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A review- Recent research on microsponge a novel new drug delivery system

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Abstract

Microsponge is recent novel technique for control release and target specific drug delivery system. Therefore many scientist or researcher attracted towards the microsponge drug delivery system. Also Microsponge technology has been introduced in topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. Microsponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponge systems are non-irritating, non-mutagenic, on-allergenic, and non-toxic. Microsponge drug delivery system technology is being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products.

Keywords: Solubility Enhancement, Dissolution Rate, Novel Drug Delivery System, Immediate Release Drug Delivery.

1. Introduction

Microsponges are polymeric drug delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface [1]. Moreover, they may enhance stability, reduce side effects and modify drug release favourably. Microsponge technology has many favourable characteristics, which make it a versatile drug delivery vehicle [2]. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. Microsponge drug delivery system can provide increased efficacy for topically active agents with enhanced safety, extended product stability and improved aesthetic properties in an efficient manner. To control the delivery rate of active agents to a predetermined site in the human body has been one of the biggest challenges faced by Pharmaceutical scientists. Several predictable and reliable systems have been developed for systemic delivery of drugs under the heading of transdermal delivery system (TDS) using the skin as portal of entry [3].

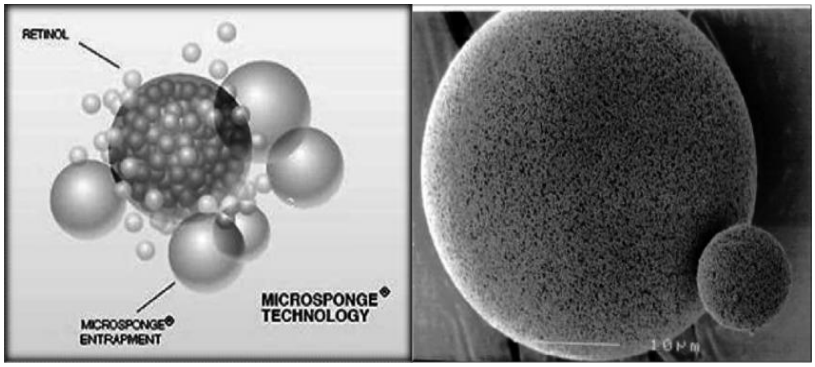

Figure 1: Microsponge Technology

The Microsponge Delivery System (Microsponge drug delivery system) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a noncollapsible structure with a large porous surface through which active ingredient are released in a controlled manner [4]. The size of the microsponges ranges from 5-300µm in diameter and a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention [5].

Potential features or characteristic of microsponge drug delivery systems

1) Microsponges exhibit good compatibility with various vehicles and ingredients.
2) Microsponges have high entrapment efficiency.
3) Microsponges are evaluated by free flowing properties [6].
4) Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to130°C).
5) The average pore size of microsponges is small (0.25 µm) in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
6) Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.
7) Microsponges can absorb oil up to 6 times their weight without drying [7].

Benefit of Microsponge drug delivery system

1) Improved formulation flexibility.
2) Improved thermal, physical, and chemical stability.
3) Flexibility to develop novel product forms.
4) Microsponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic[8]
5) Enhanced product performance.
6) Extended release.
7) Reduced irritation and hence improved patient Compliance.
8) Effective product elegancy.
9) Improved oil control as it can absorb oil up to 6 times its weight without drying[9]

Characteristics of actives moieties that is entrapped into Microsponges

1) Active ingredients that are entrapped in microsponge can then be incorporated into many products such as creams, gels, powders, lotions and soaps.
2) Certain considerations are taken into account while, formulating the vehicle in order to achieve desired product characteristics.
3) It should be either fully miscible in monomer as well as capable of being made miscible by addition of small amount of a water immiscible solvent.
4) It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
5) It should be water immiscible or nearly only slightly soluble [10].
6) It should not collapse spherical structure of the microsponges.
7) It should be stable in contact with polymerization catalyst and also in conditions of polymerization.
8) The solubility of actives in the vehicle must be limited.
9) If not, the vehicles will deplete the microsponges before the application.
10) Not more than 10 to 12% w/w microsponges must be incorporated into the vehicle in order to avoid cosmetic problems.
11) Payload and polymer design of the microsponges for the active must be optimized for required release rate for given. period of time[11]

2. Applications of Microsponge Systems

2.1 Topical Delivery

Topical agents are a mainstay in cosmetics and the treatment of dermatological disorders. However, they are associated with substantial skin irritancy, especially in

sensitive patients. The rapid release and subsequent accumulation of the active ingredients of the topical agents have been associated with this irritancy. Microsponge delivery technology provides controlled release of the active ingredients onto the skin. Several microsphere-based topical agents have been evaluated for their safety and efficacy for cosmetic purposes and in the treatment of dermatological disorders, and are currently marketed in the US. These include formulations of benzoyl peroxide, tretinoic acid, HQ plus retinol, and 5-FU. Formulations of topical agents utilizing the Microsponge drug delivery system technology have shown little or no irritancy in patients with acne, photo damaged skin, hyper pigmentation, or AK, without sacrificing the efficacy of the agents [12].

2.2 Oral Delivery

In oral drug delivery the microsponge system increase the rate of solubilization of poorly water soluble drugs by entrapping them in the microsponge system's pores. As these pores are very small the drug is in effect reduced to microscopic particles and the significant increase in the surface area thus greatly increase the rate of solubilization. A Microsponge system offers the potential for active ingredients to remain within a protected environment and provide controlled delivery of oral medication to the lower gastrointestinal (GI) tract, where it will be released upon exposure to specific enzymes in the colon. If this approach is successful then it should open up entirely new opportunities for Microsponge drug delivery system. It has been shown that microsponge system enhances the solubilization of drugs which are poorly soluble by entrapping these drugs in their pores [13].

2.3 Bone substitutes

Bone-substitute compounds were obtained by mixing pre-polymerised powders of polymethylmethacrylate and liquid methylmethacrylate monomer with two aqueous dispersions of a-tricalcium phosphate (a-TCP) grains and calcium-deficient hydroxyapatite (CDHA) powders. The final composites appeared to be porous. Osteo-conductivity and Osteo-conductivity of the final composites were tested *In-vivo* by implantation in rabbits. Formation of new trabecular bone was observed inside the pores where the inorganic powders had been placed. The material produced shows a good level of biocompatibility, good osteointegration rate and osteogenetic properties [14].

2.4 Cardiovascular engineering using microsponge technology

Biodegradable materials with autologous cell seeding, requires a complicated and invasive procedure that carries the risk of infection. A biodegradable graft material containing collagen microsponge that would permit the regeneration of autologous vessel tissue has developed. The ability of this material to accelerate in-situ cellularization with autologous endothelial and smooth muscle cells was tested with and without pre-cellularization. Poly (lactic-co-glycolic acid) as a biodegradable scaffold was compounded with collagen microsponge to form a vascular patch material. Histological results showed the formation of an endothelial cell monolayer, a parallel alignment of smooth muscle cells, and reconstructed vessel wall with elastin and collagen fibres. The cellular and extracellular components in the patch had increased to levels similar to those in native tissue at 6 months. This patch shows promise as a bioengineered material for promoting in situ cellularization and the regeneration of autologous tissue in cardiovascular surgery [15].

2.5 Microsponges for Biopharmaceuticals Delivery

The microsponge delivery system is employed for both in the delivery of biopharmaceuticals as well as in tissue engineering. Dai 2010 *et al* developed 3D scaffolds hybrid structures that have advantages of natural type I collagen and synthetic PLGA knitted mesh. The collagen microsponges facilitated cell seeding and tissue formation and mechanically strong PLGA mesh served as a skeleton. The scaffolds were divided into three groups: a) *Thin*: collagen microsponge formed in interstices of PLGA mesh; b) *Semi*: collagen microsponge formed on one side of PLGA mesh; c) *Sandwich*: collagen sponge formed on both sides of PLGA mesh [16].

Afrasim M *et al*. (2016) successfully developed Polymeric microsponge based system of Fluconazole was developed successfully using quasi-emulsion solvent diffusion method for continual topical delivery up to an extended period so as to reduce application frequency, hypersensitive reactions allied to the conventional marketed formulation, and to improve bioavailability and safety. Implemented method was found to be simple, reproducible and rapid; which led to the formation of highly porous, spherical microsponges with good flow. Varied drug-polymer ratio reflected remarkable effect on drug content, encapsulation efficiency, particle size, and drug release. Among the all prepared gels integrating FLZ-loaded microsponges, the F1 formulation was chosen for further study on the basis of its superiority in terms of physiochemical characterization, production yield, drug content, entrapment efficiency, morphology, surface topography, intact particles percent, and particle size. The *In-vitro* drug release study outcomes showed highest regression values for the zero order models, and also established proficiency of F1 formulation for extended drug release (85.38% at 8 h) with respect to conventional marketed one. The *In-vitro* antifungal evaluation and stability study too depicted promising results. Thus,

microsponge based delivery system developed and investigated in present research approach was seems to be promising with respect to eradication of face fungus, candidiasis and numerous other fungal infections, along with the practical application in pharmaceuticals and cosmeceuticals.[17]

Barde P. (2015), had concluded that Microsponges containing Terbinafine HCl were prepared using Eudragit RSPO as a polymer by quassi-emulsion solvent diffusion method. The developed microsponges formulation were optimised and further evaluated. It was observed that the polymer Eudragit RSPO and stabilizing agent PVA concentration influenced the particle size and drug content of formed microsponges. The production yield, loading efficiency, surface morphology and particle size analysis was performed. The surface morphology including the pore structure of microsponges was evaluated using scanning electron microscopy. Microparticles were then incorporated in Carbopol 934 gel base and *In-vitro* permeation studies of formulations were performed in Franz diffusion cell. Surface morphology by scanning electron microscopy showed microporous nature of microsponges. Drug release was observed comparison with marketed formulation. The present study was to design, develop, and evaluate the microsponge incorporated gel for topical drug delivery of Terbinafine HCl for extended release. Mixture of Eudragit RSPO and drug in DCM act as internal phase. Solution of PVA in water used as external phase. Terbinafine HCl is easily inactivated by the gastric environment and produce gastric disturbances such as diarrhoea, nausea, abdominal pain and vomiting. The best formulation F4 was incorporated into gels and gels were evaluated for physical parameters and showed extended release up to 12h. Stability studies at room temperature showed that there was no noticeable change in the homogeneity, pH, spreadability, extrudability, viscosity, drug content and *In-vitro* release at the end of three months. Thus it was concluded that the optimized microsponges further can be incorporated into gel for topical application use as antifungal purpose. [18]

Yadav P. *et al* (2014) had concluded that Skin has to bear various external traumas like wounds, burns, blisters, irritation etc. as well as topical diseases like psoriasis, vitilago, cancer and herpes. Various drug delivery systems like vesicles, microspheres, transdermal patches, nanoemulsions, microemulsions, microsponges etc. are available which are better than conventional drug delivery methods because these bypass systemic circulation as well as drug can be targeted directly to the required site. Microsponges are tiny sponge-like spherical particles with a large porous surface and provide controlled release. Herpes simplex is a viral disease occurring in two forms Herpes labialis and Herpes keratitis which occur on lips and epidermal layer of skin respectively. Conventional formulations used for treating herpes have various drawbacks like irritation, rashes, frequency of dosing and low bioavailability. Hence microsponge loaded topical preparations herbal gel and medicated lipstick of Acyclovir was prepared with a purpose to overcome these drawbacks. Microsponge loaded controlled release formulations of Acyclovir were prepared using quasi emulsion solvent diffusion method. The proposed formulations of Acyclovir loaded microsponges were characterized for particle size, production yield and entrapment efficiency. Porous structure of microsponges was confirmed by Scanning Electron Microscopy. After evaluation best optimized batch was incorporated in carbopol and aloe gel and lipstick base. Microsponge loaded herbal gel and lipstick were evaluated for various physical parameters. In- vitro release studies using diffusion cell revealed that the drug release followed Korsemeyer Peppas model. Microsponges containing Acyclovir were prepared by quasi emulsion solvent diffusion method using ethyl cellulose and PVA. By considering the solubility study of the drug and polymer and the rate of diffusion of the solvent used, the internal phase suitable for the preparation of microsponges to be ethanol and the external phase was found to be water. Mixture of Ethyl cellulose and drug in ethyl alcohol served as internal phase. Solution of PVA in water served as external phase. The concentration of the polymer required to produce microsponges with good physical and morphological characteristics was found to be 10-12% w/w of the drug. The minimum concentration of an emulsifier PVA required to produce microsponges was found to be 50 mg per 200ml. The particle size range increases as increase in amount of polymer in the formulation. [19]

Ravi R. (2013) had concluded that Acne is a common inflammatory skin disease that mainly affects the face, neck, chest and upper back. Treatment depends on severity. Erythromycin has bacteriostatic activity which inhibits the growth of bacteria. They mainly act by binding to the 50s subunits of bacteria, 70s r-RNA complex, and protein synthesis. Erythromycin is also used topically to treat acne. They are used to treat moderate to severe inflammatory acnes or acne that isn't getting better with other treatments. Erythromycin works to treat acne by reducing the amount of acne causing bacteria called "propionibacteria" acnes on the skin; it also lessens inflammation and redness. Erythromycin is easily inactivated by the gastric environment and produce gastric disturbances such as diarrhoea, nausea, abdominal pain and vomiting. Erythromycin microsponges were prepared using quassi emulsion solvent diffusion method. Erythromycin microsponges were then incorporated into a Carbopol-940 gel prepared by hydrogel technique for release studies. The

best formulation was found to be stable at room temperature for 3 months. Thus it was concluded that erythromycin can be formulated as microsponge gel that can release the drug up to 8hrs with reduced side effects. [20]

Mohan K *et al* (2013) had concluded that Impetigo is a chronic, contagious bacterial skin infection caused by *Staphylococcus aureus, Streptococcus pyogenes* or both and usually treated with systemic antibiotics. Mupirocin is a medium potency, synthetic, topical antibacterial agent used in the treatment of impetigo. Percutaneous absorption is a risk associated with topically administered formulations. Controlled release of the drug to the skin could reduce the side effects while reducing percutaneous absorption. Therefore, the aim of the study was to produce mupirocinen trapped microsponges to control the release of the drug to the skin. Mupirocin microsponges were prepared using an emulsion solvent diffusion method. In order to optimize the microsponge formulation, factors affecting the physical properties of microsponges were determined. FT-IR and SEM was used to study the shape and morphology of microsponges. Mupirocin microsponges were then incorporated into a vanishing cream base for release studies. It was shown that the drug: polymer ratio, stirring rate, volume of external and internal phase influenced the particle size and drug release behavior of microsponges. The results showed that an increase in the ratio of the drug: polymer resulted in a reduction in the release rate of Mupirocin from microsponges. Kinetic analysis showed that the main mechanism of drug release was by Higuchi matrix- controlled diffusion. Quasi–emulsion solvent diffusion seems to be a promising method for the preparation of MUP microsponges as it is a rapid, easy, reproducible method and has an advantage of avoiding solvent toxicity. In this method there is formation of quasi-emulsion droplets. The rapid diffusion of solvent into the aqueous medium might reduce the solubility of polymer in the droplets, since the polymer is insoluble in water. The instant mixing of the ethanol and water at the interface of the droplets induce precipitation of the polymer thus forming a shell enclosing the solvent and dissolved drug. Counter diffusion of solvent and water through the shell promotes further crystallization of the drug in the droplets of the polymer from the interior core. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via diffusion of solvent. [21]

Saboji J *et al* (2011) had concluded that Microsponge containing Ketoconazole drug with six different proportions of Eudragit RS 100 as polymer were obtained successfully using quasi-emulsion solvent diffusion method. These formulations were studied for particle size and physical characterization. The physical characterization showed that microsponge formulation MS IV and MS VI showed a better loading efficiency and production yield. These two microsponge formulation were prepared as gel in 0.35 %w/w carbopol and studied for pH, viscosity, spreadability, drug content, *In-vitro* release, antimicrobial activity and *In-vivo* antifungal activity studied on guinea pig skin. The microsponge formulation gel, MKG 1 showed viscosity 4390 cps, spreadability of 19.27 g cm/s and drug content of 85.2%. The antimicrobial studies showed zone of inhibition with 13.5 mm and 12.0 mm for microsponge formulation gel MKG 1 and MKG 2 respectively when compared with pure drug, zone of inhibition 18.2 mm. These formulations also showed better antifungal activity on fungal induced guinea pig skin when compared with control group without application of drug. The microsponge ketoconazole gel formulations showed an appropriate drug release profile and also bring remarkable decrease on gel application for fungal treatment. [22]

Sabyasachi M *et al* (2011), were prepared xanthan gum-facilitated ethyl cellulose microsponges by the double emulsification technique and further dispersed in a carbopol gel base for controlled delivery of diclofenac sodium to the skin. Scanning electron microscopy revealed the porous, spherical nature of the microsponges. Increase in the drug/ polymer ratio increased their yield, drug entrapment efficiency and mean particle diameter; when an equivalent amount of pure drug (not entrapped into microsponges) was dispersed into the gel base and the flux was compared, the microsponges. Whether the drug was dispersed either in un-entrapped or entrapped form into the gel base, the drug permeation through rat skin followed Higuchi's diffusion kinetic model. The microsponges prepared at the lowest drug/polymer ratio exhibited a comparatively slower drug permeation profile and were hence considered most suitable for controlled drug delivery application. FTIR spectroscopy and DSC analyses indicated the chemically stable, amorphous nature of the drug in these microsponges. The gel containing these optimized microsponges was comparable to that of a commercial gel formulation and did not show serious dermal reactions. Hence, the microsponge system obtained at the lowest drug/polymer ratio could be useful for controlled release of diclofenac sodium to the skin. [23]

Netal A *et al* (2009) concluded that to develop and evaluate microsponge-based topical delivery system of mupirocin for sustained release and enhanced drug deposition in the skin. Microsponges containing mupirocin were prepared by an emulsion solvent diffusion method. The effect of formulation and process variables such as internal phase volume and stirring speed on the physical characteristics of microsponges were examined on optimized drug/polymer ratio by 3^2 factorial designs. The

optimized microsponges were incorporated into an emulgel base. *In-vitro* drug release, *ex vivo* drug deposition, and *In-vivo* antibacterial activity of mupirocin-loaded formulations were studied. Developed microsponges were spherical and porous, and there was no interaction between drug and polymer molecules. Emulgels containing microsponges showed desired physical properties. Drug release through cellulose dialysis membrane showed diffusion-controlled release pattern and drug deposition studies using rat abdominal skin exhibited significant retention of active in skin from microsponge-based formulations by 24 h. The optimized formulations were stable and nonirritant to skin as demonstrated by Draize patch test. Microsponges-based emulgel formulations showed prolonged efficacy in mouse surgical wound model infected with S. aureus. Mupirocin was stable in topical emulgel formulations and showed enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections, such as impetigo, eczema, and atopic dermatitis. [24]

Jain and Singh (2009), had concluded that paracetamol loaded eudragit based microsponges were prepared using quasi-emulsion solvent diffusion method. The compatibility of the drug with various formulation components was established. Process parameters were analysed in order to optimize the formulation. Shape and surface morphology of the microsponges were examined using scanning electron microscopy. The colon specific formulations were prepared by compression coating of microsponges with pectin: hydroxyl propylmethyl cellulose (HPMC) mixture followed by tableting. The *In-vitro* dissolution studies were done on all formulations and the results were evaluated kinetically and statically. The kinetics of release study showed that the release data followed Higuchi matrix and the main mechanism of drug release from microsponges was diffusion. *In-vitro* studies exhibited that compression coated colon specific tablet formulations started the release the drug at the 6th hour corresponding to the arrival time to proximal colon. [25]

Mine O *et al* (2006) concluded that to design novel colon specific drug delivery system containing flurbiprofen (FLB) microsponges. Microsponges containing FLB and Eudragit RS100 were prepared by quasi-emulsion solvent diffusion method. Additionally, FLB was entrapped into a commercial microsponge® 5640 system using entrapment method. Afterwards, the effects of drug: polymer ratio, inner phase solvent amount, stirring time and speed and stirrer type on the physical characteristics of microsponges were investigated. The thermal behaviour, surface morphology, particle size and pore structure of microsponges were examined. The colon specific formulations were prepared by compression coating and also pore plugging of microsponges with pectin: hydroxypropylmethyl cellulose (HPMC) mixture followed by tableting. *In-vitro* dissolution studies were done on all formulations and the results were kinetically and statistically evaluated. The pore shapes of microsponges prepared by quasi-emulsion solvent diffusion method and entrapment method were found as spherical and cylindrical holes, respectively. Mechanically strong tablets prepared for colon specific drug delivery were obtained owing to the plastic deformation of sponge-like structure of microsponges. *In-vitro* studies exhibited that compression coated colon specific tablet formulations started to release the drug at the 8th hour corresponding to the proximal colon arrival time due to the addition of enzyme, following a modified release pattern while the drug release from the colon specific formulations prepared by pore plugging the microsponges showed an increase at the 8th hour which was the time point that the enzyme addition made. This study presents a new approach based on microsponges for colon specific drug delivery. [26]

3. Conclusion

As formulators consider new and creative ways to deliver actives, they can realize the full capabilities of these unique materials providing enhanced safety, improved stability, reduced side effects from actives, enhanced multi functionality and improved ingredient compatibility. Complemented by novel development approaches and creative formulation techniques, Microsponge delivery system can be a winning strategy for a new generation of Pharmaceutical and Cosmetic industry. Microsponges have a distinct advantage over the existing conventional topical dosage forms for the treatment of tropical diseases; it is a unique technology for the controlled release of topical agents also use for oral as well as biopharmaceutical drug delivery. This shows advantageous over other products by non-mutagenic, non-toxic, non-irritant. So microsponge drug delivery system has got a lot of potential and is a very emerging field which is needed to be explored in the future with most research study.

Reference

[1]. Gupta M, Goyal AK, Paliwal SR, Paliwal R, Mishra N, Vaidya B, Development and characterization of effective topical liposomal system for localized treatment of cutaneous candidiasis. *J Liposome Res* 2010; 20:341-50.

[2]. Bidkar S, Jain D, Padsalg A, Patel K, Mokale V. Formulation development and evaluation of fluconazole gel in various polymer bases. *Asian J Pharm* 2007; 1:63-8.

[3]. Schafer-Korting M, Mehnert W, Korting HC. Lipid nanoparticles for improved topical application of drugs for skin diseases. *Adv Drug Deliv Rev* 2007; 59: 427-43.

[4]. Osmani RA, Aloorkar NH, Kulkarni AS, Harkare BR, Bhosale RR.A new cornucopia in topical drug delivery: Microsponge technology. *Asian J Pharm Sci Tech* 2014; 4:48-60.

[5]. Teichmann A, Heuschkel S, Jacobi U, Presse G, Neubert RH, Sterry W, *et al.* Comparison of stratum corneum penetration and localization of a lipophilic model drug applied in an o/w microemulsion and anamphiphilic cream. *Eur J Pharm Biopharm* 2007; 67: 699-706.

[6]. Pawar AP, Gholap AP, Kuchekar AB, Bothiraja C, Mali AJ. Formulation and evaluation of optimized oxybenzone microsponge gel for topical delivery. *J Drug Deliv* 2015; 2015: 261068.

[7]. Castro GA, Coelho AL, Oliveira CA, Mahecha GA, Oréfice RL, Ferreira LA. Formation of ion pairing as an alternative to improve encapsulation and stability and to reduce skin irritation of retinoic acid loaded in solid lipid nanoparticles. *Int J Pharm* 2009; 381:77-83.

[8]. Bothiraja C, Gholap AD, Shaikh KS, Pawar AP. Investigation of ethyl cellulose microsponge gel for topical delivery of eberconazole nitrate for fungal therapy. *Ther Deliv* 2014; 5:781-94.

[9]. Jadhav KR, Kadam VJ, Pisal SS. Formulation and evaluation of lecithin organogel for topical delivery of fluconazole. *Curr Drug Deliv* 2009; 6:174-83.

[10]. Abdel-Mottaleb MM, Mortada ND, El-Shamy AA, Awad GA. Physically cross-linked polyvinyl alcohol for the topical delivery of fluconazole. *Drug Dev Ind Pharm* 2009; 35:311-20.

[11]. Yehia SA, El-Gazayerly ON, Basalious EB. Fluconazole mucoadhesive buccal films: *In-vitro*/*In-vivo* performance. *Curr Drug Deliv* 2009; 6:17-27.

[12]. Jelvehgari M, Siahi-Shadbad MR, Azarmi S, Gary P, Martin, Nokhodchi A. The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. *Int J Pharma* 2006; 308:124-132.

[13]. Tansel C, Baykara T. The effects of pressure and direct compression on tabletting of microsponges. *Int J Pharm* 2002; 242: 191–95.

[14]. Martin A, Swarbrick J, Cammarrata A. In: Physical Pharmacy- Physical Chemical Principles in Pharmaceutical Sciences 1991; 3: 527.

[15]. Emanuele AD, Dinarvand R. Preparation, Characterization and drug release from thermo responsive microspheres. *Int J Pharma* 1995: 237-42.

[16]. Orr JRC. Application of mercury penetration to material analysis. *Powder Technol.* 1969; 3: 117–123.

[17]. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyama S. Characterization of polymorphs of tranilast anhydrate and tranilast monohydrate when crystallized by two solvent change spherical crystallization techniques. *J Pharm Sci* 1991; 81: 472-478.

[18]. Afrasim M. and Rohit R. Bhosale, Umme Hani, Fabrication, characterization, and evaluation of microsponge delivery system for facilitated fungal therapy, *Journal of Basic and Clinical Pharmacy*, 2016; 7(2): 39-46.

[19]. Barde P. and Basarkar G., Formulation, Development and In-vitro Evaluation of Terbinafine HCL Microscope Gel, *Int. J. Pharm. Sci. Rev. Res.*, 2015; 32(1): 310-4.

[20]. Yadav P. and Nanda S., Development and evaluation of some microsponge loaded medicated topical formulations of acyclovir, *IJPSR*, 2014; 5(4): 1395-1410.

[21]. Ravi R., Senthil Kumar S.K., Parthiban S., Formulation and evaluation of the microsponges gel for an anti acne agent for the treatment of acne, *Indian Journal of Pharmaceutical Science and Research*, 2013; 3(1): 32-38.

[22]. Mohan K., Veena N, Manjula B P., Formulation and evaluation of microsponges for topical drug delivery of mupirocin, *International Journal of Pharmtech Research*, 2013; 5(3): 1434-1440.

[23]. Saboji, J. K.,1 Manvi, F. V., Gadad, A. P. and Patel, B. D., Formulation and evaluation of ketoconazole microsponge gel by quassi emulsion solvent diffusion, *Journal Of Cell and Tissue Research*, 2011; 11(1): 2691-2696.

[24]. Sabyasachi Maiti, Santanu K, Somasree B., Development and evaluation of xanthan gum-facilitated ethyl cellulose microsponges for controlled percutaneous delivery of diclofenac sodium, *Acta Pharm.* 2013; 61: 257–270

[25]. Netal A., Amrita B. and Madhu Madan, Development of microsponges for topical delivery of mupirocin, *AAPS Pharmscitech*, 2009; 10(2): 402-409.

[26]. Jain V. and 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.

[27]. Mine O., Erdal C., Ahmet A., Design and Evaluation Of Colon Specific Drug Delivery system Containing Flurbiprofen Microsponges, *International Journal of Pharmaceutics* 2006; 318: 103–117.