ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Online - 2455-3891
Print - 0974-2441

Vol 9, Suppl. 1, 2016

Review Article

A COMPREHENSIVE REVIEW ON NOVEL MICROSPONGES DRUG DELIVERY APPROACH

PUSHPA KUMARI, SHASHI KIRAN MISHRA*

University Institute of Pharmacy, Chhatrapati Shahu Ji Maharaj University, Kanpur, Uttar Pradesh, India. Email: saushi123@rediffmail.com

Received: 10 May 2016, Revised and Accepted: 21 May 2016

ABSTRACT

Microsponges drug delivery approach (MDA) has been introduced in topical products to facilitate the controlled and targeted release of active drug into the skin to decrease systemic exposure and minimize local cutaneous reaction. Microsponges are highly cross-linked, polymeric sponge, porous in nature, spherical shape consisting of high drug content within their interconnecting voids, releasing bioactive agent at a target site within predetermined time. They are mostly used for prolonged topical administration, enhanced efficacy for topically therapeutic agent with safety, stability and reduced side effects followed by improved aesthetic properties in an efficient and novel manner. More ever, it is found to be stable over wide pH range and compatible with most vehicles. We here complied recent data regarding properties of microsponges, their methodology pharmaceutical application and list of patent till date.

Keywords: Microsponges, Bioactive, Porous, Interconnecting voids, Aesthetic.

INTRODUCTION

The microsponges approach was developed by Won in 1987 [1,2]. Microsponges' delivery system is a patented polymeric sponge, porous, spherical particles consisting high drug content system. They consisting of a myriad of interconnecting vacuum within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. Its size ranges from 5 to 300 µm in diameter and a typical 25 µm sphere can have up to 2,50,000 pores (Fig. 1) and an internal pore structure alternative to 10 ft in length, providing a total pore volume of about 1 ml/g for widespread drug retention and pore volume range from 0.1 to 0.3 cm^3/g [3,4]. They are designed to distribute a pharmaceutically active ingredient efficiently at minimum dose and also to better stability, with reduce side effects and modify drug release profiles. They can be included into conventional dosage forms such as creams, lotions, gels, ointments, tablets and powder, a broad package of benefits and thus produce formulation flexibility [5,6].

Microsponges are stable over a range of pH 1-11 and temperature up to 130°C and are compatible with most vehicles and ingredients and self-sterilizing as their average pore size is 0.25 µm where bacteria cannot penetrate these formulations are free flowing and can be cost-effective [7-9]. Microsponges approaches are applied occupied for the improvement of performance of topically applied drugs to overcome difficulties like greasiness, stickiness related with topical formulations [10,11].

At the current time, this interesting approach has been licensed to Cardinal Health, Inc., for use in topical products. The scanning electron microscopy (SEM) of the microsponges particle reveals that its internal structure appears as the bag of marbles. The porosity is due to the interstitial spaces between the pores that can entrap many wide ranges of active ingredients such as emollients, fragrances, essential oils, sunscreens, anti-infective, and anti-inflammatory therapeutic compounds [12].

PROPERTIES OF MICROSPONGES [13-15]

Microsponges when employed to the skin, its bioactive agent progressively release on the skin at a predetermined time mode and response to stimuli such as rubbing, temperature and pH effect with enhanced efficacy.

- These formulations are stable over range of pH 1-11
- It is stable at the temperature up to 1300°C
- They are compatible with most vehicles and excipients
- Self-sterilizing as their average pore size is about 0.25 µm, whereas the bacteria cannot penetrate the pores
- They have high entrapment up to 50-60%
- They are free flowing and cost-effective
- These particles are appropriated in size to absorb into the skin
- Microsponges formulation can absorb oil up to 6 times its weight without drying
- It provides continuous action up to 12 hrs, i.e., extended release
- They have superior formulation flexibility.

BENEFIT OF MICROSPONGE DRUG DELIVERY APPROACHES (MDAs)

When Microsponges are applied to the skin, its drug release can be controlled through diffusion. Microsponges release active ingredient in programmed manner on target site of skin, thus provide benefits of improved product efficacy, reduced irritation usually associated with potent therapeutic agents as benzoyl peroxide [19]. Several benefits of Microsponges based drug delivery approaches are mentioned below (Fig. 2).

THERAPEUTICALLY AGENT UTILIZED FOR MICROSPONGES APPROACHES [20-22]

Microsponges are capable to absorb skin secretions consequently, reducing oiliness and shine from the skin. However, these particles are extremely minute, inert, indestructible spheres unable to pass through the skin, but they arranged in the minute nooks and crannies of the skin and slowly release the entrapped drug to the skin. Furthermore, these formulations can prevent excessive accumulation of ingredient within the interior parts of the skin. They significantly minimize irritation of effective drugs without affecting efficacy [23]. Several drugs which have been utilized in microsponge delivery system are enlisted as shown in Fig. 3.

APPROACHES FOR FORMULATION OF MICROSPONGES

Liquid-liquid suspension polymerization [24-26]

In this vehicle of polymerization, the monomers are dissolved along with the active ingredients, i.e., surfactant in suitable solvent followed by addition of additives, suspending agent are added to the formation of suspension. The polymerization is such as initiated by adding catalyst or by increasing temperature; ultimately solvent is removed leaving the spherical structure porous. After the polymerization process, the

solvent is removed leaving the spherical porous structure microsponges (Fig. 4).

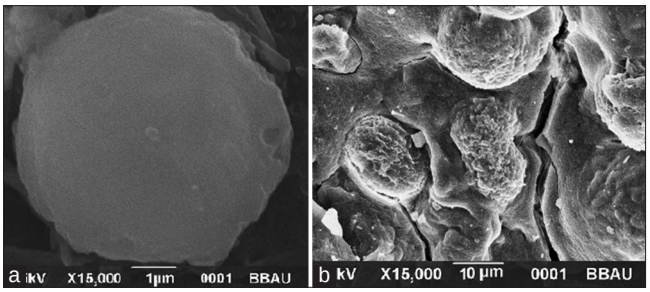

Fig. 1: Typical image of microsponge (a) and its porous surface morphology (b)

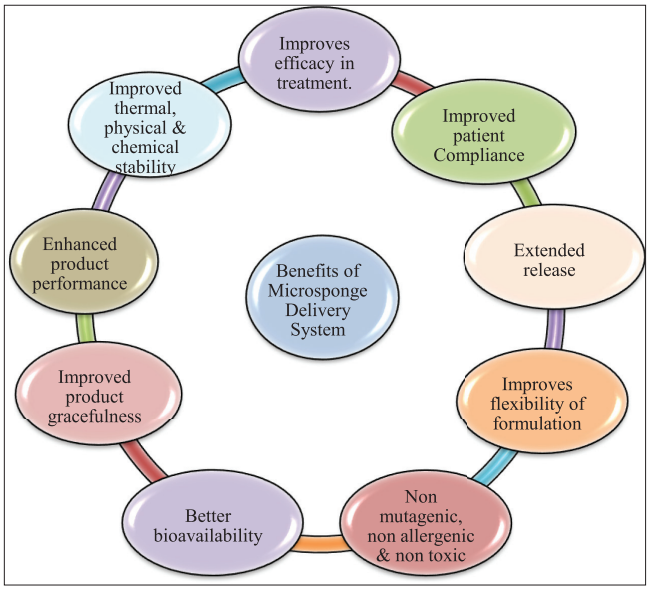

Fig. 2: Benefits of microsponge drug delivery

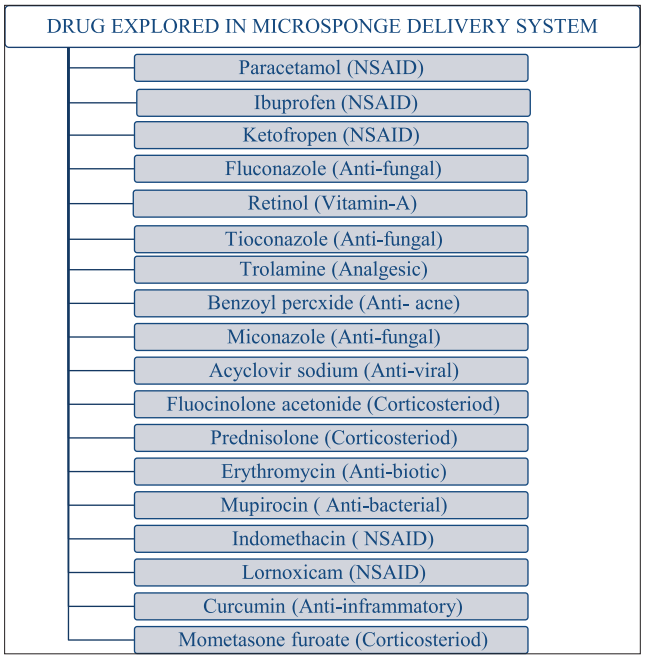

Fig. 3: Drug explored in microsponge delivery system

Quasi-emulsion solvent diffusion [27-29]

Microsponges can be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner organic phase, polymer dissolved in suitable solvent followed by addition drug dissolved under ultrasonication at 35°C. This solution made inner phase. The inner phase is poured into the outer phase (polyvinyl alcohol solution in water). After stirring, the mixture is filtered to separate the developed microsponges. The microsponges are dried in an air heated oven at a temperature which is compatible for polymer (Fig. 5).

IDEAL CRITERIA OF BIOACTIVE AGENT FOR FORMULATION OF MICROSPONGE

Therapeutics or bioactive agent should be miscible in selected polymers and immiscible in water. Moreover, they possess stability under process condition, i.e., should not collapse [30-32].

DRUG RELEASE MECHANISM OF MDAs

The topical agent formulation containing microsponges are prepared in many different forms, such as a gel, cream, or lotion. While applying

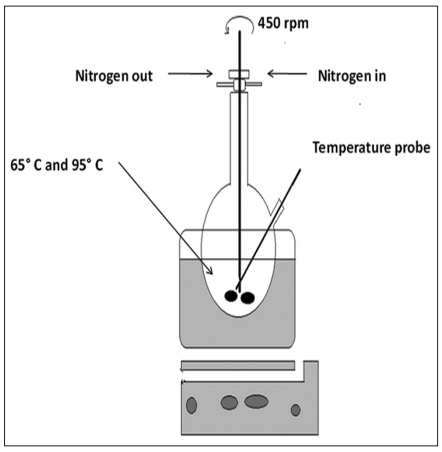

Fig. 4: Liquid-liquid suspension polymerization

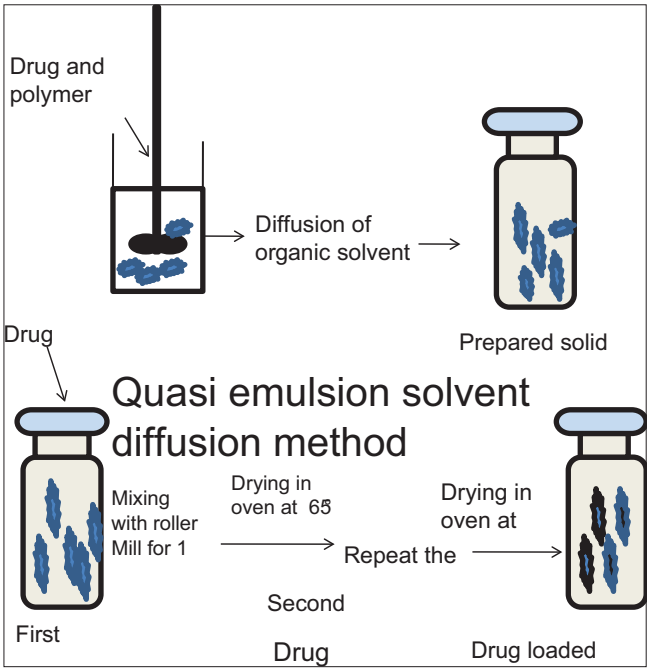

Fig. 5: Quasi-emulsion solvent diffusion methods

topically to the desired area of the skin, the active ingredients dispersed out of the globule into the vehicle and reaches to the target site (Fig. 6). The rate of release of the active ingredient from the formulation can be preplanned; the release can be initiated or stimulation by many release triggers as given in Fig. 6 [33-36].

EVALUATION OF MICROSPONGES

Preformulation studies

Preformulation parameters are designed to identify those physicochemical properties, melting point, and excipients that may affect the formulation design, method of manufacture, pharmacokinetic and biopharmaceutical properties. Organoleptic property as a chemical state, taste, odor and color of the drug are studied out [37].

Identification and drug-polymer compatibility

Differential scanning calorimetry (DSC) analysis

DSC analyses are carried out to confirm compatibility and thermal behavior of drugs, physical mixture of drugs, polymer, and their formulation. DSC studies microsponge of fenoprofen showed a sharp endothermic peak at 98.08°C which corresponded to the melting point of drug in the crystalline form. Their result showed that there is no incompatibility between the drug and polymers was observed. DSC thermograph of tioconazole microsponge showed a sharp endothermal peak between 168°C and 170°C), indicating the melting point of the tioconazole. Nief *et al.*, 2014, analyzed DSC study of meloxicam microsponge with sharp characteristics endothermic peak at 262°C corresponding to the melting point of the drug in the crystalline form [38].

Fourier transform infrared spectroscopy (FTIR) analysis

Identification of functional groups present in pure drug, physical mixture of drug, and polymer are interpretated by FTIR spectrometer. Shinde *et al*., 2014, observed the FTIR spectra of Fenopropen conforming presence of -OH stretching of hydrate band at 3648/cm, asymmetric stretching and symmetric stretching band at 1565 and 1423/cm and aromatic ring stretching band at 1481, 1369/cm. The result showed that no chemical interaction or changes take place during the preparation of formulation, and the drug was found to be stable [39].

Particle size analysis of microsponge

Particle sizes of the microsponge are carried out by laser light diffractometry, optical microscopy any other appropriate method. Rajurkar *et al*. observed the particle size of the microsponge of naproxen gel using an optical microscope and found microsponge in uniform size. The average particle size was 110.30 µm and the pore size was smaller than 1 µm. The particle size of clotrimazole microsponge was determined by using an optical microscopy range from 48 to 65.2 µm with a mean particle of 58.37±0.52 µm. They were spherical in shape and mean pore size of 8.31±0.38 µm was obtained [40].

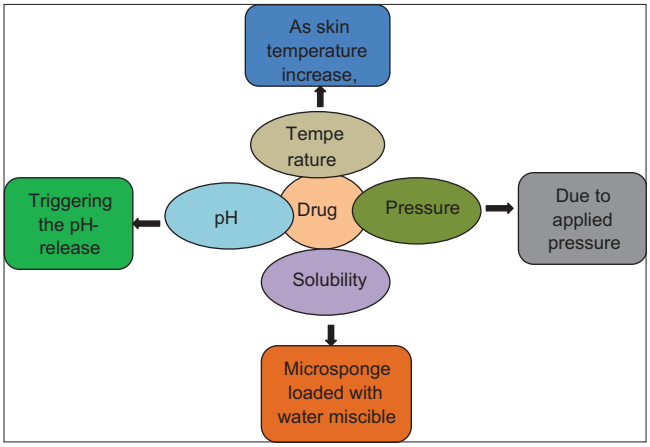

Fig. 6: Drug release mechanism of microsponge

Analysis of morphology and surface topography of microsponges

The presence of pores is an essential feature of microsponges, its internal and external morphology and surface topography can be obtained by using SEM and transmission electron microscopy (TEM). Rajurkar *et al*. studied microsponge of naproxen and observed microsponge were spherical and uniform with no drug crystal on the surface. The particle size, shape and surface morphology of miconazole nitrate were examined by SEM and TEM found porous, spherical shape in µm size [41].

Analysis of pore structure

The rate of drug release from microsponges can effect by pore diameter of microsponges. Several porosity parameters of microsponges such as total pore surface area, intrusion-extrusion isotherms, pore size distribution, average pore size diameters, shape and morphology of the pores, bulk and apparent density are also be analyzed [42].

Determination of loading efficiency and production yield [43]

The loading efficiency (%) is calculated using the following equation:

$$\text{Loading efficiency} = \frac{(\text{Actual drug content in microsponges})}{(\text{Theoretical drug content})} \times 100$$

The production yield of the microparticles can analyzed by calculating accurately the initial weight of the raw materials and the final weight of the microsponge obtained.

$$\text{Production yield} = \frac{(\text{Practical mass of micro sponges})}{\text{Theoretical mass } (\text{Polymer} + \text{drug})} \times 100$$

Mehta *et al*. was observed production yield and loading efficiency of clotrimazole microsponge formulation, i.e., production yield less than 40% whereas loading efficiency in the range of 80-95% was evaluated [44].

In vitro dissolution analysis

Dissolution profiles of microsponges are studied by dissolution apparatus USP XXIII with a modified basket consisted of 5 µm stainless steel mesh and the speed of rotation is 150 rpm. Mehta *et al*. observed the drug release profile of microsponges formulation of clotrimazole gel determined drug release 88-89%, 98.1% and 99.4% drug release in 12 hrs. Mohan *et al*. Studied *in vitro* dissolution studied carried out using USPXXI dissolution assembly (basket type) in 900 ml of pH 7.4 saline phosphate buffer solution at 37°C±5°C and rotated at 50 rpm of mupirocin microsponge showed that a biphasic release in the first hour 27-36% of the drug was released. Cumulative release from micro sponge after 8 hrs ranged from 62% to 95% [45].

Analysis of true density

Ultrapycnometer is utilized for determination of true density of microsponges [46].

Viscosity measurement

The viscosity measured by Brookfield viscometer. Mayur *et al*., 2013, observed rheology of gel formulation containing tioconazole was studied by Brookfield digital viscometer DV-2P-L using spindle S96, at 20 rpm and torque 60% to 100%, at 25°C±10°C. Naproxen microsponge gel was measured DV-III+Rheometer with spindle No. 2 at 25°C and found pseudoplastic nature studied by Rajurkar *et al*., [47].

Spreadability study

Spreadability study of gel formulation was determined by measuring diameter of l g gel between horizontal plates (20×20 cm^2) after 1 minute. The standardized weight tied on the upper plate was found to be 125 g. The spreadability calculated using the following formula:

$$\text{Spreadability}=\frac{M.L}{T}$$

Where M=wt. tied to the upper slide

L=Length of glass slides

T=Time taken to separate the slides

Spreadability of microsponge loaded controlled release topical gel of acyclovir sodium was determined spreadability (g.cm/sec) 12.5, 11.75, 11.25, 11.17 [48,49].

pH determination

Rajurkar *et al*. determined for the pH of microsponge of naproxen gel pH 6.2±0.2 by using digital pH meter and the reading were taken for an average of 3 times. Rajshree *et al*., 2014, were optimized pH of microsponge of miconazole nitrate loaded hydrogel was determined using digital pH meter result was required by formulation pH 6.7±0.06, 6.8±0.06.

Stability test

Stability studies of microsponge are studied out of various formulations at different temperature and relative humidity. Mupirocin microsponge was tested for stability at 5°C, 25°C/60% RH, 40°C/75% RH, on storing in glass bottles and was evaluated after 15, 30 and 45 days. Rajurkar *et al*. observed the stability study of microsponge naproxen gel as per ICH guidelines, on keeping at 40°C with RH 45% for the period of 90-day.

APPLICATION OF MDAs

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microsponges are designed to deliver bioactive agent efficiently at minimum dose with enhance stability, reduced side effects and modify drug release [50]. The system can have following applications as shown in Table 1.

MARKETED FORMULATION USING THE MICROSPONGE APPROACHES

MDA is considered suitable drug delivery system for skin and personal care products. As they maintain several times their weight in liquids, respond to a difference of release stimuli, and absorb large amounts of excess skin oil, along with providing graceful feel on the skin's surface. This approaches is recently involved almost number of products sold by major cosmetic companies worldwide skin cleansers, conditioners, oil control lotions, moisturizers, deodorants, razors, lipstick, makeup, powders, eye shadows, etc., are formulated by through this technology and provide specific advantages (better physical and chemical stability, controlled release of the active ingredients, minimized skin irritation and sensitivity) [61]. Marketed formulation based on MDAs is shown in Table 2.

PATENTS FILED RELATED TO MICROSPONGES APPROACHES (TABLE 3) [66]

Intellectual property asset (patents) is the core of many organization and transactions related to technology. Licenses and assignments of intellectual property rights are common operations in the technology markets, as well as providing loan security. Few patents are mentioned in table 3 related to Microsponges approach in pharmaceutical sciences

MICROSPONGE TECHNOLOGY HOLDS CONSIDERABLE POTENTIAL BOTH IN PHARMACEUTICAL AS WELL AS CONSFNETIC FIELD

Nanosponges are formulated which play role as carrier for the delivery of gases and targeting cancerous cells [67]. Nanoferrosponges, a

Table 1: Application of microsponge delivery system and their advantages [51-60]

Serial number	Application	Advantages
1	Sunscreens	Long lasting product efficacy with better protection against sunburns, with minimized irritancy and sensitivity
2	Anti-acne e.g., Benzoyl peroxide, erythromycin	Maintained efficacy with decreased skin irritation and sensitivity
3	Anti-inflammatory e.g., Hydrocortisone, lornoxicam, naproxen	Long lasting activity with minimized of skin allergic response and dermatoses
4	Anti-fungal e.g., Miconazole, clotrimazole, tioconazole, terbinafine HCL	Sustained release of actives
5	Anti-dandruffs e.g., Zinc pyrithione, selenium sulfide	Decreased unpleasant odor with reduced irritation with extended safety and efficacy
6	Skin depigmenting agents e.g., Hydroquinone	Better stabilization against oxidation with enhanced efficacy and aesthetic appeal
7	Rubefacients	Prolonged activity with lesser irritancy greasiness and odor
8	Anti-pruritics	Extended and better activity
9	Anti-viral e.g., Acyclovir	Viral infection
10	Anticholinergic drug e.g., Dicycloamine	Provide effective local action
11	Analgesic e.g., Indomethacin	Reduced the side effect like GI irritation
12	Antibacterial e.g., Mupirocin	Treatment of impetigo, enhance stability, reduce side effects
13	Antiprotozoal agent e.g., Tinadazole	Treatment of parasitic infection
14	Musculoskeletal e.g., KETOPROFEN, meloxicam	Relief pain, reduce swelling, joint stiffness from arthritis
15	Anti-pyretic e.g., Paracetamol	Treat mild to moderate pain and to reduce fever

GI: Gastrointestinal

Table 2: Marketed formulations based on microsponge drug delivery system [62-65]

Serial number	Name of product	Treatment	Manufacturer
1	Glycolic Acid Moisturizer w/SPF 15	Anti-wrinkles, soothing	AMCOL Health & Beauty Solution
2	Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc.
3	Line eliminator dual retinol facial treatment	Anti-wrinkle	Avon
4	Retinol 15 Night cream	Anti-wrinkle	Sothys
5	Retinol cream	Helps maintain healthy skin	Biomedic
6	Epi Quin Micro	Hyper pigmentation	SkinMedica Inc.
7	Sports cream RS and XS	Anti-inflammatory Embil	Pharmaceutical Co. Ltd.
8	Salicylic Peel 20	Excellent exfoliation	Biophora
9	Oil free matte block SPF 20	Sunscreen	Dermalogica
10	Lactrex™ 12% Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc.
11	Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin
12	Ultra guard	Protects baby's skin	Scott Paper Company
13	Carac Cream, 0.5%	treatment of actinic keratoses	Dermik Laboratories, Inc.
14	Micro Peel Plus/Acne Peel	Freezing the skin of all dead cells while doing no damage to the skin	Biomedic
15	Oil Control Lotion	Tightness to promote healing. Acne-Prone, oily skin conditions	Fountain Cosmetics
16	Aramis Fragrances	24 hrs high performance antiperspirant spray sustained release of fragrance	Aramis Inc.

Table 3: Patents filed related to microsponges approaches

Serial number	Inventors	Publication date	Patent number
1	Won	1987	US4690825
2	Dean *et al.*	1989	US4863856
3	Schaefer *et al.*	1989	US5292512
4	Katz *et al.*	1992	US5135740
5	Chantal *et al.*	1994	US5679374
6	Robert *et al.*	1994	US5316774
7	Ray	1996	US5725869
8	Straub *et al.*	1999	US6395300
9	Tomlinson *et al.*	2001	US6211250
10	Shefer *et al.*	2002	US20030232091
11	Singh	2003	US20030008851
12	Maurizio	2004	US20040247632
13	Steven *et al.*	2005	US20050271702
14	Malek	2007	US20070141004
15	Halliday	2008	US20080160065
16	Karyion Inc.	2009	US7604814
17	Sara Vargas	2010	US7740886
18	Celmatrix Corporation	2011	US7749489
19	Karykion Corporation	2012	US8323672
20	Ferring B. V	2013	US8361273
21	Stiefel Research Australia Pty Ltd.	2014	US8758728
22	Galderma Research & Development	2015	US8936800

novel approach composed magnetic trigger which enforces the carriers to penetrate to the deeper tissue, display its action on target site [68]. Porous microspheres or porous microbeads are also utilized in microsponge technology for effective encapsulation process of siRNA [69,70].

CONCLUSION

MDA holds considerable potential both in pharmaceutical as well as cosmetics field. This technique is attractive and creates many ways to release bioactive agents with full efficiency, safety, improved stability, provided reduced side effects. Microsponges also offer great advantages over other formulation with respect to mutagenic and irritancy of drug, hence contain a lot of potential for developing novel formulations for the topical disease.

ACKNOWLEDGMENT

The authors express deep sense of gratitude toward institute of pharmacy, C.S.J.M. University for providing favorable environment to complete the study.

REFERENCES

1. Won R. 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 ingredients as a porogen. Patent No. 4690825. US; 1987.
2. Chowdary KP, Rao YS. Mucoadhesive microspheres for controlled drug delivery. Biol Pharm Bull 2004;27(11):1717-24.
3. Embil K, Nacht S. The Microsponge Delivery System (MDS): A topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. J Microencapsul 1996;13(5):575-88.
4. Nachit S, Kantz M. The microsponge: A novel topical programmable delivery system. Top Drug Deliv Syst 1992;42:299-325.
5. Chadawar V, Shaji J. Microsponge delivery system. Curr Drug Deliv 2007;4(2):123-9.
6. Newton DW. Biotechnology frontier: Targeted drug delivery. US Pharmacist 1991;16:36-52.
7. Delattre L, Delneuville I. Biopharmaceutical aspects of the formulation of dermatological vehicles. J Eur Acad Dermatol Venereol 1995;5:70-1.
8. Viral S, Jain H, Krishna1 J, Patel P. Microsponge drug delivery system: A review. Int J Res Pharm Sci 2010;1(2):212-8.
9. Yang L, Chu JS, Fix JA. Colon-specific drug delivery: New approaches and *in vitro*/*in vivo* evaluation. Int J Pharm 2002;235(1-2):1-15.
10. Kydonieus AF, Berner B. Transdermal Delivery of Drugs. Vol. 261. Boca Raton: CRC Press; 1987. p. 52-65.
11. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery-Novel Carrier System. 1st ed. New Delhi: CBS Publication; 2002. p. 453-1.
12. Namrata J, Patel V, Mungekar S, Karpe M, Kadam V. Microsponge delivery system: An updated review current status and future prospects. World J Pharm Pharm Sci 2007;2(6):6463-85.
13. Aritomi H, Yamada K, Honda H, Koshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method. J Pharm Sci Technol 1996;56(1):49-56.
14. D'souza JI, Masvekar RR, Pattekari PP, Pudi SR, More HN. Microspongic delivery of fluconazole for topical application. Indo-Japanese Int Conf Adv Pharm Res Technol 2004;456:76-81.
15. Partibhan KG, Manivannan R. Krishnarajan D, Chandra S, Raj N. Microsponges role in Novel drug delivery. Int J Pharm Res Dev 2011;3(4):117-1258.

16. Soni M, Saxena C, Soni P, Sharma DK. Microsponge: A versatile vesicular approach for Transdermal drug delivery system. J Global Pharm Tech 2010;2(3):154-64.
17. Aloorkar NH, Kulkarni AS, Ingale DJ, Patil RA. Microsponges as Innovative drug delivery systems. Int J pharm Sci Nonotechnol 2012;5(1):143-151.
18. D'souza JI. The microsponge drug delivery system: For delivering an active ingredient by controlled time release. Pharmainfo. Net 2008:6(3):47-62.
19. Patravale VB. Microsponges: A path-breaking cosmetic innovation. Emerging Technol Household Personal Care Today 2008;4:45-9.
20. Pradhan SK. Microsponges are as the versatile tool for drug delivery system. Int J Res Pharm Chem 2011;40(1):196-201.
21. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Control of prolonged drug release and compression properties of ibuprofen microspheres with acrylic polymer, eudragit RS, by changing their intraparticle porosity [corrected]. Chem Pharm Bull (Tokyo) 1992;40(1):196-201.
22. Wester RC, Patel R, Nacht S, Leyden J, Melendres J, Maibach H. Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy. J Am Acad Dermatol 1991;24:720-6.
23. Santanu K, Sabyasachi M, Ghosh KA, Banerjee S. Micrsponge: A noval strategy for drug delivery system. J Pract Technol Res 2011;5(2):243-28.
24. Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed., Vol. 2. New York: McGraw-Hill; 2006. p. 1021-7.
25. Vikrant K, James S, Anne J and Manish SK. Microparticles: A novel approach to enhance the drug delivery. Int J Pharm Res Dev 2011;3(8)170-83.
26. Jain N, Sharma PK, Banik A. Recent advances in mirosponges drug delivery system. IJPSRR 2011;342:13-4.
27. Kilicarslan M, Baykara T. The effect of drug & polymer ratio on the properties of the Verapamil hydrochloride loaded microspheres. Int J Pharm 2003;252:99-109.
28. Mine O, Erdal C. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. Int J of Pharm 2006; 318:103-117.
29. Martin A, Swarbrick J, Cammarrata A. In: Physical Pharmacy & Physical Chemical Principles in Pharmaceutical Sciences. Vol. 3. New Delhi, India: B. I. Waverly; 1991. p. 527-36.
30. Vyas LK, Tapar KK, Laddha BH, Lahoti AO, Nema RK. Formulation and development of anti-blemish preparation using microsponge technology. J Chem Pharm Res 2010;2(5):562-71.
31. Ruckenstein E, Hong L. Concentrated emulsion polymerization pathway to hydrophobic and hydrophilic microsponge molecular reservoirs. Chem Mater 1992;4:1032-7.
32. Zaki Rizkalla CM, latif Aziz R, Soliman II. *In vitro* and *in vivo* evaluation of hydroxyzine hydrochloride microsponges for topical delivery. AAPS Pharm Sci Tech 2011;12(3):989-1001.
33. Shah VP. Determination of *in-vitro* release from hydrocortisone creams. Int J Pharm 1989;53:53-9.
34. Christensen MS, Hargens CW rd, Nacht S, Gans EH. Viscoelastic properties of intact human skin: Instrumentation, hydration effects, and the contribution of the stratum corneum. J Invest Dermatol 1977;69(3):282-6.
35. Sato T, Kanke M, Schroeder HG, DeLuca PP. Porous biodegradable microspheres for controlled drug delivery. I. Assessment of processing conditions and solvent removal techniques. Pharm Res 1988;5(1):21-30.
36. Guyot M, Fawaz F. Microspheres preparation and physical characteristics. Int J Pharm 1998;175:61-74.
37. Kaity S, Maiti S, Ghosh AK, Pal D, Ghosh A, Banerjee S. Microsponges: A novel strategy for drug delivery system. J Adv Pharm Technol Res 2010;1(3):283-90.
38. Roaa AN, Hussein AA. Preparation and evaluation of meloxicam microsponges as transdermal delivery system. Iraqi J Pharm Sci 2014;23(2):62-74.
39. Anilkumar JS, Mano B, Sawant SS. Development and evaluation of fenoprofen microsponges and its colonic delivery using natural polysaccharides. Int Publ Am J Pharm Sci Nanotechnol 2014;1(1):27-42.
40. Markhand M, Amish P, Viral HS, Upadhyay U. Formulation and in-intro evaluation of release microsponge gel for topical delivery of clotrimazole. Int J Adv Pharm 2012;2:93-101.
41. Makwana R, Patel H, Petal V, Photostability enhancement of miconazole nitrate by microsponge formulation. Int J Curr Trends Pharm Res 2014;2(3):437-58.
42. Emanuele AD, Dinarvand R. Preparation characterization and drug release from thermo responsive microspheres. Int J Pharm 1995;118:237-45.
43. Shah V, Jain H, Jethva K, Patel P. Microsponge drug delivery an overview. Int J Res Pharm Sci 2010;1(2):212-8.
44. Harinath N, D'Souza IJ. Topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system. Res J Pharm Technol 2008;1(4):72-9.
45. Mohan KV, Veena NM, Manjula BP. Formulation and evaluation of microsponges for topical drug delivery of Mupirocin. Int J Pharm Technol Res 2013;5(2):1434-40.
46. Barkai A, Pathak V, Benita S. Polyacrylate (eudragit retard) microspheres for oral controlled release of Nifedipine formulation design and process optimization. Drug Dev Ind Pharm 1990;16:2057-75.
47. Rajurkar VG, Tambe AB, Deshmukh VK. Topical anti-inflammatory gels of Naproxen entrapped in eudragit based microsponge delivery system. Adv Chem Engg 2015;5(2):251-8.
48. Chandramoul Y, Firoz S, Rajalakshmi R, Vikram A, Yasmeen RB, Chakravarthi RN. Preparation and evaluation of microsponge loaded controlled release topical gel of acyclovir sodium. Int J Biopharm 2012;3(2):96-102.
49. Panday P, Shukla N, Sisodiya D, Jain V, Mahajan SC. Design and characterization of microsponge loaded controlled release epicutaneous gel of lornoxicam. Appl Med Res 2015;3(2):16-20.
50. Wakiyama N, Juni K, Nakano M. Preparation and evaluation *in vitro* of polylactic acid microspheres containing local anesthetics. Chem Pharm Bull (Tokyo) 1981;29(11):3363-8.
51. Khopade AJ, Jain S, Jain NK. The microsponge. Eastern Pharmacist 1996;6(3):49-53.
52. Jelvehgari M, Siahi-Shadbad MR, Azarmi S, Martin GP, Nokhodchi A. The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. Int J Pharm 2006;308(1-2):124-32.
53. Amrutiya N, Bajaj A, Madan M. Development of microsponges for topical delivery of mupirocin. AAPS PharmSciTech 2009;10(2):402-9.
54. Fincham AE, Kamik KA. Patient counseling and derm therapy. US Pharm 1994;19:56-7.
55. Embil VP. OTC External analgesic cream, topical analgesic-anti-inflammation, counterirritant utilizing the microsponge delivery system (MDS) for controlled release of actives Patent Application No: 0101058; UK-2000.
56. Comoglu T, Gönül N, Baykara T. Preparation and *in vitro* evaluation of modified release ketoprofen microsponges. Farmaco 2003;58(2):101-6.
57. Hibab A, Shaimaa MB. Microsponge as promising vehicle for drug deliver and targeting preparation, characterization and application. Afr J Pharm Pharm 2013;7(17):873-81.
58. Jain V, Singh R. Dicyclomine loaded eudragit based microsponge with potential for colonic delivery: Preparation and characterization. Trop J Pharm Res 2010;9(1):67-72.
59. Jain V, Singh R. Development and characterization of eudragit RS 100 loaded microsponges and its colonic delivery using natural polysaccharides. Acta Pol Pharm 2010;67(4):407-15.
60. Mishra KM, Shikhri M, Sharma R, Goojar MP. Optimization, formulation development and characterization of Eudragit RS 100 loaded microsponges and subsequent colonic delivery. Int J Drug Discov Herbal Res 2011;1(1):8-13.
61. Jain NK, Sharma SN. A Textbook of Professional Pharmacy. 4th ed. New Delhi: Vallabh Prakashan; 2006. p. 257-72.
62. Shyam SM, Vedavathi T. Novel approach microsponge drug delivery system. Int J Pharm Sci Res 2012;1(3):967-80.
63. Srivastava R, Pathak K. Microsponges: A futuristic approach for oral drug delivery. Expert Opin Drug Deliv 2012;9(7):863-78.
64. Rossi S, Buckley N. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pvt., Ltd.; 2006. p. 3572-9.
65. Baselt R. Disposition of Toxic Drugs and Chemicals in Man. 8th ed. Foster City: Biomedical Publications; 2008. p. 29-31.
66. Gangadharappa HV, Gupta NV, Prasad MS, Shivakumar HG. Current trends in microsponge drug delivery system. Curr Drug Deliv 2013;10(4):453-65.
67. Trotta F, Cavalli R, Tumiatti W. Cyclodextrin-based nanosponges for drug delivery. J Incl Phenom Macrocycl Chem 2006;56:209-13.
68. Hu SH, Liu TY, Liu DM, Chen SY. Nano-ferrosponges for controlled drug release. J Control Release 2007;121:181-9.
69. Li NH, Benson JR, Kitagawa N. Polymeric microbeads and method of preparation. International Publication No. WO1995033553; 2003.
70. Lee JB, Hong J, Bonner DK, Poon Z, Hammond PT. Self-assembled RNA interference microsponges for efficient siRNA delivery. Nat Mater 2012;11(4):316-22.