Therapeutic Application of Microsponges-Based Drug Delivery System

Mahfoozur Rahman[1], Waleed HAlmalki[2], Sunil K Panda[3], Aman Kumar Das[1], Saad Alghamdi[4], Kirti Soni[5],Abdul Hafeez[6], Mayank Handa[7], Sarwar Beg[8*], Ziyaur Rahman[9*]

[1]Department of Pharmaceutical Sciences, Shalom Institute of Health & Allied Sciences, Sam Higginbottom University of Agriculture, Technology &Sciences, Allahabad, India

[2]Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Saudi Arabia

[3]Menovo Pharmaceuticals Research Lab, Ningbo, People's Republic of China

[4]Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia

[5]Formulation Development, Dabur Research Foundation, 22 Site IV Sahibabad Industrial Area, Ghaziabad, Uttar Pradesh, India

[6]Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Saharanpur, Uttar Pradesh, India

[7]Department of Pharmaceutics, NIPER, Raebareli, Lucknow, Uttar Pradesh, 226002

[8]School of Pharmacy and Biomedical Sciences, Faculty of Clinical and Biomedical Sciences, University of Central Lancashire, Preston PR1 2HE, UK

[9]Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Texas A&M University, College Station, TX 77843

***Address for correspondence:**

Dr. Sarwar Beg, School of Pharmacy and Biomedical Sciences, Faculty of Clinical and Biomedical Sciences, University of Central Lancashire, Preston PR1 2HE, UK, Email: sarwar.beg@gmail.com

Dr.Ziyaur Rahman, Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Texas A&M University, College Station, TX 77843, Email: rahman.ziyaur@gmail.com

Abstract

Microsponges delivery systems (MDS) are highly porous, cross-linked polymericsystems that activate in the presence of temperature, rubbing, and pH. MDS offer a wide range of advantages, like controlled drug release, site-specific action, stability over a broad range of pH, less irritation, cost-effectiveness, and improved patient compliance. They can be transformed into various dosage forms like creams, gels, and lotions. MDS-based systems are suitable for the treatment oftopical disorders like acne, psoriasis, dandruff, eczema, scleroderma, hair loss, skin cancer, and other dreadful diseases. MDS application for drug delivery is not limited to topical drug delivery but isalso explored for oral, parenteral, and pulmonary drug delivery.Microsponges were studied for colon targeting of drugs and genes.Additionally, MDS haveseveralapplicationssuch assunscreen, cosmetics, andover-the-counter (OTC) products. Furthermore, MDS do not actuate any irritation, genotoxicity, immunogenicity, or cytotoxicity. Therefore, this review extensively highlights microsponges, their advantages, key factors affecting theircharacteristics, their therapeutic applicationsin topical disorders and in cancer, their use as cosmetics, as well as recent advances in MDS and the associated challenges.

Keywords: Microsponges;Nanosponges;Oraldelivery; Topical applications;Skin irritation; intestinal membrane.

1. Introduction

Oral-based conventional dosage forms release the drug in the gastrointestinal (GIT) fluid which causes variation in absorption of the drugs throughout the intestinal membrane. A wide range of conventional formulations are administered orally for immediate drug release activity. However, oral route of drug administration suffers from incomplete drug absorption and rapidly cleared from the body leading to compromised therapeutic performance. The conventional topical dosage forms allow permeation of active pharmaceutical ingredients (API) through the skin to the underlying skin layers [1,2]. The release of drug from the conventional topical dosage forms into epidermis remains fundamentally restricted due to skin barriers which also provides short duration of therapeutic action [1,3,4]. Furthermore, topical route encounters with limitations like aesthetically unappealing, unpleasant smell, oiliness, stickiness, and may causes irritation, allergic reactions and suboptimal response in the patient. Additionally, these carriers needed in higher concentrations to deliver an active ingredients for better therapeutic action [5]. Novel drug delivery systems surpass these limitations associated with conventional topical and oral delivery systems. These advancements in the field of delivery systems imparts enhancement in the efficacy and reduced cost of the treatment [6]. Therefore, emergence of microsponges-based delivery systems can uniquely solve the problems associated with the conventional topical and oral dosage forms.

Microsponges delivery systems (MDS) are porous, highly cross-linked, polymeric systems constituted from the porous microspheres. MDS captures various drugs and provides tailored release profile when administered via skin/GIT. These carriers its activation under temperature and pH [7]. The microsponges can be transformed into dosage forms like creams, gels and lotions for the treatment of various topical disorders like acne, psoriasis, dandruff, eczema, scleroderma, hair loss, skin cancer, and other dreadful diseases [4,8]. MDS has a wide range of advantages like controlled drug release, site-specific action, stability over a wide range of pH, cost effective manufacturing, poor irritation and improved patient compliance. Microsponges have good ability for drug adsorption or absorption. They can encapsulate more than 3-fold of their weight, and makes an alluring carrier from other types of delivery systems [2,9–12]. In addition, it limits the irritation of effective medications without compromised efficacy. Further, controlled drug release into the skin can be accomplished through diffusion mechanism and

provides advantages like enhanced product efficacy, tolerability, mildness, and reduced irritation [13]. MDS is not limited to topical drug delivery, but it is broadly studied for oral, parenteral, and pulmonary drug delivery applications. This review, therefore, extensively highlights about microsponges, and their advantages, key factors affecting the microsponges characteristics, therapeutic application of microsponges in topical disorders and cosmetic preparation, along with recent advances in MDS preparation, characterization, stability and toxicity evaluation.

2. Microsponges compositions

On the basis of dermal toxicity studies, various polymers have been explored so far. The modelling of microsponges consists of Eudragit© or polymethacrylates polymers (Eudragit RSPO, Eudragit RS100, Eudragit S100), polylactic acid, polylactide-co-glycolic acid, polyhydroxy butyrate, polydivinyl benzene, ethyl cellulose. From above mentioned polymers, Eudragit RS100 is the primarily used and widely studied polymer because of its universal nature and biocompatibility. Eudragit-based polymers differ in characters like water permeability, and solubility which accounts for designing pre-determined drug release profiles in MDS system. Thus, it facilitates numerous alternatives to achieve the desired physicochemical properties [14–16]. Polymethacrylate polymers are non-toxic, safe and budgetary excipients, that widely accepted in pharmaceutical formulation and approved by US Food and Drug Administration (FDA). Different polymethacrylate polymers can be combined and exhibits controlled drug release behaviour[17]. Ethyl cellulose is used as the base material for the preparation of microsponges, as it is non-toxic, non-allergenic and non-irritating in nature [18,19]. Polydivinyl benzene is used for fabrication of porous microspheres with the help liquid-liquid suspension polymerization method[20,21].

Till now, a wide range of polymers used in MDS are explored, but biodegradable polymers are least studied. Biodegradable polymers are promising excipients for microsponges development as carriers for drug delivery and targeting [22]. Additionally, triethyl citrate is employed as plasticizer for stabilization of the microsponges [2,23]. Cellulose ethers and polyvinyl alcohol (PVA) are used as emulsifying agents for maintenance of aqueous phase consistency by using quasi-emulsion solvent diffusion method [24]. Whereas, sodium bicarbonate or hydrogen peroxide forms equitable distribution and interconnection of pores as well as the availability of higher surface area for high drug loading. These interconnected pores, provide high entrapment

efficiency to these micro-colloidal drug delivery systems [25,26]. As per the literature review, pre-gelatinized starch and sucrose are utilized as inducers for pore, that improves the drug release characteristics[27,28].

3. Characterizations of microsponges

There are certain factors that affect microsponges characteristics include shape, particle size, encapsulation efficiency, porosity, surface morphology, drug loading and drug release.

3.1. Particle size and distribution

The particle size and its distribution are essential parameters in the preparation of microsponges. Various factors that affect size of microsponges include its internal phase volume, polymer-drug ratio, stirring speed, emulsifier concentration, etc. [14]. The particle size range for the topical application is 10-25 μm [29]. The particle size affects drug loading and release profile from microsponges. It is important to characterize the particle size and its distribution as it greatly affects the texture and stability of the formulation. Increasing drug-polymer ratio produces small particles, while increase in the amount of emulsifier results in large-sized microsponges.

3.2. Surface topography and morphology

Different methods like scanning electron microscopy (SEM), photon correlation spectroscopy (PCS), transmission electron microscopy (TEM) have been employed to understand the morphology and surface topography of microsponges [30]. Various researchers have reported the microsponges morphology and demonstrated presence of pores on the carriers' surface. Temperature and solvent in inner phase affects the microsponges morphology during the process of formulation. Another parameter, related to the solvent system is about the production of snappy polymer precipitation that results in less or non-porous surface [31,32].

3.3. Pore structure, Production yield and Loading efficiency

Pore diameter and volume are crucial in regulation of drug release. The production yield parameters are affected by polymer-drug ratio, amount and type of emulsifier used, and mixing speed. Jain and Singh formulated dicyclomine microsponges that have exceptionally less yield with polymer-drug ratio of 1:1, while at polymer-drug ratio of 5:1, results in higher production yield. Drug loading in microsponges is carried out by two methods such as passive loading

(single-step process) and active loading (double-step process). Passive loading is simple, advantageous and more effective than active loading. The drug loading efficiency can be enhanced by enhanced drug-polymer ratio and decreases the particle size[33].

3.4.Compatibility Studies

Fourier transform infrared spectroscopy (FT-IR) and thin layer chromatography (TLC) are used to investigate the drug compatibility with reaction adjuncts. Differential scanning calorimetry (DSC) and Powder X-ray diffraction (XRD) are used for the assessment of any polymerization effect on drug crystallinity [11,34].

4. Microsponges: Preparation methods

The method for the preparation of micro sponges was described by Kawashima *et al.,* in 1998 [35]. Usually, microsponges preparation is done by two techniques such as quasi-emulsion solvent diffusion and liquid-liquid suspension polymerization method as shown in **Figure 1 and Figure 2**[5].

4.1.*Quasi-emulsion solvent diffusion (QESD)*

QESD is a two-step process for the preparation of microsponges[36]. The internal phase of the polymer-drug solution is prepared in organic volatile solvent such as acetone or ethanol under ultrasonication at 35°C temperature, and plasticizers like triethyl citrate (TEC) are added. The plasticizer is incorporated to promote the plastic properties of microsponges. This is followed by the addition of internal to the external phase under continuous aqueous polyvinyl alcohol (PVA) blending for 2-3 h [37]. Due to vigorous stirring, formulation of quasi-emulsion globules takes place, which allows microsponges separation from mixture by filtration. Washing of microsponges and drying is performed at 40°C for 10-12 h [37]. The key advantage of QESD formulated microsponges includes minimal exposure of the drug to external environment, with miniscule amounts of solvent residues.

4.2. *Liquid-liquid suspension polymerization*

Microsponges preparation can be done by liquid-liquid suspension polymerization method. The microsponges can be prepared by using methyl methacrylate and ethylene glycol dimethacrylate or styrene and divinylbenzene as the starting materials. The polymerization of styrene or methyl

methacrylate is done in a round bottom flask. In this method, a solution is prepared that consists of water immiscible monomers and API.

With the help of agitation this phase is allowed to suspend in an aqueous phase, ordinarily comprising additives, like dispersants and surfactants, to enhance the suspension formation. When the suspension in the desirable size is obtained, the polymerization process is initiated by enacting the monomers either due to catalysis or irradiation or elevated temperature. As if the polymerization process proceeds, the spherical structures are obtained with incorporation of thousands of microsponges grouped together like grapes, and shape of interconnecting reservoirs. After completion of the polymerization process, the solid particles obtained are recoupled from suspension. After that processing with solid particles is done until they are considerably prepared for use [38,39].

5. Microsponges: Drug release mechanistic insights

Microsponges consist of porous microspheres with an entangled channel of interconnecting voids and a non-collapsible structure. For the topical application of formulation to the target area on the skin, API must diffuse out of porous microspheres into the vehicle. Also, API release rate from the formulation can be pre-fixed to achive a customized drug release profile. In oral applications, the microsponge system has been shown to increase the rate of solubilisation of poorly water soluble drugs by entrapping such drugs in the pores of the microsponges. 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 increases the rate of solubilisation.

The release can be governed by one or more triggers like changes in the pH, pressure, temperature, solubility, etc. [7,12,40,41].

- ***Pressure*:** Active ingredients gets released from microsponges to the skin due to continuous rubbing or application of optimal pressure [10,42].
- ***Solubility*:** Microsponges containing soluble/less soluble API are released to the skin through a diffusion process and majorly relies on ingredient partition coefficient between the microspongesand external skin surface.
- ***pH***: The change in pH triggers API release from the microsponge formulation. This can be done by adjustment to microsponges covering.

- ***Temperature change*:** Alteration in temperature regulates drug release from the microsponges. At certain room temperature, some API continuously diffused from microsponges into the skin. This can be troublesome and to counterfeit this issue, modification in the skin temperature helps in controlling the drug diffusion rate and the overall drug release profile. In topical semisolid formulations, the drug release can be investigated with the help of Franzstatic diffusion cells [42].

6. Therapeutic Application of Microsponges

6.1.Topical applications

Microsponges are used for topical delivery for cosmetic and dermatological applications varies only in their technological parameters (as shown in **Table 1**). This might be due to the market demand, industrial scalability, regulatory constraints, and short introduction time for dermatological products. Because of high absorbent nature of porous microsponges, various microsponge loaded antiperspirants, deodorants as well as sunscreens are currently available in the market. Localized and site-specific action of MDS prevents unnecessary retention of the drug into the percutaneous blood circulation and found to be effective for topical disorders such as like acne, psoriasis, skin cancer, wounds, wrinkles, hyperhidrosis, sunburn, and alopecia, etc. [41]. Bhatia and Saini formulated curcumin microsponges by QESD technique using polyvinyl alcohol (PVA) and ethyl cellulose as carriers. *Ex vivo* drug deposition studies of microsponges loaded in carbopol gel demonstrates 77.5% curcumin permeation within 24 h. Thus, curcumin loaded microsponges can be a promising alternative for topical delivery systems with advantages like curcumin delivery in a continued way to decrease the recurrence of administration and enhances its bioavailability [43]. Acetazolamide is a carbonic anhydrase inhibitor useful for the treatment of glaucoma from a long time. Higher oral doses of acetazolamide are used to bring down the intraocular pressure. This usually has several side effects and decreased patient compliance results in discontinuation of the therapy. To overcome this problem of oral acetazolamide, Obiedallah *et al* prepared acetazolamide microsponges. *In situ* gel was formulated with an aim for ocular drug delivery and enhanced therapeutics efficacy and lowers the systemic side-effects. The prepared in-situ gel was further assessed for physical and chemical properties (like pH, rheological properties, and gelling time) along with *in-vivo* investigations. The formulation with polymer-drug ratio 1:2 demonstrated shigher entrapment efficiency of

~82%, average particle size of 10 µm, that are appropriate characteristics for ocular delivery. Furthermore, it is non-irritant to rabbits' eye and improved therapeutic efficacy in contrast with the free drug in gel. Thus, acetazolamide-loaded microsponges in situ gel formulations can be a superior option in contrast to oral acetazolamide for glaucoma treatment [44]. Some prominent examples of microsponges based cosmetic products commercially available are enlisted in **Table 2.**

6.2. *Microsponges for anti-acne drugs*

Chronic inflammatory disorders like acne, are related to pilosebaceous unit (PSU) and described by different variations in immunological host responses, sebum productions, bacterial proliferation, follicular epithelial desquamation, inflammation [45]. Acne occurs for the most part on the face, chest and back [46]. Acne normally starts during pubescence and is outlined by puberty. It usually happens in females and males, which are aged between 14-17 and 16-19 years, respectively. Acne pathogenesis is controlled by hypersecretion of sebum in distorted follicles, that results in follicular hyperproliferation and microcomedones that ultimately leads to inflammation, and comes out with pustules, papules, cysts, and nodules. The main causative agent of acne is *Propionibacterium acne (P. acne)* [47]. For moderate and mild acne topical treatment is the best option while for moderate and severe acne systemic treatment is beneficial. Acne treatment usually normalizes the keratinization process, reduces the interfollicular *P. acne*, and significant reduction of inflammation and sebaceous gland activity. Localized topical acne treatment comprises of moieties, primarily or first line keratolytic agents (retinoids and its derivatives, benzoyl peroxide, azelaic acid, salicylic acid) along with antibiotics (erythromycin and its zinc complexes, clindamycin). These are ordinarily utilized topical agents. However, these agents are associated with side-effects such as skin dryness, irritation and peeling or bacterial resistance. Such issues limit compliance of patient and compromised therapy. To defeat such issues and to minimize the dose of anti-acne agents, demands the proposal for novel drug delivery systems [45]. Roughly novel carriers with potential, vesicular and particulate drug delivery systems such as microemulsions, liposomes, microspheres, solid lipid nanoparticles, nano-lipid carriers' investigation has been underway for improved anti-acne topical therapy [45]. Benzoyl peroxide (BPO), which is utilized as a topical first line anti-acne agent, has prominent bactericidal activity towards *P. acne*[48]. BPO moiety is superior to all antibiotics due to failure

of bacterial protection from it. In any case, significant disadvantage related to BPO treatment includes skin irritation effect. Jelvehgari*et al.,* formulated microsponges for facilitation of BPO delivery. QESD method was selected for ethyl-cellulose-based microsponges preparation. BPO-loaded microsponges were loaded into creams and investigated for drug release. The morphology of the microsponges was studied using SEM. The micrograph depicted porous spherical microspheres. Dispersed phase volume, polymer-drug ratio, stirring rate affects the microsponges particles size and drug release pattern. These studies predicted an enhancement in the drug-to-polymer ratio and reduce BPO release from microsponges. This may be ascribed to decrement in porosity. The controlled release of BPO to skin can change the dose relationship between skin irritation and efficacy [49]. Another drug of choice is erythromycin for acne treatment because of its bacteriostatic action against *P. acnes* [50]. In any case, the drug induces nausea, vomiting, gastric irritation, pain in the abdomen and is easily metabolized at gastric pH. Ravi and coworkers formulated erythromycin loaded microsponges loaded gel which exhibited lesser skin bothering, slow drug release, and high skin tolerance. Osmani *et al.,* prepared microsponges-loaded miconazole nitrate topical cream as an empowering localized formulation for acne and topical infections[9,51].

6.3.Microsponges for anti-psoriasis drugs

Psoriasis is another chronic inflammatory skin disorder that affects roughly 2% of the total population. It is interceded by the cells and molecules of innate and adaptive immune systems. Psoriasis includes chronic plaque psoriasis, pustular psoriasis, nail psoriasis, guttate psoriasis, erythrodermic psoriasis [52,53]. It is described by extraordinarily expanded proliferation along with incomplete epidermal differentiation, and significant increment in cutaneous blood flow, and leukocytic penetration into epidermis and papillary dermis [54]. The majority of patients initially prescribedwith topical therapy (Dithranol and tar, Vitamin D_3 analogues, topical corticosteroids, Retinoids, calcineurin inhibitors, etc.) followed by phototherapy and systemic treatment with biological agents such as cyclosporine, infliximab, ixekizumab, secukinumab, guselkumab, etc. Limitations with topical agents include skin staining, calcium metabolism, teratogenicity etc. and biologicals (high relapse rate) with confined application[55]. Clobetasol propionate (CP) belongs to class of super potent dihalogenated topical corticosteroid used against psoriasis due to its vasoconstrictive, anti-inflammatory, antiproliferative activities. It has regular

side-effects such as steroid acne, skin atrophy, allergic contact dermatitis, hypopigmentation and systemic penetration on topical usage. The use of novel topical carrier and delivery systems address the side effects related to CP and give a prolonged term of action via controlled drug release. *Neelam et al*. utilized microsponges to facilitate the delivery of CP. They used quasi-emulsion solvent diffusion method to develop CP loaded micro sponges. Further, CP loaded microsponges were formulatedintocarbopol gel base. Polymer to drug ratio, aqueous and organic phase volume, stirring rate, surfactants were likewise considered. Enhancement of drug to polymer ratio results inenhanced entrapment efficiency of microsponges. Microsponges as a delivery system brought about extended release of CP and improved therapeutic action, with least toxic effects [56]. Microsponges for psoriasis are summarized in **Table 2.**

6.4. Microsponges for atopic dermatitis

Atopic dermatitis (AD) is a typical chronic skin disease portrayed by relapsed eczema with pruritis as an essential sore [57,58]. It happens in around 17-24% paediatric population and in 4-7% of adults [59]. It is a multifocal skin disease with numerous etiologies. The treatment level of AD is based on its severity. Present treatments of AD is focused on the reclamation of skin's barrier function, principally through moisturizers and therapeutics include corticosteroids for inflammation, immunosuppressive drugs, topical calcineurin inhibitors in chronic cases. Newer biological agents like interleukin (IL)-4/IL-13 antibodies, micro and nanotechnologies are also available [60]. An antihistaminic drug hydroxyzine hydrochloride is also used for the treatment of atopic dermatitis and urticaria. Oral administration of this drug causes most common side effects like dizziness, blurred vision and anticholinergic responses. Microsponges were utilized as nanocarrier, for topical hydroxyzine hydrochloride administration with an aim to lower side effects and targeting to a specific action. Zaki and coworkers tailored the release of hydroxyzine hydrochloride from the formulation could bring downside effects as well as absorption via percutaneous route. Eudragit RS100-based drug-loaded microsponges were prepared by a diffusion method utilizing oil as solvent, acetone as dispersing solvent and liquid paraffin as the continuous phase. Magnesium stearate was added to the dispersed phase for inhibition of flocculation while pore inducers like sucrose along with PGS was utilized to improve the drug release rate. Microsponges with about 60-70% porosity and 98% encapsulation efficiency were obtained. *In-vitro* study was done on histamine-sensitized rabbits to investigate the

pharmacodynamic effect of prepared microsponges [61]. Fluocinolone acetonide (FA) is an engineered hydrocortisone subsidiary, that is fundamentally used in dermatology to decrease skin inflammation [62]. Fluocinolone acetonide entrapped microporous particles were prepared by D'souza and Harinath[63]. This approach limits the percutaneous absorption by tailored release of drug from the formulation. Mometasone is a synthetic 16-α-methyl derivative of beclomethasone and topical glucocorticoid useful in the management of scalp psoriasis, atopic dermatitis, seborrheic dermatitis, etc.[64,65]. It lowers the side effects and sufficient percutaneous absorption is achieved after topical application. Rekha and coworkers developed mometasone furoate-loaded microsponges by using QESD method[66]. The factors that affect the physical parameters of formulation were determined in order to optimize the formulation. FTIR spectroscopy was done to study the excipient and drug compatibility. Microsponges morphology, loading efficiency and production efficiency were also studied. It was seen that particle size and drug release pattern of microsponges were influenced by the polymer:drug ratio, stirring rate, volume of internal and external phase. Paeonol, is bioactive phenol obtained from plants like *Paeonia lactiflora, Paeonia suffruticosa, Arisaema erubescens* and *Dioscorea japonica*[67]. Paeonol ointment is used for treatment of dermatitis [68]. However, it is unable to permeate the stratum corneum because of its poor aqueous solubility and limited partition coefficient. QESD method was employed for the preparation of microsponges-loaded Paeonol. *Ex vivo* and *in vivo* drug permeationand release studies demonstrated enhanced permeation rate and enhanced drug residence in skin, respectively. A decrease in the fraction of drug administered to the systemic circulation renders an additional advantage of decreasing the adverse effects linked with the drug[14].

6.5. Microsponges for skin cancer

Skin cancer is the most widely recognized, especially in Caucasian populations (White-skinned), affecting almost one million Americans per year [69–71]. Skin cancer is a broad term used to define any malignant lesion of the skin. Skin cancers can be broadly classified into two types depending upon its nature: melanoma and non-melanoma skin cancer (NmicrospongesC). NmicrospongesC can be partitioned into cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [70–72]. The aetiology of cancers is due to environmental exposures and specifically to solar UVB (ultraviolet-B) [71]. When the UV radiation falls on the skin produces

explicit keratinocytes mutations resulting to NmicrospongesC. BCC for the most part happens on face as well as the back of hands, while SCC occur on both the neck and head. Cutaneous malignant melanoma (CM) is the deadliest form of skin cancer and mostly occurs on the lower legs of women and on the men trunk. Major treatment strategies for skin cancer are radiotherapy and surgery; whereas topical chemotherapy along with fluorouracil (FU), retinoids, diclofenac sodium, imiquimod, oral therapy with retinoids, photodynamic therapy, cisplatin, laser surgeries. A genuine worldwide health trouble is actinic keratosis (AK), thatmay advance to SCC [73]. 5-Fluorouracil is FDA affirmed for the topical treatment of AK, Bowen's disease and superficial BCC. 5-FU is a pyrimidine analogue, an anti-neoplastic antimetabolite blocks the enzyme liable for the synthesis of thymidine (DNA), alters the DNA replication and subsequent induction of apoptosis [69,72]. 5-FU topical cream (5%) is one of the first-line treatment choices.However, its local tolerance and skin permeation are poor and cause inflammation, itching and irritation [74]. FU contained hydrophilic petrolatum or simple base of propylene gel for topical application. The *in-vitro* drug release has been examined on porcine skin and human skin. *Levy et al.* used human cadaver skin to compare the *in-vitro* skin permeation of three microsponges formulations-loaded with 0.5% FU in Efudex cream[75]. The applied dose is about 10 mg/cm^2, along with mass balance studies were performed. Every one of the three microsponges formulations released more noteworthy amounts of FU in skin (86-92%) in contrast with commercial formulations (54% drug release) [72]. From the study, that include trials on 356 patients affected with actinic keratosis (actinic keratosis may progress to SCC), the 5-FU microsponge based formulation is more efficacious in comparison to respective vehicle when applied for one week. The therapy was successful in all patients during the entire treatment duration [73]. The optimized microsponge formulation has better aesthetic properties, improved stability and ease to prepare with cheaper ingredients and can be substitute for conventional counterpart for skin cancer treatment [74].

6.6. Microsponges for cosmetics

Cosmetics intended for use can be defined as "articles intended to be poured, rubbed, sprayed sprinkled on, introduced into, or otherwise applied to the human body for altering the appearance, beautifying, cleansing, and promoting attractiveness" [76]. Cosmetics in the present time should be free of perfumes, mineral, oils and lanoline; so that they will be safe, last long,

cheapr and act as moisturizers [77,78]. Microsponge system is excellent for skin, cosmetics and care products. They are capable of retaining several times their weights in liquids, react to different triggers and absorb the excessive skin oil. This provides an exquisite feeling on the surface of the skin. Various cosmetic and toiletry companies are currently using this technology to prepare several cosmetic and OTC products. These microsponge-based products have superiority over conventional formulations in terms of enhanced chemical and physical stability, tailored release of API, higher release rates, less skin irritation and unique palpable characteristics [79]. The microsponges delivery system allows the preparation of formulations containing at least two ensnarement's that have commonly contrary API like retinol and hydroquinone. Also, aqueous gels containlipophilic material and prepared without using of any emulsifier. This is possible because the entrapped materials are inside the permeable microsponge particles, and these are handily wetted and suspended in the aqueous phase. On the contrary, highly lipophilic products can be prepared using entrapped hydrophilic materials, again without the use of emulsifiers or surfactants because the microsponge particles are handily wetted and suspended in the lipid stage because of the amphiphilic nature of the polymer used in microsponges fabrication [80].

6.6.1.Cosmeceuticals

Cosmeceuticals are one of the rapidly growing fields in the skin care business. Some of the examples of cosmeceutical substances are like retinol, alpha-hydroxy acids (AHAs), vitamin-K, etc. These ingredients provide several benefits but are accompanied with some side effects like peeling, drying, erythema, etc. Thus, cosmeceutical ingredients entrapped in microsponge polymers can be a better alternative. Retinol, an exceptionally unadulterated type of vitamin A has a great capacity to manage aging and youthful skin appearance [81]. It is highly reactive and gets unstable when blended with different ingredients. A microsponge-based retinol formulation, is cosmetically elegant, stabilized and low skin irritation has been successfully produced and commercially available [79]. Retinol was entrapped in an aesthetically pleasing moisturizing base. These products have shelf-life of 2-3 years and can hold 90% of their initial concentration. Retinol entrapped formulations mixed with other cosmeceutical agents like vitamin K (phytonadione) that is likewise in the captured structure and lessens the presence of dark circles

under the eyes. These entrapped active ingredients make the formulations milder and, thus, appropriate for routine application [80].

6.6.2.Starch microsponges-based topical sunscreen product

Topical sunscreen products are utilized as UV channels engrossing UVA as well as UVB radiations, that shields from destructive solar radiations. Yet, majority of the sunscreen show allergic effects as well as safety issues because of diffusion from the skin into the systemic circulation. Oxybenzone/Benzophenone-3 (BNZ) is USFDA endorsed sunscreen, but topical retention is a major challenge because of its higher penetrability. Various investigations have shown that repeated usage of BNZ containing products, leads to accumulations of higher percentages of BNZ in breast milk and urine. This ultimately leads to melanoma, contact eczema, breast cancer. So, Bhuptani *et al.* prepared starch microsponges-based sunscreen formulation encapsulated in benzophenone-3 organic sunscreen and characterized by SEM, DSC, nitrogen adsorption/desorption analysis and powder X-ray diffraction. The outcome indicates that starch microsponges had a high surface area for BET (85.45 m^2/g) and porous spherical morphology in the size < 200 nm. The optimized formulation was prepared, characterized and clinically tested. Starch microsponges-based sunscreen product possessed good spreading properties, non-sticky, rich texture, and good patient compliance[82]. *In vitro* and *Ex-vivo* studies showed that starch microsponges offer higher SPF, enhanced photoprotection, and lowered the cutaneous penetration contrasted with commercial cream (as shown in **Figure 3**). After preclinical studies, clinical studies confirmed that the prepared starch micro-sponge loaded sunscreen cream was safe to skin and biocompatible (as shown in **Figure 4**).

6.7. Microsponges for Peroral Drug Delivery

Microsponges have capacity to expand the drug release rate for poorly water-soluble drugs and entrapment of such drugs in their porous microstructure. This enhances the pharmacological effect and bioavailability and decline in the side effects [24,83]. Hence, microsponges-based drug delivery system is appropriate for drug delivery via peroral route. Preliminary studies done by A. P. Pharma, Inc., Redwood City, CA, USA, revealed that microsponges increase oral bioavailability of drugs. It enhances the drug dissolution rate and absorption of drugs. A microsponge system helps in shielding the drug from gastric condition and control the conveyance of drugs to the lower GIT. Microsponges can be formulated into capsules or enteric

tablets as colon-targeting of drugs [24]. The rationale for selecting microsponges as colon-targeted drug delivery because of their particle size is less than 200µm. It becomes easily available for the macrophage's presence in colon tissue, thus shows a viable confined drug activity at the target site. The compression of 1000-2000 KgF/cm^2 should be maintained to shape the tablets and prevent the structural deformity of microsponges. The plasticity of Eudragit RS100 takes into consideration the simpler pressure to create a tablet, while plasticity of low plastic polymer can be increased by incorporating a plasticizer like triethyl citrate. Entrapping the core with polymer, solubilizes in acid and externally with enteric polymer helps the formulation remain intact in stomach and begin to dissolve in the small intestine (pH > 6). Consecutively, the dissolution of acid soluble covering relies on the availability of colon bacteria and break up the polysaccharide covering by lowering of pH. *In vitro* release study was performed using distinctive dissolution media sequentially to simulate GIT conditions and confirmation about enteric coating enteric coating effectiveness against external pH values. For this, artificial intestinal fluid pH 1.2 was used for 2 h, trailed by artificial gastric fluid pH 7.4 for 6 h and simulates the colon fluid with pectinase as long as 16 h. Srivastava and co-workers proposed that tablet, makes drug release to the colon area with transition at 5 h. Jain and coworkers also reported a delay of 6 h until the beginning of release [33]. Orlu *et al.* fabricated flurbiprofen for colon targeting using pectin-coated tablets with microsponges as core. Their study explained that highly porous spherical microsponges can be obtained by decreasing polymer-drug ratio. They also fabricated tablet for colon-specific targeting with the help of pore plugged method using the same polymeric mixture. Tablet obtained by this method showed zero-order release kinetics. Likewise, Gupta and co-workers explained 5-FU-loaded immediate release in 3 h and commercial product in 4 h. On the other hand, microsponges loaded with HPMC (Hydroxypropyl Methylcellulose) capsule released 97.07% drug in 8 h, indicatesreformulation with a requirement for enteric coating[84]. Enteric polymers like Eudragit L100 and Eudragit S100 in various proportions were considered for coating the capsules. Polymers are appropriate for enteric coating and controlled release in the colon[85]. Jain and Singh fabricated dicyclomine-loaded microsponges for colonic relase with the QESD method [33]. They observed the particle size of microsponges increases with enhancement in the amount of emulsifier and increase in drug-polymer ratio brought about smaller particles and decreased production yield but elevated amount of drug. The release pattern of the drug from microsponges

best match with Higuchi model. The drug release from floating microsponges (has density lower than gastric fluid) is affected by different pH. Arya *et al.* interpreted curcumin release of 88.4-90.8% toward the finish of 8 h for floating microsponges made of Eudragit RS100 and ethyl cellulose. The loratadine exhibited release of 66.75% and cinnarizine of 57.9% after 8 h from ethyl cellulose microsponges while 97.5% famotidine was released after 12 hours from Eudragit RS100. Higuchi model was found to show better model fitting to describe the drug release from the floating microsponges, which were composed of eudragit, ethyl cellulose, ethyl alcohol and dichloromethane. All the drugs cinnarizine, famotidine, curcumin, and loratadine displayed low water dissolvability. Raghuvanshi and Pathak studied the effect of change in pH on the drug (cinnarizine) release profile. They described that at low pH, the drug exhibited high rate of release [34]. Similarly, Bhatia and Saini also formulated curcumin microsponges by QESD technique using ethyl cellulose and polyvinyl alcohol (PVA) as carriers. They filled the optimized microsponges-loaded in the hard gelatin capsule shell (HGCS) and afterward stacked in carbomer gel to study its ability in peroral and topical delivery system, respectively [43]. Their study results showed that curcumin release was 93.2% by microsponges filled in HGCS and observed only 11.7% curcumin was released from conventional capsule. Also, microsponges based carbomer gel showed 77.5% curcumin release within 24 h. Thus, curcumin microsponges can be a promising alternative for conventional formulation in topical and peroral delivery systems with advantages like controlled and prolonged release of drug. Sulpiride (SUL) is an antidopaminergic drug utilized in the treatment of mental disorders. However, this drug encounters with GIT problems and compromised antiemetic efficacy. Its conventional oral formulation showed an unpredictable and low absorption of the drug with an oral bioavailability of 30%. Younis *et al.* prepared a floating microsponges based gastro-retentive oral formulation of SUL through a QESD method and evaluated their physicochemical aspects. They used Taguchi experimental design and contour plots to streamline some autonomous factors influencing microsponges performance. The encapsulation efficiency, yield, *in vitro* drug release for floatation of optimized SUL microsponges were found to be 79.82 ± 2.37%, 89.11 ± 2.28% and 65% after 8.0 h, respectively. The pharmacokinetics of optimized formulation were performed in rabbits and contrasted with commercial SUL product, Dogmatil® capsules. The optimized SUL microsponges demonstrated a relatively higher C_{max} ($p<0.05$), AUC and 2-fold increment via peroral administration in comparison to commercial formulations. Additionally,

the optimized formulation remained available in the stomach for 8 h after administration when imaging was performed through X-ray radiographs in rabbits. Consequently, it may be inferred that floating microsponges can be a better alternative to upgrade the oral bioavailability and pharmacokinetics of Sulpiride[86]. Chlorpheniramine, chemically known as [3-(p-chlorophenyl)-3-(2-pyridyl)-N,N-dimethylpropylamine] is apotent antihistaminic used to mitigate the manifestations of common cold along with allergic responses [87]. Researchers have also investigated coated microsponges as possibility for continued chlorpheniramine maleate release. Drug-loaded cellulose microsponges were entrapped in Eudragit RS100 to produce powder-coated microsponges. They observed that these systems showed lower C_{max} and longer T_{max} in comparison to powder chlorpheniramine maleate, followed by peroral route in dogs. Ibuprofen is a nonselective, nonsteroidal anti-inflammatory drug (NSAID) with good antipyretic activity and effective in management of acute pain associated with acute injuries and migraine headache with moderate and severe intensity [88]. In 2006, Devrim and co-workers fabricated ibuprofen microsponges and investigated the effects of polymers such as Eudragit RS100, Eudragit RL100 and Eudragit RS PM on rheological properties, particle size and drug release profile. They expressed that each and every microsponges had good flow properties, which is essential for controlling dose and uniformity in weight during capsule filling or tablet compression[89]. They additionally found that Eudragit RS 100 was superior to other grades of Eudragit since little particles with improved drug release profile were got with Eudragit RS 100 [56].Ketoprofen is a NSAID regularly used for treatment of joint inflammation. The ketoprofen microsponges (ketoprofen and Eudragit RS100) for oral administration were prepared through a QESD method by Baykara and collaborators and investigated the role of process variables such as polymer-drug ratio, stirring speed, polymer-solvent ratio, etc. that affects drug release profile and physical characteristics[90]. Their study results showed that the enhancement in the drug–to-polymer ratio results in decreased microsponges particle size. These researchers additionally inspected the impact of compression pressure for tabletting of ketoprofen microsponges by employing a difference in pressure values to mass and report optimal pressure value for tablet compression. The microsponges demonstrated improved compressibility compared to physical mixture of the drug and polymer due to the plastic distortion of sponge-like structure and created precisely solid tablets. They also proved the superiority of ketoprofen microsponges tablets in terms of improved bioavailability to convention ketoprofen tablets. Ketoprofen microsponges

demonstrated effective drug release and absorption that indicates about the tabletting of microsponges. It increases the lag time for drug appearance in plasma and continues the concentration of drug for a longer time period [91].Nitrendipine belongs to a class of anti-hypertensive drugs and is poorly water soluble with low oral bioavailability because of elevated first-pass effect. Controlled systems can be beneficial in enhancing the bioavailability of this drug [92]. Cui *et al*., prepared nitrendipine microsponges by alteration in the QESD method that act like a solid dispersion. The solid dispersion carrier consists of hydroxypropyl methyl cellulose (HPMC), whereas ethyl cellulose and Eudragit RS 100 was used as impeding agent along with anhydrous silicic acid as dispersing agents [93]. Their study suggested that the release rate increases with the increase in the carrier content and dispersing agent. The oral application of nitrendipine microsponges in male dogs showed three times increment in relative bioavailability over ordinary nitrendipine tablets. Kadam *et al.* developed microsponges-based aceclofenac and discovered that such a system lowers crystallization ability of drug particles along with compacted tablets can be useful for chronic diseases.

7. Recent Advancement in MDDS

MDDS already has a wide range of applications in topical and cosmetic products as well as fewer in oral formulations. But as the time changes, the optimal goal is to bring newer advancement in existing technologies. As a result different advances were made by adjustment of the techniques to shape nanoferrosponges, nanosponges, porous microbeads. As to present scenario nanotechnology rules all scientific regions are porous systems in nanosized and being drawn closer to further progression to correlated micronized. Nanosponges (NS) are further hyper-cross-linked to cyclodextrins (CD) and can be acquired from α-CD, β-CD and γ-CD, either singly or as a blend containing suitable amounts of dextrin, which is structurally linear and cross-linked with a relevant cross-linking agent [94]. The NS exists in solid form and formulated in the form of topical, parenteral, oral, and inhalation dosage [95]. NS offer focusing of dermal delivery to prompting retention on skin and complete reduction in dose and prevent systemic absorption. A limited number of researchers attempted for investigation of nanoporous carriers that entrap dermally suitable elements. Sharma and coworkers developed ethyl cellulose NS as a substitute for econazole nitrate targeting to the skin by incorporating into the hydrogel formulation. Swaminanthan and co-workers developed CD-NS for enhancing itraconazole

solubility. β-cyclodextrin nanosponges were developed for delivery of hydrophilic drugs, in comparison to polymeric microsponges or NS. These NS were developed by cross-linking β-CD moieties by reacting β-CD to diphenyl carbonate. These improved nanosponges were investigated for oral application of DOX hydrochloride, dexamethasone, itraconazole, flurbiprofen, serum albumin, resveratrol, 5-fluorouracil and tamoxifen as exemplary drugs [94,96]. Some researchers incorporated cytotoxic agent in a NS carrier system for enhancing the efficacy of the drugs to target malignant cells [97]. Ferrosponges, i.e., magnetic sponge-like hydrogels were produced by the utilization of an *in-situ* magnetic nanoparticles (MNPs) synthesis by the use of different concentrations of gelatins [98]. Nanoferrosponge an innovative approach consists of self-working carriers with improved entry to the target site because of the external trigger from magnet and upholds carriers to infiltrate deeper tissue along with afterward expels of magnetic material and leaves porous system. Nanoferrosponges preparation can be done by polymer co-precipitation with magnetite. Ferrosponges exhibit elasticity, swelling ratios in the higher range, hydrophilicity and swift response to an external magnetic trigger for rapid and repeatable swelling-deswelling activities [98]. These have application in a significant number of therapeutic biomolecules and drugs such as NSAIDs, cardiovascular drugs and anticancer agents [99]. Due to the enhanced properties of permeable microspheres, technique was developed to deliver permeable microbeads. These are particles with solid spheres with a diameter range from 5μm-1mm. These are basically synthesized from polypropylene (PP), polyethylene (PE), polyethylene terephthalate (PET), nylon plastics or polymethylmethacrylate (PMMA). They are popularly used in personal care products and cosmetics as exfoliants, in injectable biomaterials as diagnosis in drug delivery as vehicles and in diagnostic devices as diagnostic agents [100].

Passive targeting and active targeting are two major strategies in tumor-targeted drug delivery, which are limited by low permeable vasculature and complex physiological barriers, respectively. For transport cells like stem cells, monocytes/macrophages, and neutrophils, which possess tumor homing capability following cytokine/chemokine gradients, cell-mediated drug delivery can be the most viable strategy to intelligently deliver the drug to the tumor site. Moreover, compared to functionalized exogenous cells as delivery systems, targeting transport cells in peripheral blood can avoid the time-consuming isolation and culture, and further reduce the regulatory hurdles. The most crucial step in achieving this goal is to develop a non-toxic

carrier to be recognized and taken up by transport cells in peripheral blood and achieve triggered drug release when arriving at the tumor sites. Peptide-based nanosponges are one of the most promising particles for cell-mediated delivery because of their desirable biocompatibility, bioimitability, and high drug loading capacity.

8. Stability and Safety Considerations

8.1.Stability Aspects

Pharmaceutically, stability can be stated as the capacity of formulation in particular closure system or container to restrict any change in its physical, chemical, therapeutic, microbiological and toxicological specifications [101]. Microsponges can remain stable over a wide biological pH and, in this way can be utilized as multipurpose carrier systems. They are thermally stable up to 130° C. Microsponges-based formulations have self-disinfecting properties which limits bacterial dispersion because of their minute pore size (0.25µm). Microbial passage to the mass is restricted yet they can develop on micro-sponges surface. International Council on Harmonization (ICH) guidelines should be followed for performing stability testing of the microsponges-loaded formulations. Osmani and coworkers developed diclofenac diethylamine-loaded microsponges and stability evaluation of the gel formulation revealed no change in appearance, pH, and *in vitro* drug release behavior. During the stability study, no alteration in physical appearance and pH was found. The results suggested no critical alteration in the percentage of drug release and drug content of the formulation. Moreover, a similarity index of greater than 50 was observed which indicates good stability during 3 months of stability. In addition, researchers conducted FT-IR of curcumin-loaded microsponges, notwithstanding above examined parameters. FTIR spectrum reported no indication of drug instability, recommending the great time span of usability of microsponge delivery system[40,102–106].

8.2. *Safety* considerations

In other words, the release pattern of the active agent from the MDS was thought to be such a way that it does not actuate any irritation, genotoxicity, immunogenicity or cytotoxicity[106,107].

8.2.1.*Cytotoxicity studies*

Evaluation of the cytotoxicity of microsponge-based drugs is an essential aspect in the improvement of formulation. API and its ingredients may shows cytotoxic impact on the microsponges delivery system. The IC_{50} and % cell viability values ought to be determined for the drug singly, where drug-loaded microsponges and blank microsponges were evaluated for their cytotoxic activity. Such a similar assessment will portray clarity on cytotoxic effects of readied formulations. Of late, Kumar and coworkers prepared silver sulfadiazine-loaded microsponges gel and evaluated through Draize cytotoxicity test [14]. Silver sulfadiazine is utilized as topical antibacterial agent for burn wounds. *In vitro* cellular toxicity of upgraded gel assessment was done using MTT assay in murine NIH-3T3 Cell line (embryonic fibroblast) and HaCaT Cell line (epidermal keratinocyte) cultures. As per MTT assay, the upgraded gel demonstrated immaterial cytotoxicity, whereas cell feasibility somewhat diminished with increased silver sulfadiazine concentration. The results predicted that silver sulfadiazine did not block cell expansion at 1000×10^{-3} mg/ml or even at higher concentrations on both cell lines. Therefore, the upgraded gel demonstrated minimum toxicity on both cell lines which indicated that the prepared formulation had a very less cytotoxicity on dermal cells [102]. Arya and Pathak verified the gastro-retentive capability of microsponges through enhancement of targeted floating curcumin microsponges. The C_{max} of plain curcumin and curcumin from microsponges was found to be 0.233 µg/mL and 2.934 µg/mL respectively. An approximately 10-times increase in C_{max} value showed enhanced absorption of curcumin, likely because of novel dosage form. A significant increment (4-times) in T_{max} was seen in microsponges in comparison with curcumin suggests moderate absorption of curcumin from microsponges and stretched blood circulation [103–105].

9. Conclusions and future perspectives

The number of marketed oral formulations with major limitations such as immediate/burst release and suboptimal drug absorption or rapid clearance from the body. In the novel drug delivery systems, the emergence of micro sponges can uniquely solve problems associated with the conventional oral and topical formulations. Microsponges can capture many hydrophilic and hydrophobic drugs to provide tailored drug release profile in biological medium over the longer period of time. Further, they can absorb the drug 3-fold larger than their own weight. These particular characteristics made them superior over other carrier systems. In addition, this

particular drug delivery not only limited to topicals and oral systems, but also applied to parenteral delivery, colon targeting and pulmonary drug delivery. Furthermore, the microponges can remain stable at a wider range of pH and temperature up to 130°C. Moreover, their safety parameters also makes them effective for human drug delivery applications.

Microsponges with highly porous cross-linked nanostructured architecture are highly effective to accommodate a variety of drugs with well monitored control drug release characteristics over the extended period of time. On the basis of toxicity studies, various FDA approved polymers such as Eudragit RS100, polymethacrylates polymers, polylactide-co-glycolic acid (PLGA) are used in the development of microsponges. Further, their surface modifications and well transformed behavior into gel structure provides ease of application in the form of creams, gels and lotions. Furthermore, microsponges are used to treat the various disorders like as acne, psoriasis, dandruff, eczema, hair loss and other various dreadful disorders, including cancers. In addition, innovations in technologies led to develop more advanced nano-forms of sponges like as nanoferrosponges, nano-sponges, and porous microbeads which have been documented for variety of drug delivery applications. Further, stability and safety studies on microsponges have confirmed that no significant alteration was observed in the stability without any toxicity.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options,expert testimony, grants or patents received or pending, or royalties.

Consent for Publication

Not applicable.

Funding

None.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgements

The authors extend their appreciation to the Deputyship for Research & lnnovation, Ministry of education in Saudi Arabia for funding this research work through the project number 20-UQU-IF-P1-001.

References

1. Weiss SC. Conventional topical delivery systems. Dermatol Ther. 2011 Sep;24(5):471-6
2. Ingale DJ, Aloorkar NH, KulkarnI AS, Patil RAP. Microsponges as Innovative Drug Delivery Systems. Int J Pharm Sci Nanotechnol. 2012 Apr;5(1):1597-606
3. Pradhan SK. Microsponges as the Versatile Tool for Drug Delivery System. Int J Res Pharm Chem. 2011;1(2):243-58
4. Kaity S, Maiti S, Ghosh AK, Pal D, Ghosh A, Banerjee S. Microsponges: A novel strategy for drug delivery system. Journal of Advanced Pharmaceutical Technology and Research. 2010 Jul;1(3):283.
5. Srivastava R, Pathak K. Microsponges: A futuristic approach for oral drug delivery. Expert Opinion on Drug Delivery. 2012 Jul 1;9(7):863-78.
6. Jadhav N, Patel V, Mungekar S, Bhamare G, Karpe M, Kadams V. Microsponge Delivery System: An updated review, current status and future prospects. J Sci Innov Res. 2013 Sep 21;2(6):1097-110.
7. Ahire P V., Darekar AB, Saudagar RB. Review on Microsponges As a Novel Drug Delivery System. Int J Curr Pharm Rev Res. 2017;8(3):293-7.
8. Kumari P, Mishra SK. A comprehensive review on novel microsponges drug delivery approach. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(1):25-30.
9. Osmani RA, Aloorkar NH, Kulkarni AS, Harkare BR, Bhosale RR. A NEW CORNUCOPIA IN TOPICAL DRUG DELIVERY: MICROSPONGE TECHNOLOGY. Asian J Pharm Sci Technol. 2014;4:48-60.
10. Bharathi M, Mullaikodi O, Rajalingam D, Gnanasekar N, Kesavan M. A Review on

Microsponge Drug Delivery System. Int J Rev Life Sci . 2020 Sep 19;10(2):53–9. Available from: https://scienztech.org/ijrls/article/view/1280

11. Patil R shivaji, Kemkar V uddhav, Patil SS. Microsponge drug delivery system: A novel dosage form. Am J PharmTech Res. 2012 Jul;2(July):227-51.

12. VISHWAKARMA P, Choudhary R. Microsponges: A Novel Strategy to Control the Delivery Rate of Active Agents with Reduced Skin Irritancy. J Drug Deliv Ther. 2019 Dec 15;9(6-s):238-47.

13. Aldawsari H. Microsponges as promising vehicle for drug delivery and targeting: Preparation, characterization and applications. African J Pharm Pharmacol. 2013 May 8;7(17):873-81.

14. Mahant S, Kumar S, Nanda S, Rao R. Microsponges for dermatological applications: Perspectives and challenges. Asian Journal of Pharmaceutical Sciences. 2020 May 1;15(3):273-91.

15. Joshi M. Role of Eudragit in targeted drug delivery. Int J Curr Pharm Res. 2013 Mar 9;5(2):58-62.

16. Singh S, Neelam, Arora S, Singla Y. An overview of multifaceted significance of eudragit polymers in drug delivery systems. Asian Journal of Pharmaceutical and Clinical Research. 2015 Sep 1:1-6.

17. Obeidat WM, Abu Znait AH, Sallam ASA. Novel combination of anionic and cationic polymethacrylate polymers for sustained release tablet preparation. Drug Dev Ind Pharm. 2008 Jan 1;34(6):650-60.

18. Rekhi GS, Jambhekar SS. Ethylcellulose - A Polymer Review. Drug Dev Ind Pharm . 1995 Jan 20;21(1):61–77. Available from: http://www.tandfonline.com/doi/full/10.3109/03639049509048096

19. Ahmadi P, Jahanban-Esfahlan A, Ahmadi A, Tabibiazar M, Mohammadifar M. Development of Ethyl Cellulose-based Formulations: A Perspective on the Novel Technical Methods. Food Reviews International. 2020 Apr 10:1-48.

20. Li K, Stöver HDH. Synthesis of monodisperse poly(divinylbenzene) microspheres. J Polym Sci Part A Polym Chem . 1993 Dec;31(13):3257–63. Available from: https://onlinelibrary.wiley.com/doi/10.1002/pola.1993.080311313

21. Cong H, Xing J, Ding X, Zhang S, Shen Y, Yu B. Preparation of porous sulfonated poly(styrene-divinylbenzene) microspheres and its application in hydrophilic and chiral separation. Talanta. 2020 Apr 1;210:120586.

22. Prajapati SK, Jain A, Jain A, Jain S. Biodegradable polymers and constructs: A novel approach in drug delivery. Eur Polym J . 2019 Nov;120:109191. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014305719305920

23. Zhu Y, Shah NH, Malick AW, Infeld MH, McGinity JW. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int J Pharm. 2002 Jul 25;241(2):301-10.

24. Junqueira MV, Bruschi ML. A Review About the Drug Delivery from Microsponges. AAPS PharmSciTech. 2018 May;19(4):1501-11.

25. Bae SE, Son JS, Park K, Han DK. Fabrication of covered porous PLGA microspheres using hydrogen peroxide for controlled drug delivery and regenerative medicine. J Control Release.2009 Jan 5;133(1):37-43.

26. Kabiri K, Omidian H, Zohuriaan-Mehr MJ. Novel approach to highly porous superabsorbent hydrogels: Synergistic effect of porogens on porosity and swelling rate. Polym Int. 2003 Jul;52(7):1158-64.

27. Hong Y, Liu X. Pre-gelatinized Modification of Starch. In: Physical Modifications of Starch . Singapore: Springer Singapore; 2018. p. 51–61. Available from: http://link.springer.com/10.1007/978-981-13-0725-6_4

28. Yutani R, Komori Y, Takeuchi A, Teraoka R, Kitagawa S. Prominent efficiency in skin delivery of resveratrol by novel sucrose oleate microemulsion. J Pharm Pharmacol . 2016 Jan 25;68(1):46–55. Available from: https://academic.oup.com/jpp/article/68/1/46-55/6128296

29. Huang B, Aslan E, Jiang Z, Daskalakis E, Jiao M, Aldalbahi A, et al. Engineered dual-

scale poly (ε-caprolactone) scaffolds using 3D printing and rotational electrospinning for bone tissue regeneration. Addit Manuf. 2020;36(February):101452.

30. Pravin Gupta DKMK. Microsponge Technology as a Versatile Drug Delivery Vehicle: Review. Glob J Pharm Educ Res. January-December. 2017;6(1-2).

31. Handa M, Tiwari S, Yadav AK, Almalki WH, Alghamdi S, Alharbi KS, et al. Therapeutic potential of nanoemulsions as feasible wagons for targeting Alzheimer's disease. Drug Discov Today . 2021 Jul; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1359644621003251

32. Handa M, Sharma A, Verma RK, Shukla R. Polycaprolactone based nano-carrier for co-administration of moxifloxacin and rutin and its In-vitro evaluation for sepsis. J Drug Deliv Sci Technol. 2019;54(June).

33. Jain V, Singh R. Dicyclomine-loaded Eudragit®-based Microsponge with Potential for Colonic Delivery: Preparation and Characterization. Trop J Pharm Res . 2010 Mar 1;9(1). Available from: http://www.ajol.info/index.php/tjpr/article/view/52039

34. Badhe KP, Saudagar RB. A Review on Microsponge a Novel Drug Delivery System. Asian J Pharm Res. 2016;6(1):51-7.

35. KAWASHIMA Y, NIWA T, TAKEUCHI H, HINO T, ITO Y. Control of Prolonged Drug Release and Compression Properties of Ibuprofen Microsponges with Acrylic Polymer, Eudragit RS, by Changing Their Intraparticle Porosity. Chem Pharm Bull . 1992;40(1):196–201. Available from: http://www.jstage.jst.go.jp/article/cpb1958/40/1/40_1_196/_article

36. Osmani RAM, Aloorkar NH, Thaware BU, Kulkarni PK, Moin A, Hani U, et al. Microsponge based drug delivery system for augmented gastroparesis therapy: Formulation development and evaluation. Asian J Pharm Sci. 2015 Oct 1;10(5):442-51.

37. Jyoti J, Kumar S. INNOVATIVE AND NOVEL STRATEGY: MICROSPONGES FOR TOPICAL DRUG DELIVERY. J Drug Deliv Ther . 2018 Sep 6;8(5):28–34. Available from: http://jddtonline.info/index.php/jddt/article/view/1885

38. Parikh BN, Gothi GD, Patel TD, Chavda H V., Patel CN. Microsponge as novel topical

drug delivery system. Journal of Global Pharma Technology. 2010;2(1):17-29.

39. Akashdeep G, Archana D, Divya J. Microsponges laden gels for topical delivery: A novel approach. Pharma Innov J TPI. 2016 Jun 1;5(6, Part A):39.

40. Soumya S, Sahu D. A review on novel drug delivery system: Microsponges. International Journal of Drug Delivery Technology. 2017;7(04):298-303.

41. Mishra P, Handa M, Ujjwal RR, Singh V, Kesharwani P, Shukla R. Potential of nanoparticulate based delivery systems for effective management of alopecia. Colloids Surfaces B Biointerfaces . 2021 Dec;208:112050. Available from: https://linkinghub.elsevier.com/retrieve/pii/S092777652100494X

42. Shukla R, Handa M, Pardhi VP. Introduction to Pharmaceutical Product Development. In: Pharmaceutical Drug Product Development and Process Optimization . Includes bibliographical references and index.: Apple Academic Press; 2020. p. 1–32. Available from: https://www.taylorfrancis.com/books/9781000731323/chapters/10.1201/9780367821678-1

43. Bhatia M, Saini M. Formulation and evaluation of curcumin microsponges for oral and topical drug delivery. Prog Biomater. 2018 Sep;7(3):239-48.

44. Obiedallah MM, Abdel-Mageed AM, Elfaham TH. Ocular administration of acetazolamide microsponges in situ gel formulations. Saudi Pharm J. 2018 Nov 1;26(7):909-20.

45. Castro GA, Ferreira LAM. Novel vesicular and particulate drug delivery systems for topical treatment of acne. Expert Opin Drug Deliv . 2008 Jun 5;5(6):665–79. Available from: http://www.tandfonline.com/doi/full/10.1517/17425247.5.6.665

46. Usatine RP, Quan MA. PEARLS IN THE MANAGEMENT OF ACNE. Prim Care Clin Off Pract . 2000 Jun;27(2):289–308. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0095454305701962

47. Kanlayavattanakul M, Lourith N. Therapeutic agents and herbs in topical application for acne treatment. International Journal of Cosmetic Science. 2011 Aug;33(4):289-97.

48. Krautheim A, Gollnick HPM. Acne: Topical treatment. Clin Dermatol . 2004 Sep;22(5):398–407. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0738081X04000422

49. 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 Feb 3;308(1-2):124-32.

50. Gollnick H, Schramm M. Topical Drug Treatment in Acne. Dermatology . 1998;196(1):119–25. Available from: https://www.karger.com/Article/FullText/17844

51. Osmani R, Aloorkar N, Kulkarni A, Kulkarni P, Hani U, Thirumaleshwar S, et al. Novel Cream Containing Microsponges of Anti-Acne Agent: Formulation Development and Evaluation. Curr Drug Deliv. 2015 Oct 1;12(5):504-16.

52. Carrasquillo OY, Pabón-Cartagena G, Falto-Aizpurua LA, Santiago-Vázquez M, Cancel-Artau KJ, Arias-Berrios G, et al. Treatment of erythrodermic psoriasis with biologics: A systematic review. J Am Acad Dermatol. 2020 Jul 1;83(1):151-8.

53. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of Psoriasis. Annu Rev Immunol . 2014 Mar 21;32(1):227–55. Available from: https://www.annualreviews.org/doi/10.1146/annurev-immunol-032713-120225

54. Rahman M, Akhter S, Ahmad J, Ahmad MZ, Beg S, Ahmad FJ. Nanomedicine-based drug targeting for psoriasis: Potentials and emerging trends in nanoscale pharmacotherapy. Expert Opinion on Drug Delivery. 2015 Apr 3;12(4):635-52.

55. Feldman SR, Horn EJ, Balkrishnan R, Basra MK, Finlay AY, McCoy D, et al. Psoriasis: Improving adherence to topical therapy. J Am Acad Dermatol . 2008 Dec;59(6):1009–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0190962208010700

56. Devi N, Kumar S, Prasad M, Rao R. Eudragit RS100 based microsponges for dermal delivery of clobetasol propionate in psoriasis management. J Drug Deliv Sci Technol. 2020 Feb 1;55:101347.

57. D'auria E, Banderali G, Barberi S, Gualandri L, Pietra B, Riva E, et al. Atopic dermatitis: recent insight on pathogenesis and novel therapeutic target. Asian Pacific J Allergy

Immunol . 2016; Available from: http://thailand.digitaljournals.org/index.php/APJAI/article/view/30240

58. Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, et al. Japanese guidelines for atopic dermatitis 2020. Allergology International. 2020;69(3):356-69.

59. Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. Journal of Allergy and Clinical Immunology. 2017 Jun 1;139(6):1723-34.

60. Saini S, Pansare M. New Insights and Treatments in Atopic Dermatitis. Pediatric Clinics of North America. 2021 Nov 1;41(4):653-65.

61. Zaki Rizkalla CM, Latif Aziz R, Soliman II. In vitro and in vivo evaluation of hydroxyzine hydrochloride microsponges for topical delivery. AAPS PharmSciTech. 2011 Sep;12(3):989-1001.

62. Pradhan M, Singh D, Murthy SN, Singh MR. Design, characterization and skin permeating potential of Fluocinolone acetonide loaded nanostructured lipid carriers for topical treatment of psoriasis. Steroids. 2015 Sep 1;101:56-63.

63. D'souza J, More H. Topical Anti-Inflammatory Gels of Fluocinolone Acetonide Entrapped in Eudragit Based Microsponge Delivery System. Res J Pharm Technol. 2008;1(4):502-6.

64. Prakash A, Benfield P. Topical mometasone: A review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. Drugs. 1998 Jan;55(1):145-63.

65. Peharda V, Gruber F, Prpić L, Kaštelan M, Brajac I. Comparison of mometasone furoate 0.1% ointment and betamethasone dipropionate 0.05% ointment in the treatment of psoriasis vulgaris. Acta Dermatovenerologica Croat. 2000;8(4):223-6.

66. Rekha U, Manjula BP. Formulation and evaluation of microsponges for topical drug delivery of mometasone furoate. Int J Pharm Pharm Sci. 2011;3(4):133-7.

67. Sun Q, Leng J, Tang L, Wang L, Fu C. A Comprehensive Review of the Chemistry, Pharmacokinetics, Pharmacology, Clinical Applications, Adverse Events, and Quality Control of Indigo Naturalis. Front Pharmacol . 2021 May 31;12. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2021.664022/full

68. Hu YS, Han X, Yu PJ, Jiao MM, Liu XH, Shi JB. Novel paeonol derivatives: Design, synthesis and anti-inflammatory activity in vitro and in vivo. Bioorg Chem . 2020 May;98:103735. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0045206820301280

69. Cullen JK, Simmons JL, Parsons PG, Boyle GM. Topical treatments for skin cancer. Advanced Drug Delivery Reviews. 2020 Jan 1;153:54-64.

70. Simões MCF, Sousa JJS, Pais AACC. Skin cancer and new treatment perspectives: A review. Cancer Lett . 2015 Feb;357(1):8–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0304383514006557

71. Bickers DR, Athar M. Novel Approaches to Chemoprevention of Skin Cancer. J Dermatol . 2000 Nov;27(11):691–5. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1346-8138.2000.tb02259.x

72. Haque T, Rahman KM, Thurston DE, Hadgraft J, Lane ME. Topical therapies for skin cancer and actinic keratosis. European Journal of Pharmaceutical Sciences. 2015 Sep 18;77:279-89.

73. Korting HC, Schäfer-Korting M. Carriers in the topical treatment of skin disease. Handbook of Experimental Pharmacology. 2010:435-68.

74. Jain SK, Kaur M, Kalyani P, Mehra A, Kaur N, Panchal N. Microsponges enriched gel for enhanced topical delivery of 5-fluorouracil. J Microencapsul . 2019 Oct 3;36(7):677–91. Available from: https://www.tandfonline.com/doi/full/10.1080/02652048.2019.1667447

75. Levy S, Furst K, Chern W. A pharmacokinetic evaluation of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. Clin Ther. 2001 Jun 1;23(6):908-20.

76. Lochhead RY. Basic Physical Sciences for the Formulation of Cosmetic Products. In: Cosmetic Science and Technology . Elsevier; 2017. p. 39–76. Available from:

https://linkinghub.elsevier.com/retrieve/pii/B9780128020050000033

77. Wolf R. A glance into the crystal ball: Winners and losers in cosmetics. Clin Dermatol. 2001 Jul 1;19(4):516-23.

78. Katz LM, Dewan K, Bronaugh RL. Nanotechnology in cosmetics. Food Chem Toxicol. 2015;85:127–37.

79. Lionetti N, Rigano L. Labeling of cosmetic products. Cosmetics. 2018.

80. Rosen MR. Delivery System Handbook for Personal Care and Cosmetic Products: Technology, Applications and Formulations. Delivery System Handbook for Personal Care and Cosmetic Products: Technology, Applications and Formulations. 2005 Sep 23.

81. Kafi R, Kwak HSR, Schumacher WE, Cho S, Hanft VN, Hamilton TA, et al. Improvement of naturally aged skin with vitamin A (Retinol). Arch Dermatol. 2007;

82. Bhuptani RS, Patravale VB. Starch microsponges for enhanced retention and efficacy of topical sunscreen. Mater Sci Eng C. 2019 Nov 1;104:109882.

83. Shukla R, Handa M, Lokesh SB, Ruwali M, Kohli K, Kesharwani P. Conclusion and Future Prospective of Polymeric Nanoparticles for Cancer Therapy . Polymeric Nanoparticles as a Promising Tool for Anti-cancer Therapeutics. Elsevier Inc.; 2019. 389–408 p. Available from: http://dx.doi.org/10.1016/B978-0-12-816963-6.00018-2

84. Gupta A, Tiwari G, Tiwari R, Srivastava R, Rai AK. Enteric coated HPMC capsules plugged with 5-FU loaded microsponges: a potential approach for treatment of colon cancer. Brazilian J Pharm Sci . 2015 Sep;51(3):591–605. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1984-82502015000300591&lng=en&tlng=en

85. Dhawale SC, Bankar AS, Patro MN. Formulation and evaluation porous microspheres of 5- fluorouracil for colon targeting. Int J PharmTech Res. 2010;

86. Younis MA, El-Zahry MR, Tallat MA, Tawfeek HM. Sulpiride gastro-retentive floating microsponges; analytical study, in vitro optimization and in vivo characterization. J Drug Target. 2020 Apr 20;28(4):386-97.

87. Kasuya F, Igarashi K, Fukui M. Metabolism of chlorpheniramine in rat and human by use of stable isotopes. Xenobiotica. 1991 Jan 1;21(1):97-109.

88. Motov S, Butt M, Masoudi A, Palacios W, Fassassi C, Drapkin J, et al. Comparison of Oral Ibuprofen and Acetaminophen with Either Analgesic Alone for Pediatric Emergency Department Patients with Acute Pain. J Emerg Med . 2020 May;58(5):725–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0736467920301062

89. Devrim B, Canefe K. Preparation and evaluation of modified release ibuprofen microspheres with acrylic polymers (Eudragit) by quasi-emulsion solvent diffusion method: effect of variables. Acta Pol Pharm . 2006;63(6):521–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17438870

90. Çomoglu T, Gönül N, Baykara T. The effects of pressure and direct compression on tabletting of microsponges. Int J Pharm. 2002 Aug;242(1–2):191–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378517302001552

91. Çomoğlu T, Gönül N, Baykara T. Preparation and in vitro evaluation of modified release ketoprofen microsponges. Farmaco. 2003 Feb 1;58(2):101-6.

92. Yusuf M, Khan M, Khan RA, Ahmed B. Preparation, characterization, in vivo and biochemical evaluation of brain targeted Piperine solid lipid nanoparticles in an experimentally induced Alzheimer's disease model. J Drug Target. 2013;21(3):300–11.

93. Cui F, Yang M, Jiang Y, Cun D, Lin W, Fan Y, et al. Design of sustained-release nitrendipine microspheres having solid dispersion structure by quasi-emulsion solvent diffusion method. J Control Release . 2003 Sep;91(3):375–84. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016836590300275X

94. Trotta F, Zanetti M, Cavalli R. Cyclodextrin-based nanosponges as drug carriers. Beilstein Journal of Organic Chemistry. 2012 Nov 29;8(1):2091-9.

95. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system - Review. J Pharm Pharm Sci. 2012 Jan 17;15(1):103-11.

96. Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosponge formulations as oxygen delivery systems. Int J Pharm . 2010 Dec 15;402(1–2):254–7.

Available from: https://linkinghub.elsevier.com/retrieve/pii/S037851731000726X

97. Trotta F, Dianzani C, Caldera F, Mognetti B, Cavalli R. The application of nanosponges to cancer drug delivery. Expert Opin Drug Deliv . 2014 Jun 8;11(6):931–41. Available from: http://www.tandfonline.com/doi/full/10.1517/17425247.2014.911729

98. Hu SH, Liu TY, Liu DM, Chen SY. Nano-ferrosponges for controlled drug release. J Control Release. 2007 Aug 28;121(3):181-9.

99. Zhang H, Pan D, Duan X. Synthesis, Characterization, and Magnetically Controlled Release Behavior of Novel Core−Shell Structural Magnetic Ibuprofen-Intercalated LDH Nanohybrids. J Phys Chem C . 2009 Jul 16;113(28):12140–8. Available from: https://pubs.acs.org/doi/10.1021/jp901060v

100. King CA, Shamshina JL, Zavgorodnya O, Cutfield T, Block LE, Rogers RD. Porous Chitin Microbeads for More Sustainable Cosmetics. ACS Sustain Chem Eng . 2017 Dec 4;5(12):11660–7. Available from: https://pubs.acs.org/doi/10.1021/acssuschemeng.7b03053

101. Shah CN, Shah DP. Microsponges: A revolutionary path breaking modified drug delivery of topical drugs. International Journal of Pharmaceutical Research. 2014 Apr;6(2):1-3.

102. Kumar PM, Ghosh A. Development and evaluation of silver sulfadiazine loaded microsponge based gel for partial thickness (second degree) burn wounds. Eur J Pharm Sci . 2017 Jan;96:243–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0928098716304213

103. Arya P, Pathak K. Assessing the viability of microsponges as gastro retentive drug delivery system of curcumin: Optimization and pharmacokinetics. Int J Pharm. 2014 Jan 2;460(1-2):1-2.

104. Kadhim ZM, Mahmood HS, Alaayedi M, Ghareeb MM. Formulation of flurbiprofen as microsponge drug delivery system. Int J Pharm Res. 2020 Apr;12(3).

105. Singhvi G, Manchanda P, Hans N, Dubey SK, Gupta G. Microsponge: An emerging drug delivery strategy. Drug Dev Res . 2019 Mar 19;80(2):200–8. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ddr.21492

106. Borawake PD, Kauslya A, Shinde J V, Chavan RS. Microsponge as an Emerging Technique in Novel Drug Delivery System. J Drug Deliv Ther. 2021 Jan 15;11(1):171-82.

107. Ambikar RB, Bhosale A V. Formulation and Evaluation of Eudragit Rl100 Polymeric Drug Loaded Microsponge for Ophthalmic Use. J Pharm Res Int . 2021 Apr 17;45–51. Available from: https://www.journaljpri.com/index.php/JPRI/article/view/31440