REVIEW ARTICLES

A CONCISE LITERATURE REVIEW ON STUDY OF MICROSPONGES FROM ANCIENT TO RECENT

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ABSTRACT

Polymeric microspheres enclosing an extremely porous surface are termed as microsponges. Microsponges are drug loaded microporous beads having 10-25 micron diameter. These may augment stability, ease side effects and amend drug release. Microsponge systems have capability to capture ample drug substances and are then formulated into various products like gel, cream, liquid or powder. Several research studies corroborated that microsponge entities possess non-irritant, non-mutant, non-allergic and non-toxicity features. Suitable analytical techniques for characterization of microsponges can be illustrated for suitable characteristic properties such as thickness, particle size and its distribution, surface and pore properties. Many problems such as repulsive odor, greasiness and skin exasperation are resolved by MDDS (microsponge drug delivery system). MDDS generates prolonged release and site specific action. In this review article, a concise outline of MDDS covering the principle, methods of formulation and characterization have been discussed. Microsponge delivery system (MDS) is primarily utilized for topical and oral formulations but it is also being explored for cosmetic formulations.

Keywords: Polymeric, microsphere, porous, microsponge delivery system, topical, oral and cosmetic

INTRODUCTION

The drug delivery systems which have power to control the release tempo and deliver drugs to target site in the body have a major influence on drug therapy[1]. The controlled release product offer unique benefits over conventional dosage form by carrying out the optimization of pharmacodynamic (PD) and pharmacokinetic (PK) features of the drug molecule in such a manner that it lowers frequency of the dose to such a level that regularly once dose is adequate for effective drug therapy. Local and systemic side-effects can be overcome through constant plasma concentration[2-4]. Controlled release system provides continual stream of the active ingredient at zero order rate by regularly releasing in a specific span of time a proportion of drug molecules equivalent to the excreted quantity by the body[5-6].

Microsponge-based drug delivery approach (MDDS)

MDDS is a polymer based system comprising of poriferous microspheres having minute sponge like sphere-shaped moieties consisting of numerous interlinked cavities which are further surrounded by a non-collapsible assembly[7-8]. In 1987, Won expounded the microsponge technology. Advanced Polymer Systems, Inc. was granted the original patents and the company exploited distinct techniques and employed those to cosmetics in addition to OTC and other pharmaceutical products[9]. Cardinal Health, Inc. is now accredited with this remarkable technology for use in topical products[1,10]. The active moieties are discharged in a precise and controlled way from this assembly. Efficacy, safety and stability for topically active agents can be augmented by employing MDS with increased aesthetic characteristics[9-10]. The conventional topical formulations of drug molecules are proposed to perform on the superficial surface of skin and liberate their active moieties after application. This constructs intense layer of active ingredient which is rapidly

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taken up, reducing the time of contact. This necessitates a system with a time boost[11-13]. When practically applied to the superficial skin, the MDDS makes discharge of active compound in a specific time frame and also in accordance with another driving force like rubbing friction; temperature and pH[14-16]. It can prevent unnecessary amassing of excipients within the superficial layer, which radically lowers the annoyance caused through drugs with no loss of their efficacy[17-19]. Microsponges exhibits stability within the pH range 1 to 11 and at high temperature i.e. 130 ^{0}C. These are suitable with most excipients and vehicles. Microsponges have 0.25 µm pore size on an average, through which bacteria are not able to breach and so serve as self-sterilizing agents and possess high payload[20]. The microcapsules possess capsule form with absolute shells, and discharge of drug take place by rupturing, in contrast to microsponges having spongy shell and where discharge of drugs occurs with impact of temperature, pressure and partition coefficient[6,20-22]. In contrast to microcapsules, the technique of delivery of actives through microsponge based approach seems to be of high interest because of many advantage offered by microsponges. In contrast to conventional drug delivery systems, the microsponges impede the excessive accrual of drug in dermis as well as epidermis skin layers[20,22-23]. The active ingredient should possess inertness, miscibility with monomers and water immiscibility/ slight solubility[24-25].

METHODS OF FORMULATION FOR MICROSPONGES

Depending upon properties (physical and chemical features) of loading drug within microsponge, the loading process may be performed by utilizing either one step or two stage procedure. In case of inert non-polar drug, it creates porous structure which is termed as porogen. These drugs are entrapped by one step process[26-27]. Formulation of microsponges starts with selection of single type monomer in combination, formation of chain monomers by polymerization, crosslinking of these chain monomers, development of spheroidal entities by intersecting of ladder of chain monomer, then loading of microspheres resulting in microsphere batch formation and finally roping of batches to microsponges. The two methods used for the formulation of microsponge are described below:

Liquid-liquid suspension based polymerization technique

The immiscible monomers in this technique are first made miscible in an appropriate solvent along with active moieties and diffused in the aqueous phase for formation of suspension with the assistance of surfactant or suspending agents. With rising temperature, irradiation or addition of catalyst, it becomes feasible to activate polymerization process, which consequently leads to development of a

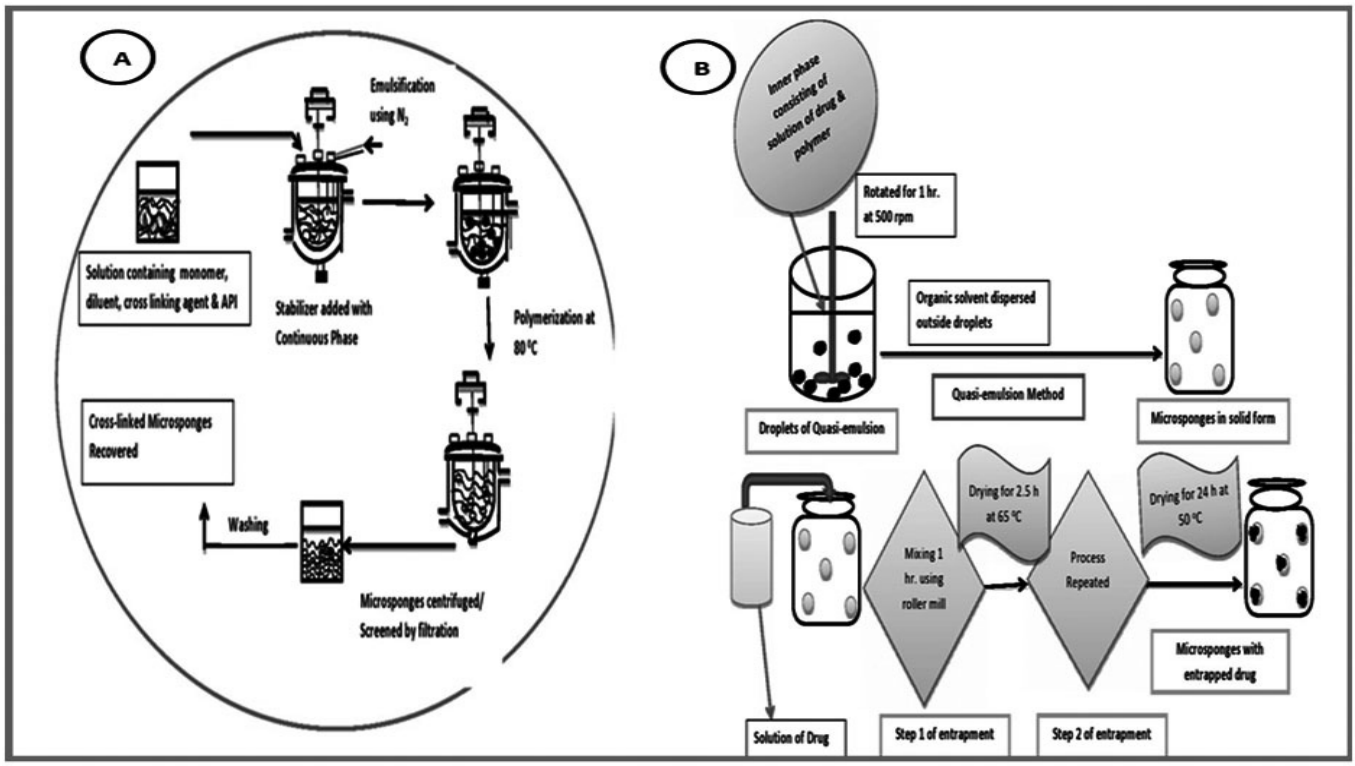

Fig. 1: Pictorial description in detail of (A) liquid-liquid polymerization method[19] and (B) quasi emulsion method[20]

reservoir type of system with globular constitution. The solvent is eliminated after the completion of polymerization, which results in formation of the microsponges[28-29]. The method describing liquid-liquid polymerization approach is explained in Fig. 1(A).

Quasi-emulsion solvent diffusion technique

It is a two-step process in which two stages i.e. inner and outer phases are formulated. The inner phase comprises of a polymer analogous to Eudragit, dispersed in ethanol and the active drug substance is gradually

Table I: List of different types of polymers and drugs used in formulation of microsponges[15, 27, 37-41, 4, 42, 22, 6, 23, 43-46, 18]

S. No	Drug candidate	Formulation	Category of Drug	Type of Polymer	Application
1.	Albendazole	Microsponge gel	Anti-helminitic	Eudragit RS-100	Parasitic worm, colonic parasites
	Lornoxicam	Microsponge gel	NSAID		Analgesic, antipyretic
	Atorvastatin	Emu oil Emulgel	HMG CoA reductase inhibitor		Cardio vascular disease/reduces bad cholesterol
	Diclofenac	Microsponge gel	NSAID		Augmented arthritis therapy
	Miconazole	Microsponge gel	Antifungal		Vaginal candidiasis
2.	Fluconazole	gel	Antifungal	Eudragit S-100	Fungal infection
	Famotidine	Floating microsponge	Histamine H_2receptor antagonist		Peptic ulcer & GERD
	Curcumin	Floating microsponge	Gastro-retentive		Gastric cancer
3.	Mupirocin	Emulgel	Antibiotic	Poly vinyl alcohol	Skin infection by *Pseudomonas fluoresens*
	Oxybenzone	Microsponge gel	Benzophenone		UV light absorber, stabilizer in sunscreens, hair sprays, cosmetics
4.	5-Fluorouracil	Microsponge gel	Anticancer	Eudragit coated pectin	For colon cancer, esophageal cancer, Stomach cancer, Breast cancer, Cervical cancer
5.	Acetazolamide	Microsponge gel (ocular delivery)	Carbonic anhydrase inhibitor	Ethyl cellulose	To treat Glaucoma
	Babchi essential oil	Microsponge gel	Essential oil/ Antioxidant		Anti-Tumor, anti-inflammatory, immunomodulatory, antifungal, antioxidant
	Tacrolimus	Microsponge gel	Immunosuppressant		Immunosuppressant
	Sertaconazole Nitrate	Cream	Antibiotic Imidazole Anti-fungal		Skin infections such as athlete's foot
	Ketotifen	Enriched gel	Bronchial asthma/ COPD		Conjunctivitis, atopic dermatitis
	Silver Sulfadiazine	Microsponge	Sulfonamide	Xanthan gum	As antibacterial for partial thickness (2nd degree) burn wounds

supplemented to the polymeric solution. The dissolution is carried by applying ultra-sonication at 35 ^{0}C. Further, a plasticizer like TEC (triethylcitrate) is included in the formulation to assist the plasticity behavior. After this, the inner phase is gradually discharged within an outer phase consisting of polyvinyl alcohol (PVA) and distilled water with thorough stirring continuously for duration of 2 h. The microsponges are separated by filtering the mixture, washed and then dried at 40 °C for 12 h in oven[19,30-31]. The pictorial description of quasi emulsion method is explained in Fig. 1(B).

Drug release mechanism of microsponge

The active moieties freely move forward and backwards from the porous surface and into the vehicle till equilibrium is attained. As the product is put on to the surface of the skin, the drug which is already accessible in vehicle is engrossed towards the skin surface. After exhaustion of vehicle, the equilibrium gets disturbed. This creates a stream of the actives from microsponge pore within the vehicle, which further acts on skin till the vehicle gets dehydrated or absorbed[29,32]. Later on substances of microsponge present on exterior layer of the stratum corneum will carry on releasing the active ingredient to the skin steadily, leading to an extended time[4,11,24]. The mechanism behind the release of drug from the microsponge can be described in four ways depending upon the stimuli to which the microsponge exposed. The mechanism of release of drug through microsponge is described in Fig. 2.

LITERATURE REVIEW ON MICROSPONGES

The microsponge technology is beneficial for delivery of several categories of medications and formulations. From the beginning till today, many advanced techniques have been developed for their formulation and for ensuring controlled release. These formulations can be used for vast routes like oral, ocular, topical, colonic, vaginal and parenteral. The use of biodegradable polymers has also being tried in formulating microsponges. Tissue engineered products also displayed superior release dynamics[12,23,33-36]. A brief summary of different types of polymers and drugs used in formulation of microsponges is given in Table I. A brief literature review on microsponge drug delivery systems is summarized as follows.

Pandey et al. described diverse applications and marketed formulations of microsponge drug delivery system[9]. The microsponge gel loaded with silver sulfadiazine optimized with factorial 3^{2} design was

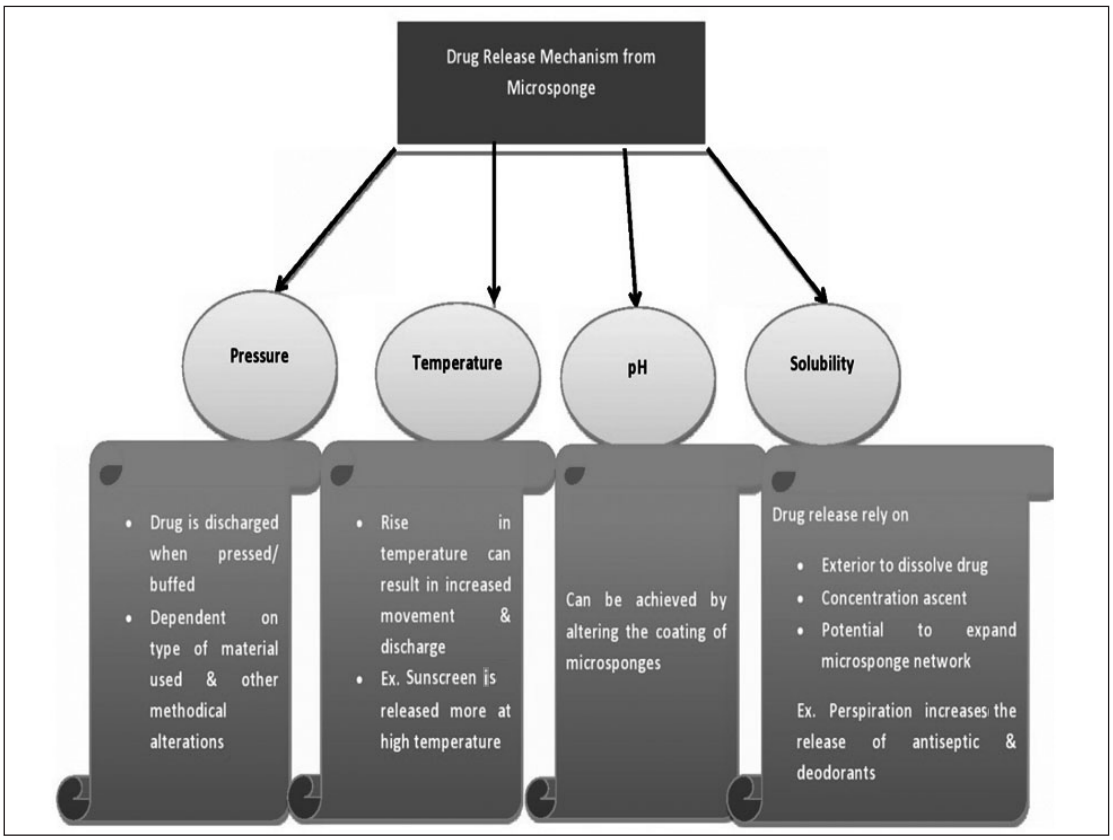

Fig. 2: Mechanism of release of drug through microsponge[29,32]

found effective in treatment of burn wounds with control on frequency of application[18]. Microsponges also exhibited their potential in ocular route in the form of gel and improved the efficiency of acetazolamide in treatment of glaucoma without any side effects[22]. Jadhav et al., described the novel methods and mechanisms for the formulation and incorporation of microsponges in suitable vehicle[28]. Treatment of arthritis can be successfully achieved with the employment of micosponge gel containing diclofenac and diethylamine with extended release[38]. The antifungal drug, miconazole, can be successfully loaded in microsponge by quasi emulsion technique with 92.9 % entrapment efficiency[39]. The essential oils can also be incorporated in microsponges and employed for the treatment of varied dermatological problems without any cytotoxic reactions[43]. Aloorkar et al. explained the impact of various variables on the physical properties of microsponges[47]. Kapoor et al. studied the advantages of microsponges for efficacious entrapment of varied ingredients[48]. Gavasane et al. explained the applicability of numerous biodegradable polymers for making the controlled release formulation[49]. The microsponges can be made nanoporous by employing polysaccharides and crosslinking agents which prove beneficial in delivery of biological agents like bovine serum albumin[50].

Table II: List of drugs along with marketed formulation in microsponge drug delivery system[17,47, 70-71]

S. No.	Drug	Formulation	Application/Uses	Manufacturer
1.	Moisturizer glycolic acid w/ sun protecting factor (SPF) 15	Topical cream	Anti-wrinkle activity, soothing activity	Amcol Pvt. Ltd.
2.	Retin A	Cream	Treats severe acne	Ortho-McNeil Pharmaceutics, Inc.
3.	Retinol cream	Cream	Aids in maintaining healthy skin	Biomedic Inc.
4.	Night cream Retinol 15	Cream	Anti-wrinkle activity	Sothys
5.	Line eliminator dual retinol facial treatment	Cream	Anti-wrinkle action	Avon
6.	EpiQuin Micro	Cream	Prevents hyper pigmentation	Skin Medica Inc.
7.	Sports cream XS and RS	Topical cream	Anti-inflammatory action	Embil Pharma Co. Ltd.
8.	Peel 20 (Salicylic acid)	Exfoliant	Exfoliation action	Biophora
9.	Oil free matte block	Invisible sunscreen	Sunscreen action of SPF 20	Dermalogica Pvt. Ltd.
10.	Lactrex™ 12 % Moisturizer	Moisturizing cream	Moisturizing activity	SDR Pharmaceuticals, Inc
11.	Dermalogica oil control lotion	Lotion	Protection of skin	Ginger and John Dermalogica Skin Care Products
12.	The ultra guard	Lotion	Protectant for infant skin	Scott Paper Company
13.	Cream Carac, 0.5%	Topical cream	Actinic keratoses	Dermik Labs, Inc. Berwyn, PA 19312 USA
14.	Micro peel plus	Peel -off- mask	Stimulates cell turnover	Biomedic Inc.
15.	Oil control lotion	Lotion	Controls oil from skin surface	Fountain Cosmetics
16.	Aramis fragrances	Spray	Antiperspirant Spray	Aramis Inc.

CHARACTERIZATION OF MICROSPONGES

Microsponges are the drug delivery based approach utilized for both topical and oral drug delivery of medicaments with great efficacy. The evaluation parameters for these involve minimal effort with good proficiency[51]. The various methods employed for characterization have been described as follows:

Particle size determination

The determination of particle size for unloaded and loaded microsponges can be carried out usually by the technique of laser light diffractometry (LLD). Particles exhibiting size more than 30 µm ensure granular texture and, therefore, particles between 10 and 25µm size are chosen for an ultimate topical formulation[52-53].

Morphology and surface topography of microsponges

SEM (Scanning electron microscopy) can be used for studying the surface topography and morphology of formulated microsponges. These have to be coated by means of gold–palladium film in an atmosphere of argon at room temperature. For illustration of ultra-structure of microsponge, the SEM of a fractured microsponge particle can be examined[54].

Evaluation of loading efficiency and production yield[55-56]

The following equation is used for calculation of loading efficiency (%) of the microsponges:

$$\text{Loading efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug amount}} \text{ X } 100$$

Similarly, the equation for determining production yield of microsponges is:

$$\text{Production yield} = \frac{\text{Initial mass of sponges}}{\text{Theoretical mass of excipients (Polymer+ Drug)}} \text{ X } 100$$

True density determination

Ultra-pycnometer is a device that can be utilized for ascertaining the true density of microsponges in helium gas atmosphere.

Pore structure characterization

Pore diameter and volume are fundamental in scheming the strength and length of usefulness of the API. The pore diameter impacts on the passage of actives from microsponges dispersed into the vehicle material[57-58].

Compatibility studies

The drug compatibility among reaction adjuncts can be studied through Fourier Transform Infra-red spectroscopy (FTIR) and thin layer chromatography (TLC). X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC) techniques can be utilized for studying the effect of polymerization on crystallinity of drug using powder material[9,48].

Monomer-polymer composition

Microsponge dimension, polymer concentration and drug loading are some factors which manage release of drug from microsponges. The composition of polymer can influence partition coefficient of entrapped drug amongst the vehicle and the microsponge system and consequently can have direct impact on entrapped drug release profile[58-59].

Dissolution behavior

USP XXIII dissolution apparatus can be utilized for studying the dissolution pattern of microsponges with a customized basket of 5 µm made up of stainless steel mesh at 150 rpm. The dissolution solution can be chosen while bearing miscibility of drug to guarantee the sink conditions. At specific time intervals, the samples can be analyzed using suitable analytical method[39].

Recent developments in microsponge drug delivery approach

Nanoferrosponges, microporous beads and nanosponges are further advanced formulations of microsponges which can be prepared by altering the standard methods. The hydrophobic and hydrophilic drugs can be formulated by incorporating into β-CD nanosponges, in comparison to micro or nanosponges. Various sophisticated approaches have been investigated for oral intake of dexamethasone, doxorubicin hydrochloride, flurbiprofen, serum albumin and itraconazole as standard drug. The nanosponges have been fabricated by cross-linking the β-CD with biphenyl carbonate. Some workers also experienced that the nanosponges were perceived to be a better transporter for the distribution of gases. Studies have also been conducted to incorporate a cytotoxic substance in a nanosponge based transporter, which proved to be better transporter, for targeting the cancerous cells. The microsponge formulation can also be effective in the formulation of tissue engineered products[54, 59-63].

Comparative analysis of microsponge and nanosponge drug delivery systems

The nanosponge drug delivery system (NDDS) is the expanded form of microsponges which is reduced in size to nanometer scale. Mean diameter of a nanosponge is between 1000 nm-500 nm, while that of microsponges is 10-25 microns[34,37,64-65]. These have the capability to encapsulate drug molecules either by making inclusion or by making non-inclusion complexes. Mainly two methods, hyper cross-linked β-cyclodextrins and emulsion solvent diffusion methods, are used to make nanosponges. The scientists DeQuan Li and Min Ma granted name cyclodextrin -nanosponges[68]. These nanosponges CD-NS unveil elevated efficacy to low solubility profiled drugs. Glutaryl chloride, terephthaloyl chloride and glutaric anhydride are examples of cross-linking agents tried for synthesizing cyclodextrin-nanosponge. Many gases can be stored in nanosponges, e.g. oxygen, carbon dioxide and 1-methylcyclopropene[47,55-56,66-69].

Applications of microsponges in different fields

MDDS possess affirmative and appealing impact on the efficiency and stability of topical products. The various formulations explored in microsponge drug delivery system have been mentioned in Table II.

These formulations may employ the following modes for topical use:

1. Reservoir: For long term delivery of the drug molecules.
2. Repository: For trapping unwanted matter like superfluous oil from skin.
3. Secure vessel: By retaining the active ingredients for apparent activity[29, 37, 70-72].

Research Gap

In the current preparation methods, mostly organic solvents serve as porogens and they set an ecological peril, since these may possess high inflammability, throwing up a safety risk. In several instances, the traces of unreached monomers have been monitored, which may lead to toxicity and health hazards. So, it should be taken as a challenge to make formulations which are devoid of any harmful chemicals and not pose any toxicity to the environment.

CONCLUSION

By studying the diverse research work performed on the microsponge delivery system from the beginning to current, it can be concluded that microsponge technique offers a good and effective technique for the entrapment of several categories of drugs like essential oil, antibacterial, antifungal, anticancer drugs and some of the tissue engineered products. This technique provides wide scope of active ingredient delivery for oral, transdermal, OTC products and cosmetic products.

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