sothys	Antiwrinkle and skin supplement	(38)
6.	LactrexTM 12% moisturising cream	Lactic acid	SDR Pharmaceuticals Inc., Andover, NJ, USA, 07,821	Moisturizer	(38,40)
7.	Oil free matte block SPF 20	Zinc Gluconate	Dermalogica, LLC, USA	Sunscreen	(39,40)
8.	Retinol 15- night cream	Pure retinol and vitamin-A	Sothys	Anti-wrinkle and anti-aging	(38)
9.	Aramis fragrances	Salicylic acid	Aramis, Inc. USA	Antiperspirant	(39,40)
10.	Sports cream Rs & Xs	Trolamine salicylate	Embil Pharmaceutical Co. Ltd.	Topical analgesic	(38)

CONCLUSION:

Owing of the market's thirst for unique and highly efficient pharmaceutical and cosmetics products, microsponge technology offers a lot of potential. MDS is a potential method for the controlled release of an active chemical loaded in MDS, resulting in fewer pharmacological adverse effects while keeping therapeutic efficacy. According to a number of studies, they are also non-toxic, non-allergic, and non-mutagenic in nature. This drug delivery technique is currently largely used in OTC skincare items, prescription medications, cosmetics, and sunscreens.

It is a very promising technology that will most likely be widely investigated in the coming years due to its numerous medication administration options.

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