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RECENT TRENDS AND ADVANCES IN MICROSPONGE DRUG DELIVERY

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Abstract: Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These have limitations such as atypical peak- trough plasma concentration-time profile; drugs with short half-life require repeated administration, unavoidable fluctuations in the drug concentration. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery systems.

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INTRODUCTION

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These have limitations such as atypical peak- trough plasma concentration-time profile; drugs with short half-life require repeated administration, unavoidable fluctuations in the drug concentration. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery systems.

A microsponge delivery system (MDS) is highly cross linked, patented, porous, polymeric microspheres that obtain the flexibility to entrap a wide range of active ingredients such as emollients, fragrances, sunscreens, essential oils, anti-infective, anti-fungal and anti-inflammatory agents etc. that are mostly used for prolonged topical administration and recently for oral administration [1]

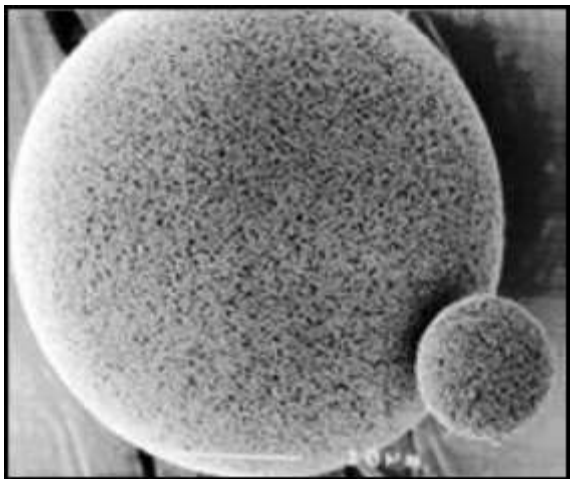
To control the release rate of active agents to a predetermined site in human body has been one of the prime challenges faced by drug industry. Several reliable systems were developed for systemic drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry [2]

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny, sponge like spherical particles that consist of a numerous of interconnecting voids within a non-collapsible structure with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably [3, 4]

Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. Microsponge particles are very small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. The microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the microsponge system can significantly reduce the irritation of effective drugs without reducing their effectiveness. The empty spheres are then washed away with the next cleansing. The microsponge delivery system (MDS) fulfills these requirements and has resulted in a new generation of very well-tolerated and highly efficacious, novel products. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they enclose a relatively high concentration of active ingredients. [5]

Microsponges are polymeric delivery systems composed of porous microsphere. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance

stability, reduce side effects and modify drug release favorably. Microsponge technology has many favorable characteristics, which make it a versatile drug delivery vehicle. Microsponge system are based on microscopic, polymer-based microspheres that can suspend or entrap a wide can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner [6, 7].



View of microsponge [8]

Methods of Preparation of Microsponge:

A Porogen drug neither hinders the polymerization process nor become activated by it and also it is stable to free radicals is entrapped with one-step process (liquid-liquid suspension polymerization). Microsponges are suitably prepared by the following methods:

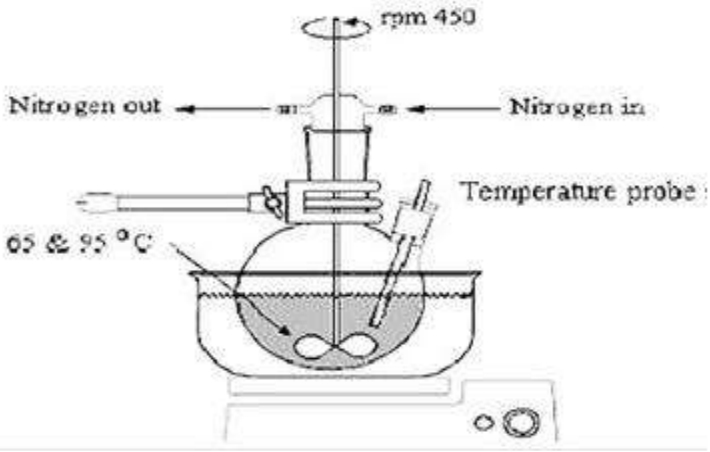
Liquid-liquid suspension polymerization: [9, 10, 11]

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In this method the monomers which are immiscible are first dissolved along with active ingredients in a suitable solvent monomer and are then dispersed in the aqueous phases which consist of additives like surfactant, suspending agents to facilitate formation of suspension. The polymerization is then activated by increasing temperature or irradiation or by addition of catalyst. The polymerization process continues the formation of a reservoir type of system with spherical structure. After the polymerization process the solvent is removed leaving the spherical structured porous microspheres, i.e., microsponges

The various steps involved in the preparation of microsponges are summarized as follows:

Step 1: Selection of monomer as well as combination of monomers.
Step 2: Formation of chain monomers as polymerization starts.
Step 3: Formations of ladders as a result of cross-linking between chain monomers.
Step 4: Folding of monomer ladder to form spherical particles.
Step 5: Agglomeration of microspheres leads to the production of bunches of microspheres.

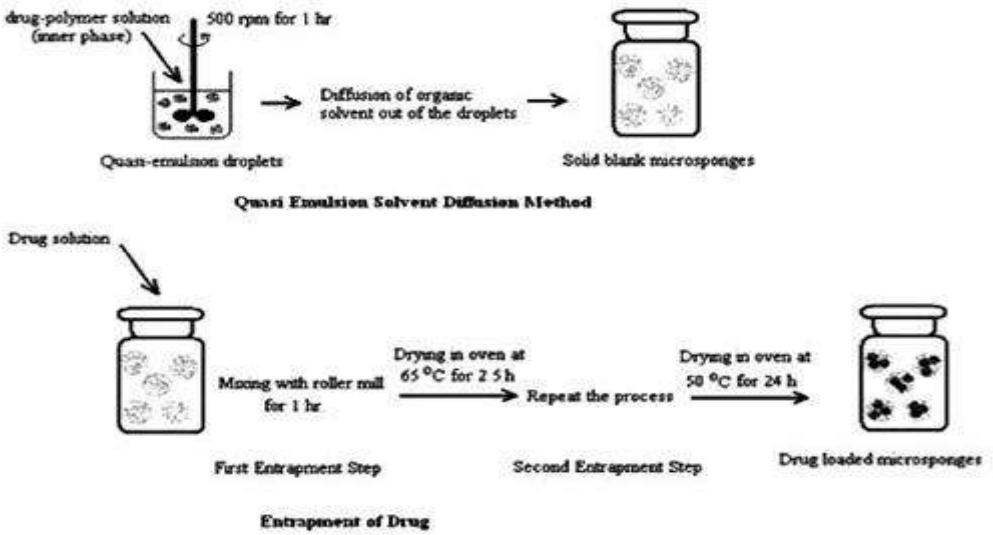
Step 6: Binding of bunches to produce microsponges.



Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization [12]

2. Quasi-Emulsion Solvent Diffusion Method: [13, 14, 15]

Porous microspheres (microsponges) were also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as Eudragit RS 100 which is dissolved in ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved under ultrasonication at 35°C and plasticizer such as triethylcitrate (TEC) was added in order to aid the plasticity. The inner phase is then poured into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 2 hours. Then, the mixture was filtered to separate the microsponges. The product was washed and dried in an air heated oven at 40°C for 12 hrs.



Method of quasi-emulsion solvent diffusion [16]

Advantages of MDS [17]

- Microsponges can absorb oil up to 6 times its weight without drying.
- It provides continuous action up to 12 hours i.e. extended release.
- Improved product elegancy.
- Lessen the irritation and better tolerance leads to improved patient compliance.
- They have better thermal, physical and chemical stability.
- These are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- MDS allows the incorporation of immiscible products.
- They have superior formulation flexibility.
- In contrast to other technologies like microencapsulation and liposomes, MDS has wide range
- Of chemical stability, higher payload and are easy to formulate.
- Liquids can be converted in to powders improving material processing.
- It has flexibility to develop novel product forms.
- MDS can improve bioavailability of same drugs.
- It can also improve efficacy in treatment.

Advantages of microsponges over other technologies and delivery systems [18, 19]

1. Microsponges offer better control of drug release than microcapsules. Microcapsules cannot usually control the release rate of the active pharmaceutical ingredient (API). Once the wall is ruptured, the API contained within the microcapsules will be released.
2. Microsponges show better chemical stability, higher payload and easier formulation compared
with liposomes.
3. In contrast to ointments, microsponges have the ability to absorb skin secretions, therefore, reducing greasiness and shine from the skin. Ointments are often aesthetically unappealing, greasy and sticky, resulting in lack of patient compliance.

Evaluation Methodology of Microsponge [20]

- Determination of particle size
- Surface topography and Morphology of microsponges
- Determination of production yield and loading efficiency
- True density determination
- Characterization of pore structure
- Compatibility studies
- Polymer/ Monomer composition

Salient Features/ Characteristics of Microsponges

- MDS are stable over range of pH 1 to 11.
- These are stable at the temperature up to 130˚C.
- Microsponge formulations are compatible with the majority of vehicles and ingredients.
- Self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These systems have higher payload up to 50 to 60% still free flowing. [21, 22, 23]
- Most liquid or soluble ingredients can be entrapped in the particles. Actives that can be entrapped in microsponges must meet following requirements.
- It should be either fully miscible in monomer or capable of being made miscible by addition of small amount of a water immiscible solvent.
- It should be water immiscible or at most only slightly soluble.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- The solubility of actives in the vehicle must be limited to avoid cosmetic problems; not more than 10 to 12% w/w microsponges must be incorporated into the vehicle. Otherwise the vehicle will deplete the microsponges before the application.
- It should not collapse the spherical structure of microsponges.
- Polymer design and payload of the microsponges for the active must be optimized for required release rate for given time period.
- It should be stable in contact with polymerization catalyst and conditions of polymerization [24].

Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin. [25]

Sr. No	Active agents	Applications
1.	Sunscreens	Long lasting product efficacy, with improved protection against sunburns and sun related injuries even at elevated concentration and with reduced irritancy and sensitization.
2.	Anti-acne e.g. Benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization.
3.	Anti-inflammatory e.g. hydrocortisone	Long lasting activity with reduction of skin allergic response and dermatoses.
4.	Anti-fungal	Sustained release of actives.
5.	Anti-dandruffs e.g. zinc pyri-thione, selenium sulfide	Reduced unpleasant odor with lowered irritation with extended safety and efficacy.
6.	Antipruritics	Extended and improved activity.
7.	Skin depigmenting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
8.	Rubificient	Prolonged activity with reduced irritancy

		greasiness and odor.

Examples of microsponge drug delivery with their formulations [26, 27, 28]

Microsponge Delivery System	Drug	Disease
Gels	Benzoyl Peroxide	Anti- Acne Treatment
	Fluconazole	Inflammation
	Mupirocin	Antibacterial activity
	Diclofenac Sodium	Inflammation
	Acyclovir	Viral Infection
	Hydroxyzine HCL	Urticaria & atopic dermatitis
	Terbinafine HCL	Antifungal
Lotions	Benzoyl Peroxide	Anti- Acne Treatment
Creams	Hydroquinone & Retinol	Melanoma
Tablets	Indomethacin	Inflammation
	Paracetamol	Anti pyretic
	Chlorpheniramine maleate	Hey fever
	Ketoprofen	Musculoskelotol pain
	Fenofibrate	Gout
	Meloxicam	Arthritis
Implants	Poly(Dl-Lactic-co-glycolic acid)	Skin tissue engineering
Grafts	Poly(Lactic-co-glycolic acid)	Cardiovascular surgery
Injections	Basic Fibroblast growth Factor	Growth factor

List of Marketed Products Based On Microsponge [29, 30, 31]

Product Name	Pharmaceutical Use	Manufacturer
Glycolic Acid Moisturiser w/SPF 15	Anti wrinkles & soothing	AMCOL Health & beauty solution
Retin A micro	Acne- vulgaris	Ortho-McNeil Pharmaceutical. Inc.
Line Eliminator Dual Retinol Facial Treatment	Anti- wrinkle	Avon
Retinol 15 Night Crream	Anti- wrinkle	Sothys
Retinol Cream	Helps maintain healthy skin	Biomedic
EpiQuin Micro	Hyper pigmentation	Skin Medica Inc.
Sports cream RS & XS	Anti-inflammatory	Embil Pharmaceutical Co. Ltd.
Salicylic peel 20	Excellent Exfoliation	Biophora
Oil free matte block SPF 20	Sunscreen	Dermalogica
Latrex TM 12% Moisturizing cream	Moisturizer	SDR Pharmacuticals Inc.
Dermalogical oil control lotion	Skin protectant	John & Ginger Dermatologic Skin Care Products
Ultra Guard	Protects baby's skin	Scott Paper Company

Drugs explored in Microsponge delivery system (MDS) [32, 33, 34]

Ketoprofen	Trolamine
Benzyl peroxide	Paracetamol,
Retinol	Dicyclomine,
Fluconazole	Flurbiprofen
Ibuprofen	Flucinolone acetonide.
Tretinoin	

Drug Used In Microsponge Delivery [35]

Dicyclomine, an anticholinergic drug, has direct smooth muscle relaxant action, and in addition to being a weak anticholinergic, it exerts antispasmodic action. Its plasma half-life is 4 - 6 h. Dicyclomine causes gastrointestinal (GI) side effects like other antispasmodic drugs. The study was designed to formulate a delivery system based on microsponges that would reduce the GI side effects of the drug. Flurbiprofen, Microsponge system containing flurbiprofen was formulated for the colonic delivery of the drug for targeted action. Benzyl peroxide, Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes

foot. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, the ethyl cellulose microsponge system was formulated containing BPO which were able to control the release of BPO to the skin.

Fluocinolone acetonide, (FA) is a corticosteroid primarily used in dermatology to reduce skin inflammation and relieve itching. The percutanous absorption increases risk associated with systemic absorption of topically applied formulation. Controlled release of drug to the skin could reduce the side effect while reducing percutanous absorption. Therefore, FA en-trapped microporous microparticles (microsponges) were formulated to control the release of drug to the skin. Retinol, the use of vitamins like tocopherol, retinol in cosmetic formulations like creams, gels is limited due to high instability so oil and water soluble microsponge delivery of the retinol has been developed.

Patents filled on microsponge [36]

Patent Number	Patent Name
5100783	Weighted microsponge for immobilizing bioactive material
1288370	Weighted collagen microsponge
4997753	Weighted collagen microsponge for immobilizing bioactive material
1275955	Weighted microsponge
4863856	Weighted collagen microsponge for immobilizing bioactive materials
4861714	Weighted collagen microsponge for immobilizing bioactive material
0217917	Weighted microsponge for immobilizing bioactive material
1986056694	Weighted microsponge for immobilizing bioactive material
WO/1986/005811	Weighted microsponge for immobilizing bioactive material
4092381	Methods of fabricating microsponge deuterated hydrocarbon polymer targets which emit neutrons when irradiated by high energy beams

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