Microsponges and Nanoparticles for Treatment of Topical Skin Infections: A Review

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Abstract

The present article is written intending to incorporate the information and compilation of advancement in the field of novel drug delivery systems (NDDS) with special emphasis on microsponges and nanoparticles in the delivery of drugs for the treatment of topical skin infections. Microsponges have several characteristics that make it a versatile drug delivery system. These are generally used for topical applications for the slow release of a drugs that can prevent excessive accumulation of ingredients at epidermis and dermis. Microsponges are too large to be adsorbed on the skin and prevent pathogens to enter the skin by entrapping in their structure. Nanoparticles (NPs) are the ultrafine particles with a size of less than 100 nm that offers a large surface area while applying on skin. NPs are now used in a wide variety of products and various technologies due to their uniformity and low toxicity. The development of NDDS of skin disorder drugs with special attention to microsponges followed by nanoparticles as an evolution to overcome the drawbacks of conventional delivery systems and enhancing the user acceptability.

Keywords: Novel drug delivery system, microsponges, nanoparticles, skin infections

Introduction

Skin infections and skin diseases are very common and affecting patients all over the world. The skin is the external protective organ of the body. It has a complex structure, maintains the homeostasis by regulating temperature and prevents unnecessary water loss. It acts as a barrier to prevent the entry of pathogens and infections due to the presence of epidermis and dermis as two major skin layers (Rio et al., 2018). The nerves present in the skin helps in tactile sensation for adaptation of the present environment by the living being. However, during diseases, the functionality of the skin affected and it does not perform the functions effectively (Liu et al., 2016). The epidermis layer of the skin consists of microbiota to prevent the growth of microbes and regulate immune responses (Gurung and Kanneganti, 2016). Several diseases are affecting the skin whose main pathophysiology is inflammation. Inflammation mainly found in epidermis and dermis which results in hyperkeratosis. It is a condition of thickened scaly skin (Akiyama et al., 2018). The skin inflammatory keratinization disorders include psoriasis, chronic urticaria, atopic dermatitis,

lichen planus, etc (Fernandez et al., 2017). The conventional treatments are not much effective in curing skin infections and other skin conditions. Several drugs and therapies have been developed for the treatment of diseased conditions but most of these approaches are incapable of effective cure and produce side effects (Rizvia and Saleh, 2018). Noticeably, in the past few decades nanotechnology has shown unprecedented attention and advancement towards a wide area of science. It is a multi-facing interdisciplinary technique applying principles of engineering and manufacturing of delivery systems at the molecular level.

Novel drug delivery systems (NDDS) are advanced drug delivery systems over a conventional delivery system. The evolution of novel drug delivery systems (NDDS) has significantly improved the delivery of drug molecules i.e. more patient compliance, effectiveness and safety (Bhagwat and Vaidhya, 2013). The NDDS has been getting more attention due to the targeted delivery of drugs in small dosages. NDDS has engaged several drug developing industries to formulate and develop such dosage forms. The advantages associated with their system of drug delivery have enhanced bioavailability, reduced dosing frequency, stability at the gastric environment, low toxicity and site-specificity. Microsponge is one of the polymeric delivery system made up of microspheres (Kaity et al., 2010). It is known for its reduced toxicity, enhanced stability, optimized drug delivery and higher loading capacity with a wide range of drugs. The unique property of this delivery system with sustained release of drug from the outer porous surface has made it successful in the delivery of drugs for topical infections. Another NDDS made up of two immiscible liquids along with emulsifying agents for delivery of hydrophobic drugs is "Nanoparticle". It is a thermodynamically stable system in which nano-sized globules allow better delivery of drugs across the skin (Shaker et al., 2019). This system has a higher drug loading capacity in comparison to other conventional drug delivery systems.

Skin infections

Skin diseases are a global health problem with significant conditions like skin infections, fungal attack, dermatitis, skin cancer and skin ulceration (Hay et al., 2015). The skin is the collection of several microorganisms including bacteria, viruses, fungi, and protozoa; skin and soft tissue infections (SSTIs) attacks mostly in immunocompromised patients (Moffarah et al., 2016). SSTIs have variable etiology in which pathogen invasion occurs in the skin layers and underlying tissues. The infection ranging from mild (ecthyma or impetigo, cellulitis, abscess) to severe conditions (necrotizing fasciitis). The common fungal infections on skin are candidiasis, tinea corporis, and capitis. Viral skin infections are warts, herpes simplex, molluscum contagiosum, etc and parasitic infection includes scabies (Rayala and Morrell, 2017). Other skin infections are furunculosis, folliculitis, carbunculosis, intertrigo, and erysipelas (Castro and Ramos-E-Silva, 2018). Inflamed skin and ulcers are very common cutaneous infections. However, impetigo results in honey-colored

crusts and blisters formation in the skin. Carbunculosis and furunculosis are severe pustular skin eruptions. Intertrigo occurs in body folds especially in the groin region of the body. On the other hand, secondary skin infections found results in enhanced skin dryness (Laube et al., 2002). The microbes live in synergy with the host that colonize to cause skin infections. Several conventional antibiotics cause resistant to these microbes and thus result in infection with other opportunistic pathogens (Roth et al., 1989).

Seborrheic dermatitis is a kind of skin infection found in all age groups especially in infants below three months and 30-60 years persons. It is also linked to immunodeficiencies in infants. The condition gets worse in men with emotional stress (Schwartz et al., 2006). This condition of the skin is characterized by erythema, itching and scaling on the skin part of the face, scalp, chest, axilla, groin, and back (Clark et al., 2015). It has been defined either as an inflammatory (inflammation in the epidermis) or a fungal disease (caused by Malassezia yeasts) and closely related to psoriasis (Dessinioti et al., 2013). It is also found in conjunction with diseases like acne vulgaris, rosacea, and blepharitis (Gupta et al., 2003). Figure – 1 shows the symptoms of seborrhea including dandruff on scalp, eyebrows; shiny patchy skin with yellow scalp; red skin; hair loss; thickening of the skin; pruritus and other inflammatory conditions; itching, etc. The common triggers for seborrheic dermatitis are hormonal changes, chemicals, detergents, stress, cold and dry weather, etc. Table – 1 shows different types of skin infections caused by several microorganism's sand other conditions that promote skin infections like in children, athletes, immune-compromised patients, geriatric patients, pregnant women, etc. Viral skin infections are molluscum contagiosum, warts, herpes simplex, etc. Bacterial infections are cellulitis, impetigo, abscess, etc. Fungal infections are tinea capitis, tinea corporis, genital candidiasis, etc. (Rayala et al., 2017).

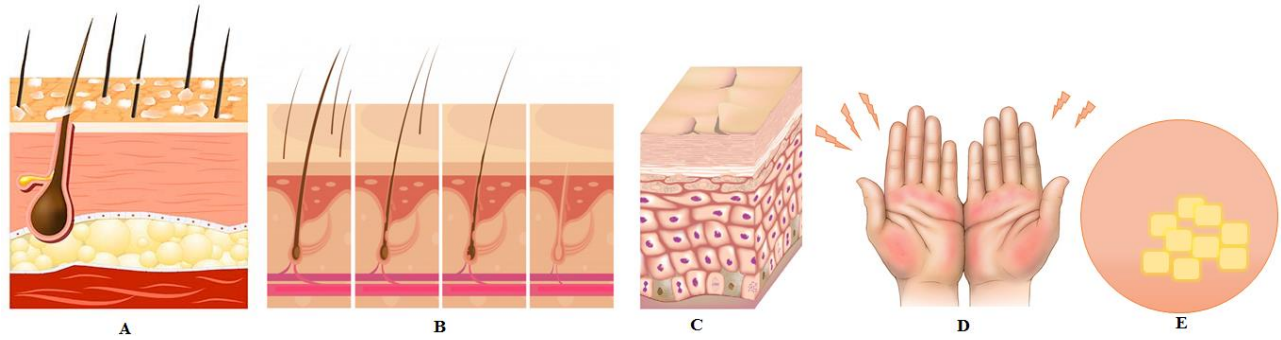

Figure – 1 Diagrammatic representation of symptoms of seborrhea

A – Abundant dandruff, B – Hair loss, C – Thickening of the stratum corneum, D – Pruritus, E – Skin peeling

Table – 1:Types of skin infections based on different conditions

S. No.	Skin infection	Consequences	References

1	Pseudomonas skin infection	Localized infections of the skin caused by a gram-negative bacillus; *Pseudomonas aeruginosa*	Wu et al., 2011
2	Skin and soft tissue infections	Mostly found in immunocompromised patients caused by bacteria, sometimes other microorganisms are also involved	Moffarah et al., 2016
3	Skin infection underwater	Traumatic abrasions found in human extremities due to contact with water (pond, lake, sea, river, etc.) by common microbe: *Mycobacterium marinum*	Hansen et al., 2017
4	Skin nontuberculous mycobacteria	ulcerative lesions and abscesses found in lupus patients by *Mycobacterium* species	Panigrahi et al., 2012
	Ocular skin infection	Eye infection is found during gonorrhea or chlamydia infection	Sadowska-Przytocka et a., 2016
5	Purulent skin infection	Found in elderly patients	Haran et al., 2017
6	Skin infections in organ transplant patients	The common skin infections are pyoderma, wound infections, or the reactivation of herpes viruses and varicella-zoster viruses after transplantation of organ	Ulrich et al., 2008
7	Skin infection due to a permanent tattoo	A cutaneous infection caused by *Herpes Compuctorum*	Caccavale et al., 2017
8	Skin infection in psychiatric patients	Parasitic infestations: delusional parasitosis found in psychiatric conditions	Moftah et al., 2013
9	Skin infection in a contact sport	Common skin infection is bacterial skin infections, conjunctivitis, head lice, tinea, molluscum contagiosum, herpes simplex virus, common warts, scabies, etc.	Peterson et al., 2019

10	Skin infection in renal transplant recipients	Herpes simplex infection, impetigo, and candidal infection are most common in this condition	Hogewoning et al., 2001
11	Skin Infection in Kidney-Pancreas	It is due to *Mycobacterium chelonae*	Stelzmueller et al., 2005

Microsponges

Microsponges are small globule particles with size ranging from 5 to 300 μm. These are spherical and capable of absorbing skin secretions. Microsponges are also known as solid-phase porous microspheres. They have numerous internal voids for the residence of bioactive compounds (Kumari et al., 2016). Microsponges have advantages over the conventional topical delivery system as non-irritant, odorless, non-greasy and patient compliance (Gangadharappa et al., 2013). Microsponges can efficiently deliver the drugs at the targeted site without loss, with enhanced stability and minimizing toxicity. These are specifically designed to deliver the drugs topically on the skin and increase the contact time of drugs with the skin (Singhvi et al., 2019). Microsponges are generally prepared by Quasi-emulsion solvent diffusion method and Liquid-liquid suspension polymerization for targeted delivery of drugs (Dubey et al., 2014). Microsponges are porous microspheres that are formed by cross-linking of polymers. It has several interconnecting spaces and releases the drug by diffusion (Kircik, 2013). Due to the tiny pore size of microsponges the bacteria ranging from 0.09 to 0.2 μm get entrapped and unable to penetrate the structure of the vehicle. Microsponge drug delivery system has shown great interest in the development of pharmaceutical drugs. The release of drugs from microsponge can be manipulated depending upon temperature, pH and catalytic degradation at the applied site (Junqueira and Bruschi, 2018). Figure – 1 shows the microsponge drug release pattern. Microsponges are the large reservoir of active compounds that can take the drug more than its weight and deliver it to the skin. Microsponges absorb the secretions from the skin and reduce oiliness and shining from the skin. Figure – 2 shows the microsponges loaded with the drug in a carrier for topical application. In this technique, microsponges are designed to maintain controlled release of the active ingredient into the skin and reduce its entry in the blood for topical skin conditions. These tiny sponges can entrap a wide range of active ingredients such as fragrances, essential oil, antifungal drugs, emollients, anti-infective, sunscreens and used as a topical carrier system (Shukla et al., 2016). Table – 1 shows the recent advancement in microsponge drug delivery for topical applications. Microsponges have shown their effectivity in drug delivery for topical skin problems and quite helpful for pharmaceutical

advancement. Microsponges are designed to the delivery large amount of active ingredients with the minimum dose and low toxicity. They can reduce the irritation of active ingredients by decreasing their efficacy. It can be washed and reused again. Several novel products have been developed using microsponge as carriers and presented in the market in conventional forms such as gels, lotions or creams (Kaity et al., 2010).

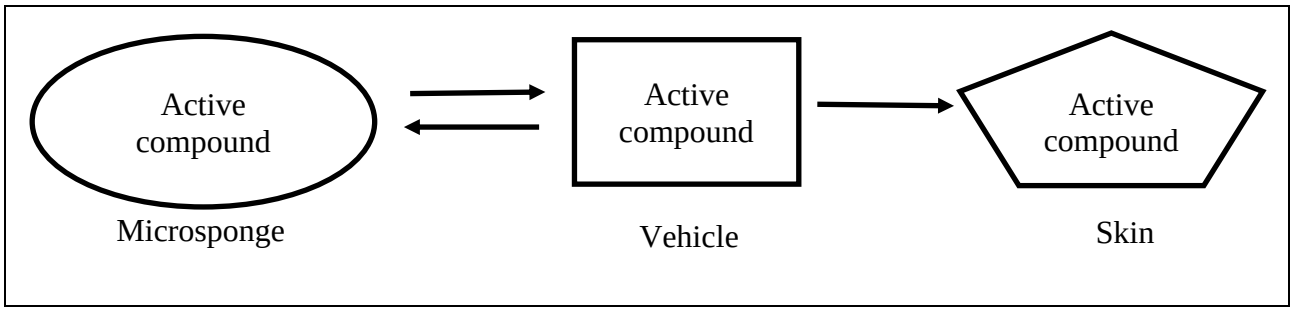

Figure – 1:Diagrammatic representation of release of drug in the skin from microsponge

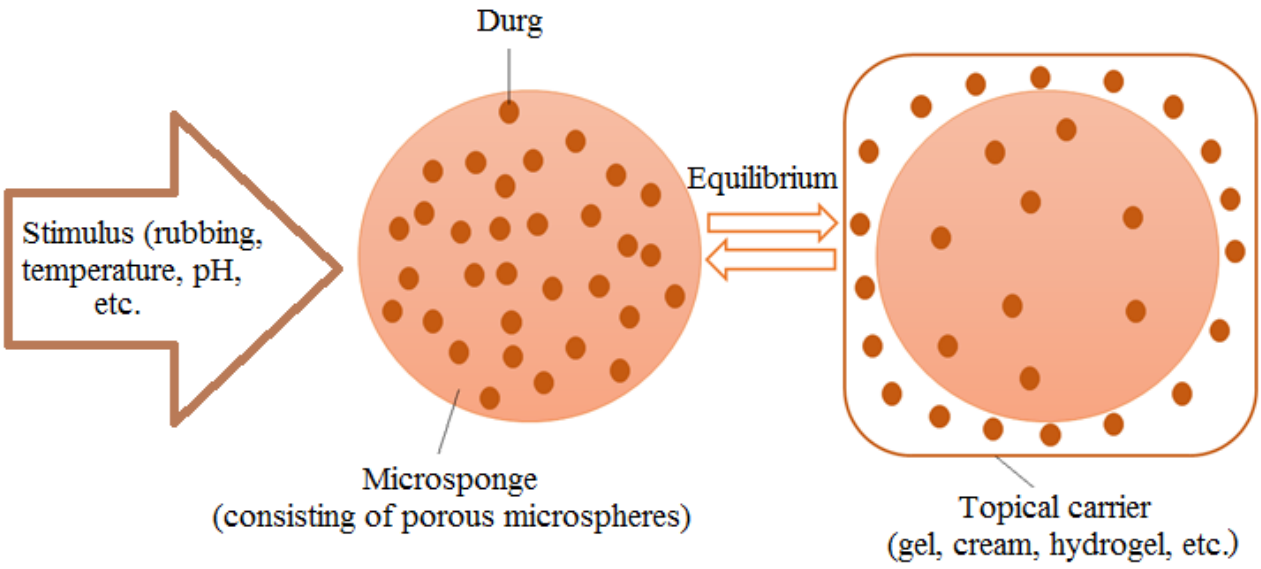

Figure – 2: Structural representation of Microsponge loaded with drug and carrier

Table - 1: Recent advancement in microsponges

S. No.	Advancement	Properties	References
1	Nanosponges were prepared for delivery of drugs in the form of cyclodextrins	Enhanced solubility of poor water soluble drugs for topical application	Gangadharappa et al., 2013
2	Microsponges of nifedipine were prepared and then embedded into	Sustained release of nifedipine	Maheshwari et al., 2017

	tablets		
3	Microsponge gel of nebivolol was prepared for diabetic wound	Microsponge gel was entrapped in the porous structure of wound and helped in fast healing	Pandit et al., 2017
4	Microsponge gel of fluconazole was prepared for antifungal therapy	The prepared gel exhibited good extrudability and spreadability with effective anti fungal effect	Moin et al., 2016
5	Microsponge gel of oxybenzone was prepared for topical delivery	Prolonged release of oxybenzone for topical retention with reduced toxicity	Pawar et al., 2015
6	Microsponge gel of silver sulfadiazine was prepared for burn wounds	The gel exhibited less frequency to apply on skin, devoid of skin irritation, reduced cell toxicity and effective in wound contraction	Kumar and Ghosh, 2017
7	Microsponge was prepared for prolonging and protecting mitiglinide calcium at gastrointestinal tract	The prepared microsponge had high production yield and entrapment efficiency along with stability in GIT and sustained release of drug	Mahmoud et al., 2018
8	Microsponge gel of dithranol entrapped with dendrimer was prepared for topical disorders	The prepared gel produced prolonged effect with possible treatment for psoriasis	Tripathi et al., 2019
9	Microsponge gel of eberconazole nitrate was prepared for topical antifungal effect	The prepared gel exhibited controlled release, nonirritant and significant antifungal activity	Bothiraja et al., 2014

10	Microsponge of sertaconazole nitrate were prepared for topical treatment	It exhibited controlled drug release	Pande et al., 2015
11	Microsponge prepared for loading with tyrosinase inhibitor	The prepared microsponge was effective in treating hyperpigmentation disorders	Deshmukh and Poddar, 2012
12	Microsponge of acetazolamide for ocular treatment	The prepared gel was non irritant, and effective for opthalmic delivery	Obiedallah et al., 2018
13	Microsponge of miconazole nitrate was prepared for acne treatment	The prepared cream was effective in treating acne	Osmani et al., 2015
14	Curcumin microsponges were prepared for topical and oral delivery	The prepared microsponge showed zero order kinetic model with effective release of drug from both topical and oral routes	Bhatia and Saini, 2018
15	Microsponges loaded with 5-fluorouracil plugged in hydroxypropyl methylcellulose capsules were prepared for colorectal cancer	The prepared microsponge capsules showed targeted release and effective in colon cancer	Gupta et al., 2015
16	DNA microsponges were used for generating DNA hollow spheres	The prepared hollow spheres had high surface-to-volume ratio, encapsulate large amount of drugs and maximize the efficacy of drug	Choi et al., 2019
17	Floating microsponges of cinnarizine were prepared as gastroretentive delivery	Microsponges were coated with capmul GMO and viability was confirmed with bioadhesive material to get extended release of drug	Raghuvanshi and Pathak, 2016

18	Microsponge gel loaded with miconazole was prepared for antifungal effect and improved vaginal retention	Miconazole microsponge gel showed more effectiveness than marketed product in removing Candida infection	Salah et al., 2018
19	Microsponge rectal gel of diltiazem hydrochloride was prepared for anal fissures	The gel was completely diseased in rectum and effective in treating anal fissure	Ivanova et al., 2019
20	Starch microsponge was prepared for topical sunscreen cream	It showed improved protection of skin, decreased cutaneous penetration, safe and effective	Bhuptani and Patravale, 2019
21	Floating microsponge of curcumin was prepared for gastroretentive effect	It showed 10 times enhanced bioavailability than plain curcumin in treatment of gastric cancer	Arya and Pathak, 2014
22	Curcumin microsponges were prepared for inflammatory bowel disease	It showed significant reduction of necrosis, edema and hemorrhage and effective in ulcerative colitis	Sareen et al., 2014
23	Microsponge gel of 5-fluorouracil was prepared for topical delivery	It showed enhanced delivery of drugs topically	Jain et al., 2019
24	Floating microsponge of Sulpiride was prepared for gastroretentive effect	It showed enhanced bioavailability and absorption	Younis et al., 2019

Nanoparticles

Nanoparticles (NPs) are the unique NDDS that offer several advantages for drug delivery such as nanoscale material loading and optimization of size and shape (Hoshyar et al., 2016). They are tiny molecules with size ranging from 1 to 100 nm. NPs are of different types based on size, shape and properties such as metallic NPs, fullerenes, polymeric and ceramic NPs. NPs have wide variety of applications in medical, catalysis, research and environmental purposes (Khan et al., 2019). The size of the NPs greatly affect their penetration through skin i.e. NPs less than 4 nm can permeate

intact skin, NPs size range between 4 to 20 nm can permeate intact skin more potentially along with damaged skin, NPs of 21 to 45 nm can permeate damage skin only, however, NPs with size more than 45 nm cannot penetrate damaged skin (Larese Filon et al., 2015). Surface to mass ratio of NPs are very high along with their quantum properties, and ability to absorb substances. They offer large surface area for binding, adsorbing and carrying drugs and other compounds. NPs are coated with various polymers such as poly(vinylpyrrolidone) (PVP), polyethylene glycol (PEG), pullulan, chitosan, dodecylamine, sodium oleate, etc. Nanoparticles have emerged as an important platform for the treatment of topical skin infections. The different types of NPs are polymersomes, nanocapsules, nano complexes and solid lipid nanoparticles. These are the ideal vehicles for the delivery of drugs by permeating the skin layers (Oyarzun-Ampuero et al., 2015; Vidlarova et al., 2016). Figure – 4 shows the structure of solid lipid nanoparticles (SLN) and their entrapment with drug. SLN can be targeted to the skin for superficial drug application based upon the topical formulations. Figure – 5 shows the different sites for drug targeting while applying on skin. It can permeate the stratum corneum to reach the dermis and provide systemic effect or remain as a reservoir in the skin strata for longer period of time for local effects or remain only on the skin surface to act as a skin protective. The particular intention of this delivery system is to maximize the delivery of drug to the targeted site and minimize drug reaching other sites (Zhang et al., 2006). Table – 2 represented the recent development of nanoparticles for skin treatment. Nanotechnology is the promising technique for drug delivery and contains several applications in the field of medicine in which nanoparticles have anticipated as advanced more efficacious carrier for specific and flexible drug delivery. The drug incorporated in NPs are versatile, customized, and economical. NPs are of interest for controlled release of drug that diffuse through the matrix and permeate the skin. The matrix is rigid and NPs are capable to maintain the structure for sustained release of drug when applied topically (Gupta et al., 2013).

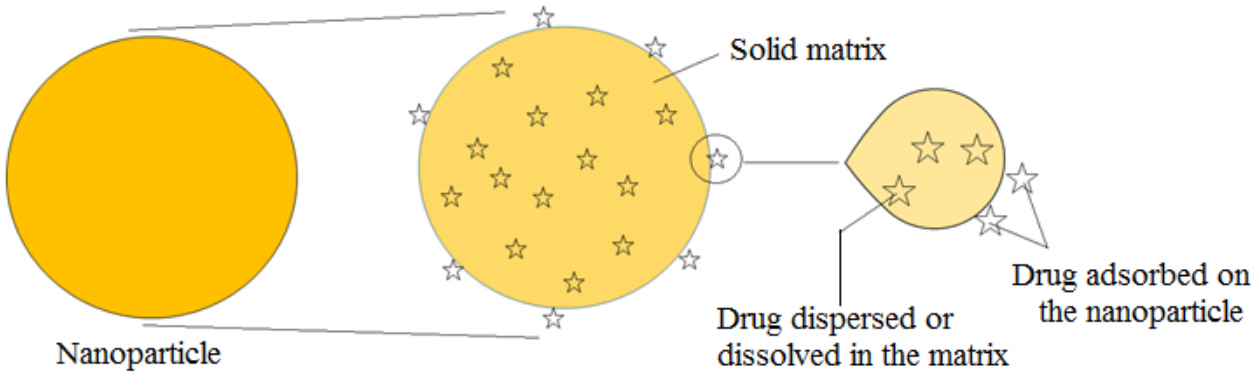

Figure – 3:Structural representation of a solid lipid nanoparticle

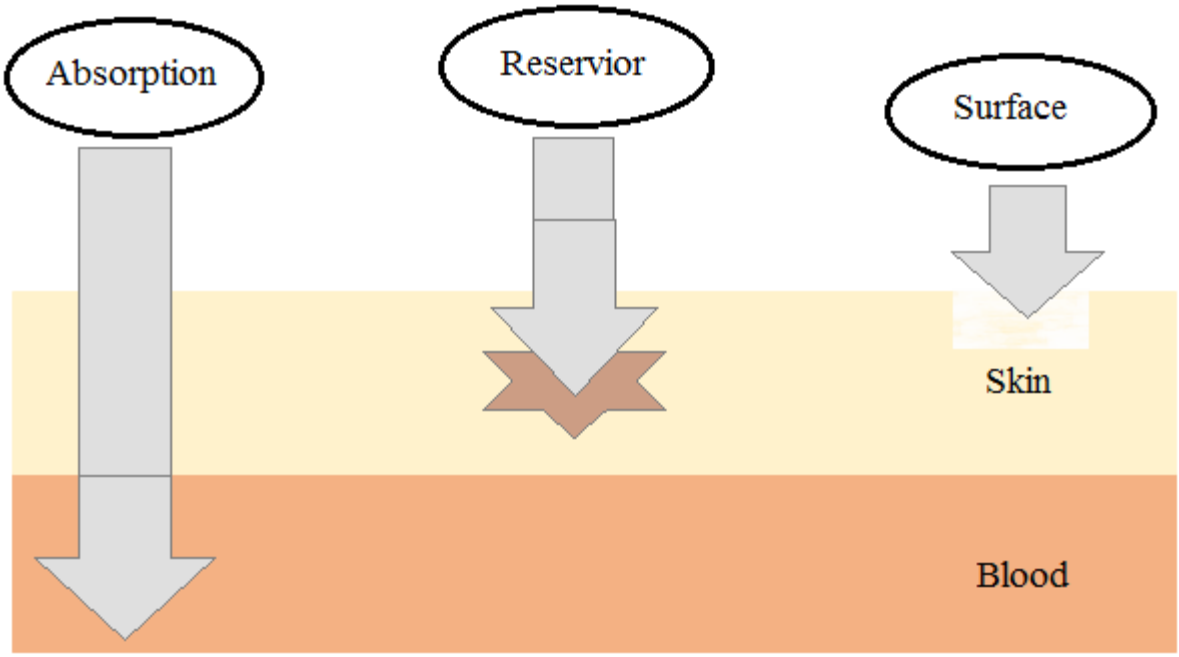

Figure – 4:Drug targeting sites for nanoparticles

Table – 2:Recent development of nanoparticles for skin treatment

S. No.	Nanoparticles	Properties	References
1	Gold nanoparticles were prepared as a non-invasive technique to detect thiols in skin.	The nanoparticle sensor was effective in detecting thiols level in the skin	Markina et al., 2017
2	Solid lipid nanoparticles loaded with resveratrol were prepared for skin dermatitis	The prepared nanoparticle gel was safe and effective in reducing irritant contact dermatitis	Shrotriya et al., 2017
3	Nanoparticles loaded with hydroxyethyl cellulose-silver were prepared for skin tissues engineering	It exhibited low toxicity and significant characteristics applications in skin tissue engineering	Zulkifli et al., 2017
4	Nanoparticles of iron oxide with tomography skin penetration were prepared	Real time image was quite clear with iron oxide nanoparticle integrated with polymeric micro needles under micro-optical coherence tomography	Seeni et al., 2017

5	Nanoparticle emulsion of polihexanide were prepared for skin penetration	Monitoring of nanoparticle for 2.5 h exhibited no bacterial growth and long lasting antiseptic activity	Ulmer et al., 2013
6	Solid lipid nanoparticle of naproxen were produced to enhanced skin permeation	The prepared NPs showed increased skin concentration of naproxen with reduced systemic absorption.	Akbari et al., 2016
7	Nanoparticles loaded with tacrolimus were prepared for the treatment of psoriasis	Liquid crystalline NPs exhibited significant increase in tacrolimus concentration in the skin against psoriasis	Thapa and Yoo, 2014
8	Nanoparticle of chitosan-5-fluorouracil were prepared along with synergistic effect of microwave to enhance skin permeation	The prepared nanoparticle showed marked skin changes for keratin and palmitic acid, however change in skin ceramide content was achieved with microwave	Nawaz and Wong, 2017
9	Nanoparticles of titanium dioxide were prepared to determine its penetration to slightly damaged skin	The prepared NPs were unable to penetrate the damaged or intact skin, thus safe while applying on skin	Xie et al., 2015
10	Nanoparticles of curcumin were prepared for the treatment of psoriasis	The penetration of curcumin loaded NPs gel was improved and significantly accumulated at normal and psoriatic skins	Sun et al., 2018
11	Dendritic core-multishell NPs of dexamethasone were prepared for skin penetration	The observation of NPs using electron paramagnetic resonance spectroscopy revealed more deeper deposition of dexamethanose	Saeidpour et al., 2017
12	Cobalt NPs were prepared for skin penetration of intact and damaged skin	*In vitro* study exhibited that cobalt NPs significantly penetrated skin and drug deposition	Larese et al., 2013

13	Silver NPs (AgNPs) were prepared for *in vitro* penetration in human and pig skin	AgNPs exhibited significant skin penetration and in comparison to emulsion vehicle. Most of the drug was retained in stratum corneum and very little was found in epidermis and dermis	Kraeling et al., 2018
14	Nanoparticles of copper oxide were prepared for topical application	The NPs did not penetrated the skin thus remained on skin surface in skin organ culture	Cohen et al., 2013
15	Chitosan nanoparticles of clobetasol proprionate were prepared for topical application	NPs gel was effective in reducing edema and use of lecithin in chitosan NPs also improved risk benefit ratio in comparison to sodium-deoxycholate gel	Şenyiğit et al., 2016

Topical delivery of drug loaded-microsponge and nanoparticle over skin

Microsponge delivery system (MDS) particularly focused on controlled release of drug on the localized area of skin surface without penetration into epidermis enter into systemic circulation. Thus, enhancing the time of drug contact to the skin for longer period of time. Microponges as vehicle maintain equilibrium with the active ingredient concentrations on the skin, as concentration depletes the vehicle release more amount of drug according to the demand of equilibrium shift (Uppadhyay et al., 2012). MDS continuously releases drug onto the skin in a steady manner. It acts as a depot to release active ingredient on the skin as shown in Figure – 5.

Lipid NPs have emerged as a successful drug delivery system for topical and transdermal applications. The nanostructured lipid carriers are more attentive for skin diseases, their delivery can be optimized by transportation pathways. NPs can be transported to the skin through one of three pathways (intracellularly, intercellularly and via dermal structures) depending upon the diseases and skin conditions as shown in Figure – 6. NPs generally follows hair follicles and intercellular routes for delivery of drugs. The intracellular delivery of drugs through corneocytes is the direct pathway via cell membranes to the epidermis. The intercellular routes are more tedious via gaps between the epidermal cells. It depends upon the size of the NPs, its morphology, charge and material. The delivery through appendageal route or dermal structure involves hair shaft, sweat

glands, sebaceous glands, or skin furrows for retention on the skin or penetration to the dermis (Palmer and DeLouise, 2016).

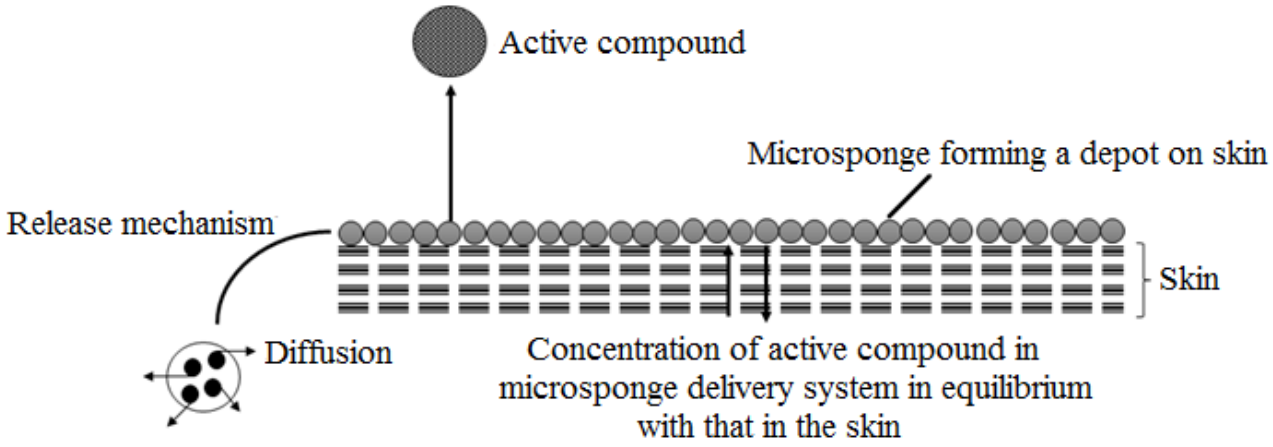

Figure – 6:Topical delivery of drug through microsponge dosage from

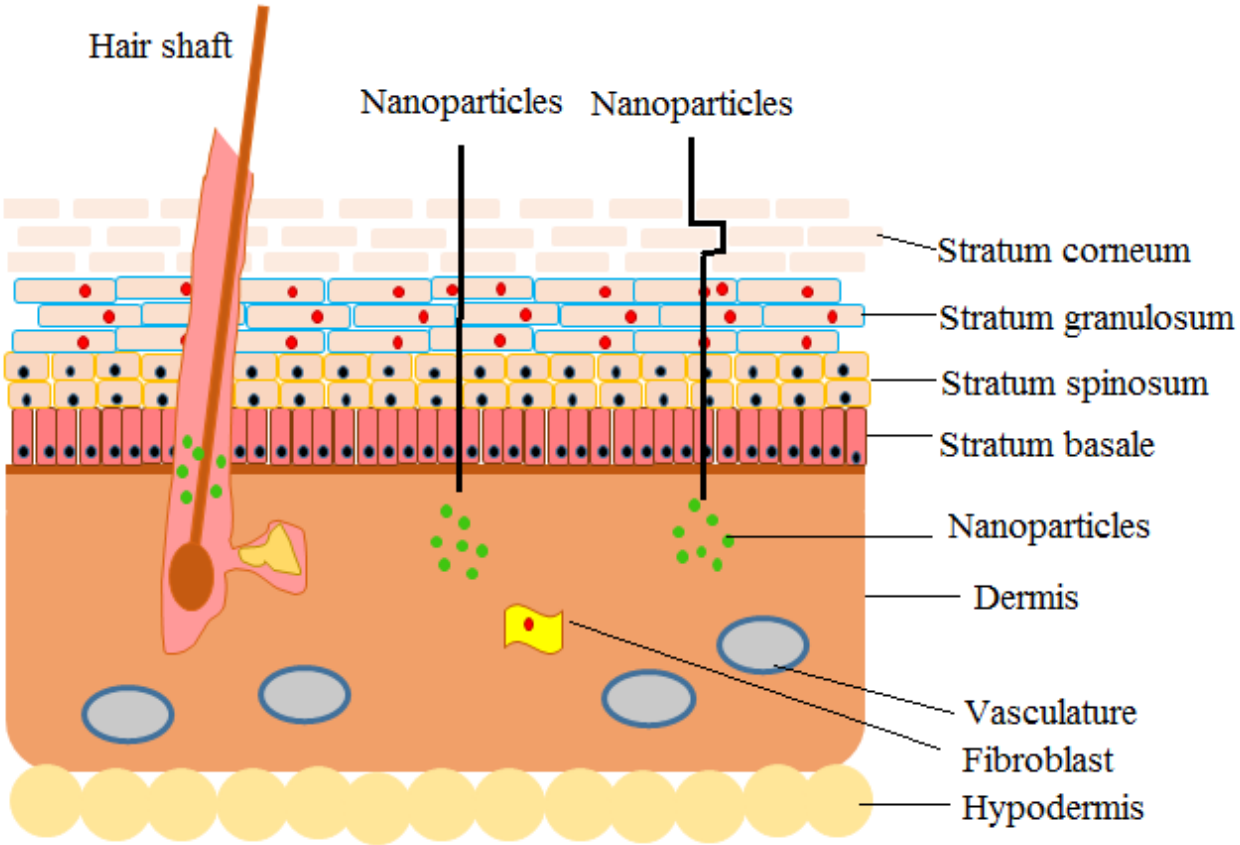

Figure – 7:Delivery of drugs through nanoparticles across skin

Conclusion

Recent advancement in understanding the pharmacological profile of drugs offer more rational approach for the development of suitable drug delivery system. An ideal drug delivery system delivers specified amount of drug to the targeted site in a particular time with the requisite amount

required by the body. However, in conventional drug delivery systems it is not possible to control rate of drug delivery to the targeted site. The non-targeted delivery of drugs in the body in an uncontrolled manner leads to undesired effects of the drugs i.e. toxic effects. Thus, NDDS plays the role of novel carrier to delivery drug in a precise manner with maintained drug concentration for a longer period of time at the desired site of the body. In the series of several novel drug delivery carriers, Microsponges and Nanoparticles are the two efficient topical drug delivery systems for skin infections. Microsponge drug delivery system is the technology allows sustained release of drug from microspheres, offers low side effects, improved stability and maintains high therapeutic effect of drug. Microsponges are frequently used in topical sunscreen lotions and creams, over-the-counter skin care products and prescription products. On the other hand, nanoparticles have yielded opportunities to address and treat several diseases. Due to the nanosize range of NPs the delivery of large amount of drug can be possible with them in a localized area. NPs are smart delivery system through size manipulation, modification of materials and surface of particles. NPs are targeted and sustained drug delivery systems that reduced drug toxicity and increase more patient compliance with less frequency of dosing.

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