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A REVIEW ON: MICROSPONGES FOR ACNE VULGARIS TRETMENT

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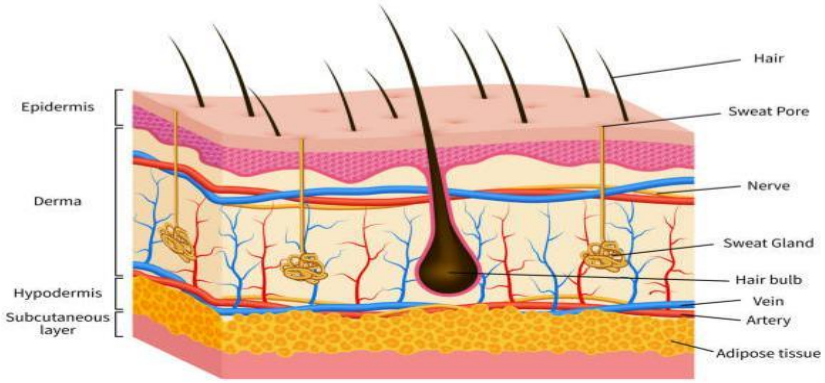
Abstract: A wide range of substances that serve as carriers can be suspended or captured by the Microsponges Delivery System (MDS), which can then be included into a designed product like a gel cream or powder. The formulation's primary goal is to get the desired medication concentration in the blood. Microsponges are a type of porous medication delivery device for small particles. They are tiny, spherical particles that resemble microscopic sponges and have a broad porous surface. In addition, they may increase stability by altering the drug's release pattern while minimizing negative effects. The serious condition impacting social life is acne vulgaris. Acne can be involved; alternation of follicular keratinization seldom causes significant systemic issues, but maturity, especially for women, which leads to drugs assist to reduce the production of sebum, which is mostly responsible for reducing the formation of acne on the skin. The use of microsponges as carriers for medications that target acne vulgaris is currently receiving more attention in research that focuses on illness detection and a brief to target acne vulgaris. Acne vulgaris is a serious condition that is currently affecting people's social lives. Increased sebum production, bacterial involvement, altered follicular keratinization, and altered follicular barrier are all characteristics of acne. Microsponge carriers is gaining access in current drug delivery. The current review is focused on the microsponges as carriers for the drug targeting the acne vulgaris, brief discussion on the present and future aspects of the microsponges to targetet acne vulgaris.

Keyword: Skin Delivery, Topical Drug Delivery, Acne Vulgaris, Microsponges

INTRODUCTION:

The skin is the biggest organ of the body, representing around 15% of the absolute grown-up body weight. It carries out numerous fundamental roles, including security against outer physical, synthetic, and biologic attackers, as well as counteraction of overabundance water misfortune from the body and a job in thermoregulation. The skin is nonstop, with the mucous films covering the body's surface. The integumentary framework is shaped by the skin and its subsidiary designs (see in figure 1).

Figure 1: Cross Section of Skin



The epidermis, dermis, and subcutaneous tissue are the three layers that make up the skin. The epidermis, which is the skin's topmost layer, is made up of a particular kind of cells called keratinocytes that produce keratin, a long, thin protein with defensive properties. Collagen, a fibrillar structural protein, makes up the dermis, the middle layer of skin. The panniculus, a subcutaneous tissue that includes tiny lobes of fat cells known as lipocytes, sits on top of the dermis. Depending on where these layers are located on the body's structure, their thickness varies greatly. For instance, the epidermis on the eyelid is the thinnest, measuring less than 0.1 millimetres, whereas the epidermis on the palms and soles of the feet is the thickest, measuring around 1.5 millimeters. The rear is where the dermis is thickest, where it is 30–40 times thicker than the epidermis that lies above it.[1]

- **Epidermis**

Varying skin types have different epidermal thicknesses. The eyelids have the thinnest layer (0.05 mm), whereas the palms and soles have the largest layer (1.5 mm). Because the epidermis lacks blood arteries, it is totally dependent on the dermis underneath it to give nutrients and remove waste by diffusion at the dermo epidermal junction. The epidermis has 5 layers, including:

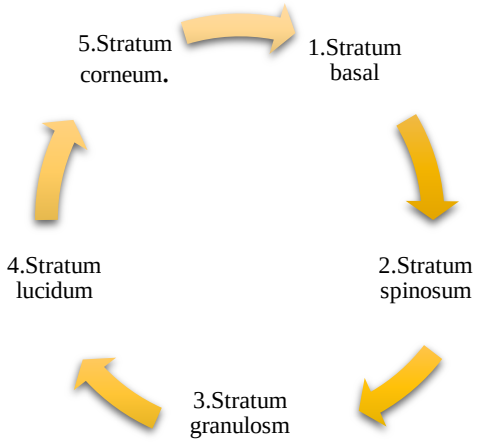


Figure 2: Epidermis Layers

The top layer of the epidermis, the stratum corneum, is made of dead, flat skin cells that shed every 2 weeks. Specialized epidermal cells: there are three types of specialized cells in the epidermis. Melanocytes produce pigment (melanin) of neural crest origin.

B. The antigen-processing Langerhans cells of bone marrow is the frontline defense of the immune system in the skin.

C. The pressure-sensing merkel's cells of neural crest origin though its function is not clearly known.

- **Dermis**

The dermis varies in thickness depending on the location of the skin. It is 0.3 mm on the eyelid and 3.0 mm on the back. Surrounding the components of the dermis is the gel-like ground substance, composed of mucopolysaccharides (primarily hyaluronic acid), chondroitin sulfates, and glycoproteins. The deep surface of the dermis is highly irregular and borders the subcutaneous layer, the panniculus adiposus, which cushions the skin.

Layers of the dermis

The two layers of the dermis are the papillary and reticular layers.

a. The upper, papillary layer contains a thin arrangement of collagen fibers.
b. The lower, reticular layer is thicker and made of thick collagen fibers, a parallel to the surface of the skin. The dermis is composed of tissues that are present throughout and not in layers like collagen which forms a mesh-like framework that gives the skin strength and flexibility and elastic tissue that gives the skin its elasticity.

Specialized Dermal Cells:

The dermis contains many specialized cells and structures.

a. The hair follicles with the erector pili muscle that attaches to each follicle.
b. Sebaceous (oil) glands and apocrine (scent) glands are associated with the follicle.
c. This layer also contains eccrine (sweat) glands, but they are not associated with hair follicles.

Blood vessels and nerves pass through this layer. The nerves transmit sensations of pain, itch, and temperature. There are also specialized nerve cells called Meissonier's and Vaterpacini Corpuscles that transmit the sensations of touch and pressure. [2,3]

❖ **Hypodermis**

A layer of fat and connective tissue containing bigger blood arteries and nerves is called the hypodermis/subcutaneous tissue. This layer controls the body's and skin's temperature. This layer's thickness varies both within and between people. The hypodermis contains specialised cells including keratinocytes, Langerhans cells, melanocytes, merkel cells, fibroblasts, sebaceous glands, and sweat glands**.**

- **Keratinocytes**: This single cell layer of keratinocytes is attached to the base membrane via hemi desmosomes. As keratinocytes divide and differentiate, they move from this deeper layer to the more superficial layers. At stratum corneum, they are fully differentiated keratinocytes devoid of nuclei and are subsequently shed in the process of epidermal turnover. In between the keratinocytes in the stratum corneum are epidermal lipids (ceramides, fatty acids, and lipids) that act as a cement between the skin cells.
- **Melanocytes**: Melanocytes, derived from neural crest cells, produces a pigment, melanin, which absorbs radiant energy from the sun and protects the skin from the harmful effects of UV radiation. Melanin accumulates in organelles termed melanosomes that are incorporated into dendrites anchoring the melanosomes to the surrounding keratinocytes. The melanosomes are transferred via phagocytosis to the adjacent keratinocytes where they remain as granules. Melanocytes are found in the basal layer of the epidermis as well as in hair follicles, the retina, veal tract, and leptomeninges. These cells are the sites of origin of melanoma.
- **Langerhans cells**: Langerhans cells originate from the bone marrow and are found in the basal, spinous, and granular layers of the epidermis. They are capable of ingesting foreign antigens, processing them into small peptide fragments, binding them with major his to compatibility complexes, and subsequently presenting them to lymphocytes for activation of the immune system.
- **Merkel cells**: Merkel cells are derived from neural crest cells and are found on the volar aspect of digits, in nail beds, on the genitalia, and in other areas of the skin. These cells are sensitive to touch.
- **Fibroblasts:** The dermis' principal cell type is the fibroblast. Procollagen and elastic fibres are created and secreted by these cells. Proteolysis enzymes cut procollagen terminally to produce collagen that aggregates and cross-links. These collagen fibers with intense cross-linking are tensile strong and resistant to shear and other mechanical stresses. In contrast to elastic fibres, which make up less than 1% of the dermis' weight,

collagen comprises about 70% of it. Elastic fibres help the skin recover its original shape by resisting deformational pressures. The pH of the moisture barrier is somewhat acidic (4.5 to 6.5) in the stratum corneum's outer layers.

The acid mantle refers to these somewhat acidic layers of the moisture barrier, and their acidity is brought on by a concoction of perspiration and sebaceous gland secretions. The keratin proteins are kept securely bonded together and kept hard by the acid mantle, which also prevents the formation of dangerous bacteria and fungus. As a result of conventional soaps' tendency to make the skin's surface alkaline, the keratin fibres become loose and brittle, losing their protective qualities and becoming more vulnerable to infection, dryness, roughness, and irritation before flaking. [4]

Origin of the skin

The prospective epidermis, which develops from a surface region of the early gastrula, and the prospective mesoderm, which comes into touch with the inner surface of the epidermis during gastrulation, come together to form the skin. In addition to producing the dermis, the mesoderm is crucial for promoting differentiation of epidermal structures, including the mammalian hair follicle. Although organized dermis is not necessary in this situation the characteristic may also be found in powdered dermis or tendon a dermal influence is necessary for the preservation of adult epidermis. Despite their tiny size, the pigment cells that make up the neural crest nevertheless significantly contribute to the skin. [5]

Functions of the skin

The skin has three main functions:

- Protection;
- Thermoregulation;
- Sensation.

Within this, it performs several important and vital physiological functions, as Outlined below;

- **Protection**

The skin acts as a protective barrier from:

- Mechanical, thermal and other physical Injury;
- Harmful agents;
- Excessive loss of moisture and protein;
- Harmful effects of UV radiation.

- **Thermoregulation**

Protecting the body from cold or heat and preserving a consistent core temperature are two of the skin's crucial jobs. Changes in the blood flow across the cutaneous vascular bed are used to achieve this. In warm weather, the skin becomes redder and sweat beads appear on the surface (vasodilatation = increased blood flow = increased direct heat loss). Vasoconstriction, which results in decreased blood flow and less heat loss, prevents heat from leaving during cold weather. Sweating from the skin's surface and its subsequent evaporation also aid in cooling the body.

- **Sensation**

The skin is the "sense-of-touch" organ that reacts when we contact or feel anything, even if it might be painful. This is crucial for people with skin conditions since, for many, the discomfort and itching may be quite severe and distressing. Touch is crucial for many patients who feel alienated due to their skin due to colour, sickness, or other people's impressions of them. Many suffer from the belief that they should not be touched because they are filthy or contagious. [6]

- To assist with vitamin D production.
- To divert blood from the skin to other areas of the body as necessary.
- To expel salts and trace quantities of waste (ammonia and urea) through perspiration.[7]

Topical drug delivery can be defined as application of drug via skin to directly treat or cure the skin disorders. When alternative routes of administration are unsuitable, local skin infections like fungal infections are typically treated using these topical drug delivery methods. It may enter the skin more deeply, improving absorption. Topical application is not superior to traditional dose forms in any way. Because of their bilayered composition and structure, they are typically thought to be more effective and less hazardous than traditional formulations. In order to maximize the local effects and limit the systemic ones, or to guarantee proper percutaneous absorption, attempts have been made to use drug carriers in the formulation of topical dosage forms that assure adequate localization or penetration of the drug within or through the skin. A topical application reduces GI discomfort and stops the liver from metabolizing the medication, increasing the medicine's bioavailability. Topical medicines are often utilized for localised effects at the application site due to medication penetration into the dermal or mucous membrane layers under the skin. Despite the possibility of some inadvertent medication absorption, it typically occurs in small doses and is of little consequence.[8]

Advantages of topical drug delivery systems

- Convenient and simple to use.
- Avoidance of the first pass metabolism.
- Avoiding the dangers and drawbacks of intravenous therapy as well as a variety of absorption situations such pH fluctuations, the presence of enzymes, and stomach emptying time.
- Simple medication discontinuation as necessary.
- Deliver drugs more precisely to a certain location.
- Steer clear of the gastrointestinal toxicity.
- Providing medicines with a limited therapeutic window and short biological half-life for use.
- Increased adherence by the patient.
- Achieving efficacy with a lower total daily dosage of medication by continuous drug intake.
- Prevents variances between and among patients as well as medication level fluctuations.
- Offer the capacity to self-medicate.
- A much larger application area than the buccal cavity.
- The capacity to administer medications more precisely to a particular location. [9]

Disadvantages of topical drug delivery systems:

- Skin irritation of dermatitis may occur due to the drug or excipients.
- Possibility of allergic reactions.
- Main limitations of micro emulsion-based gel that remains are poor absorption of micro particle via skin and entrapment of bubble during formulation.
- Some drugs of larger particle size not easy to absorb through the skin.
- Poor permeability of some drugs through skin. [10]

Routes of Administration.

Topical delivery, which often entails applying a substance directly to the skin at the target location, has certain drawbacks in that it must pass through several skin barriers, including those in the rectal, nasal, and vaginal cavities, in order to reach systemic circulation. The pace and extent of medication absorption from the delivery system increased as a result of the drug being applied directly to the mucus membrane, boosting its effectiveness.

Factors affecting topical absorption of drug

- **Physiological factors**

1. Skin thickness.

2. Lipid content.

3. Density of their follicles.

4. Density of sweat glands.

5. Skin pH.

6. Blood flow.

7. Hydration of skin.

8. Inflammation of skin.

- **Physiochemical factors**

1. Partition coefficient.

2. Molecular weight (<600dalton).

3. Degree of ionization (only unionized drugs gets absorbed well).

4. Effect of vehicles. [11]

ACNE

Acne is an inflammatory disorder of the pilosebaceous units that most frequently affects the face and trunk and presents as comedones, papulopustules, nodules, and cysts (nodulocystic acne and acne conglobata). [12] A whopping 95% of people have acne vulgaris at some point in their lives. [13] Acme, which means "the highest point" and is derived from the Greek word Akme, which means "point" or "spot," is where the term acne first appeared. In 1835, it was spelled incorrectly, with a 'n' rather than an 'm.' Acne, or acne vulgaris as it is known medically, is a skin condition that affects the oil glands at the base of hair follicles.

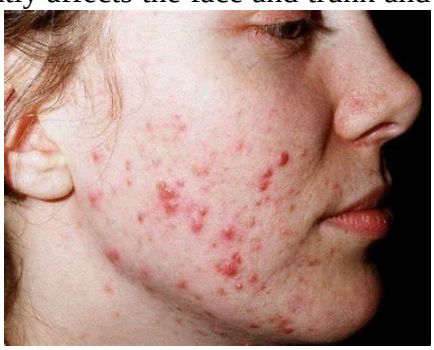


Figure 3: Acne Vulgaris Disease

These baceous (oil) glands typically develop during puberty and are driven by male hormones released by both male and female adrenal glands. Although it is not hazardous, acne can cause skin scars. The pores (tiny holes) in human skin connect to oil glands that are found beneath the skin. Through follicles or tiny channels, the glands are connected to the pores. Sebum, an oily liquid produced by these glands, is what moves dead skin cells from the follicles to the skin's surface. These follicles get clogged, causing a deposit of oil under the skin, which leads

to pimples. People typically get pimples on their face, back, chest, shoulders, and neck. When skin, sebum, and hair clump together into a clog and become infected by germs, a swelling result. When the plug starts to degrade, a pimple starts to appear. The body's defence mechanism works to eliminate the bacteria and mould in these places, resulting in the development of whiteheads, blackheads, and pustules. [14]

Epidemiology

It was estimated that 9.4% of people in the population had acne in 2010. 90% of people experience it during their adolescence and occasionally into adulthood. Moderate to severe instances affect 20% of the population. Rural places have low incidence of acne, and non-Westernized populations like Papua New Guinea and Paraguay may not have it. 9.8% of females have it, compared to 9.0% of males. About 1% of males and 5% of females among subjects over 40 have issues. It affects persons of all races, while it is unclear if race has an impact on illness rates. In the United States, acne affects 40 to 50 million individuals, or about 16% of the population, and 3 to 5 million people, or roughly. [15,16]

Etiology

Blockage of follicles, excessive keratinization, keratin plug development, and sebum production are the causes of acne (micro comedo). Sebaceous glands grow and sebum production rises as testosterone production rises. A closed comedo or an open comedo (blackhead) may develop from a microcomedone. Sebaceous glands become clogged with sebum, a naturally occurring oil, and dead skin cells, which leads to comedones. [17]

Pathogenesis of Acne Vulgaris:

The pathophysiology of acne is mostly determined by four factors: Enhanced and altered sebum production caused by androgens; follicular colonization by Propionibacterium acnes; and complicated inflammatory pathways involving both innate and acquired immunity are only a few of the factors that contribute to the development of comedones. Acne pathogenesis is also influenced by genetics (twin family history of severe acne), food (glycemic index), which includes consumption of chocolate and milk, and external factors (smoking, occlusive cosmetics, industrial exposures). Figure illustrates the pathophysiology of acne vulgaris. **[18]**

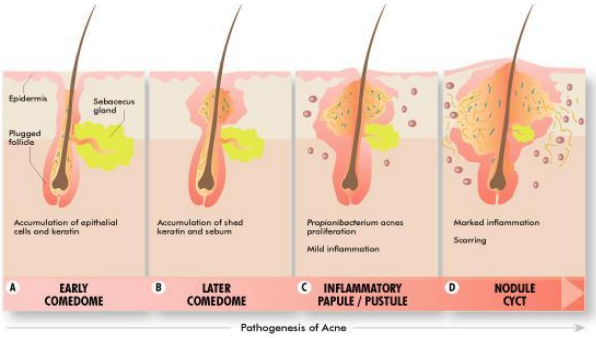


Figure 4: Pathogenesis of Acne Vulgaris

CLASSIFICATION OF ACNE VULGARIS [19]

Several classifications can be found in acne vulgaris. as:

1) Based on characteristics of acne
2) Based on the morphology of acne
3) Based on the severity of acne vulgaris
4) Based on differential diagnoses of acne vulgaris.

1) Based on the characteristics of Acne: Several types can be found out as follows:

Table 1: Classification of acne based on characteristics [20] [21]

Type of Acne	**Cause**	**Comedo Ness verity0**	**Lesions Area**
Acne Conglobata	Increasing the level of sebum production.	Multiparous comedones	Face, hand, back
Occupational Acne	Exposure to industrial chemicals.	Predominantly comedones	Forearms
Cosmetic Acne	Using cosmetics especially oil-based.	Always comedones	Chin
Drug-induced acne	Using drugs like steroids, androgens, anti-TB drugs, iodides and anti-convulsant.	Predominantly comedones	Back and Face
Infantile Acne	Presence of maternal hormone in the child.	Predominantly comedones may last for 3 years	Face
Late-onset Acne	Increase secretion of androgen, i.e., polycystic ovarian syndrome	Predominantly comedones	The lower half of the face
Acne Excoriate	Conscious, repetitive and uncontrollable desire to pick, scratch or rub acne lesions.	Predominantly comedones	Face
Post Facial massage acne	Acneiform eruption during facial massage	Few or Nocomedones	Cheeks, mandible
Acne fulminans	Fever, myalgia, and arthralgia followed the massage and hypersensitive reaction brought on by allergic cosmetics.	Predominantly comedones	Face, back, hand

2)Based on the morphology of Acne:[22]

Based on the morphology they can be classified into 3 types

- Comedonal acne -Major 2 classed Undergoes as open (blackheads) and Closed comedones (whiteheads)
- Inflammatory acne -Papules and Pustules
- Nodulocystic acne - nodules and cysts.

3)Based on the severity of Acne Vulgaris:

Table 02: Classification based on severity of Acne Vulgaris [23]

Acne Severity	**Clinical Type**	**Comedones**	**Papulesand/or Pustules**	**Nodules**	**Nodule, cysts & sinus tracts**
Mild	Comedonal acne and Papulopustular acne	Comedones are the main lesions (< 20)	Small and Few in number (<10)	None	None
Moderate	Papulopustular acne and Nodular acne	10 – 40	10 – 40	0 – 10	None
Severe	Nodulocystic acne & Conglobate acne	40 – 100 & Fused	>40	>10	Many

4)Based on the differential diagnosis of acne vulgaris: [24]

Table 03: Classification of Acne Based on Diagnosis

Disease	**Clinical findings**
Acne Rosacea	Commonly observed in middle age or later in life
Folliculitis and boils	Present with pustular lesion
Milia	Small non-follicular keratin papules

CAUSES OF ACNE:

- **Hormones**:

Teenagers' typical acne is caused by an increase in hormone production. Boys and girls both develop large amounts of androgens, or the male sex hormones, throughout puberty. The body responds to testosterone by producing more sebum, the skin's natural oil glands.

- **Bacteria**:

Bacteria can develop in hair follicles that have excess sebum blocking their openings on the face, neck, chest, and back. This leads to the development of "comedones," also known as blackheads or whiteheads, on the skin's surface. Inflammatory acne, such as pustules and papules, can sometimes result from clogging because it can push so hard on the follicle wall that it causes it to burst. Nobules are larger, tender pustules.

- **Diet**:

Consuming foods with a high glycemic index, dairy products, spicy, and oily foods increase the activity of the sebaceous glands, which causes acne. Acne can also bring on by smoking and drinking.

- **Cosmetics**:

Excessive use of cosmetics or items containing silicon clogs the pore, resulting in the development of whiteheads. When combined with sebum, dead skin cells on the skin's surface or debris create blackheads. At this point, scrubbing your face forcefully or popping a pimple makes the issue worse and might leave scars.

- **Drugs**:

Some medicines cause the skin in that area to burn over time, leaving scars. Steroids, intrauterine birth control devices (IUDs), injectable contraceptives, and oral contraceptives Acne may result from medications used by sportsmen and bodybuilders. A normally benign skin bacterium called P. acnes modifies its activity in response to this aberrant sebum, becoming more aggressive and leading to inflammation and pus development. Although acne cannot be completely treated, it may be managed with the right care.

RISK FACTORS:

a. Adolescence.
b. Hair gels or oil-based cosmetics.
c. Sports equipment such as rubbing of helmet straps.
d. Medications containing iodine, found in some cough medicines.
e. Certain prescription drugs: lithium, isoniazid, phenytoin, corticosteroids, anabolic steroids, and oral contraceptives with high androgenic activity.

Treatment of Acne vulgaris – [25]

1. By reducing bacterial colonies, bacterial inflammation can be avoided.
2. To decrease sebaceous gland activity in order to diminish sebum production activity.
3. In order to avoid the follicles being blocked
4. To lessen the scar.
5. To keep from relapsing and sustain remission
6. To avoid various physiological, social, and physical issues.
7. To get rid of the person's acne-predisposing factors
8. To provide appropriate medical care and assistance for social health.
9. A decrease in hyper keratinization.
10. Restore the hormone equilibrium.

Table 04: Current treatment of Acne vulgaris [26] [27]

Route of Administration	**Drug or Dosage form**	**Treatment features**
Oral	Tetracycline, Doxycycline, Minocycline, Isotretinoin (13- cis-retinoicacid)	Drugs should be taken daily, high patient compliance, Adverse effects limit the use of the drugs
Topical	Benzoyl peroxide, Clindamycin, Erythromycin, Tetracycline, Tretinoin, Tazarotene, Green tea extracts	Local administration of drugs, Ease of termination of drug action, Adverse effects limit the use of the drugs
Particle based DDS	Liposomes, Solid lipid nanoparticles, Nanostructured lipid carriers, Microemulsions	Sustained release of drugs, more effective than topical gel, the higher flux of drug across the skin, Effective for follicular targeting
Light-based therapy	Endogenous porphyrins (Coproporphyrin III), 5- amino-Levulinicacid	Fewer adverse effects than systemic/topical administration and Drug delivery system, Light therapy alone or along with liposomal drugs reported, not a first-line therapy for acnevulgaris

Complications [28]

- Scars
- Depression
- Anxiety
- Social Withdrawal
- Unattractive Facial Features
- Low Self-Esteem

Microsponge drug delivery for Acne vulgaris [29]

Because of their high entrapment efficiency, high stability rate, high bioavailability, precise flexibility, and capacity to prevent excessive accumulation in the dermis and epidermis, microsponge are the ideal carrier for acne vulgaris. The optimal product, including face shine and greasy shine, may be provided using this cutting-edge delivery technique. By lowering the face sebum buildup compared to control, microsponge medication delivery has demonstrated clinically superior effectiveness and tolerability in the treatment of acne.

Microsponges' delivery system

A patented polymeric sponge with porous, spherical particles, and a high drug content system makes up the delivery method for microsponges. [30,31] They are made up of several interconnected vacuums that are housed in a non-collapsible framework with a sizable porous surface that allows the regulated release of active substances. It has a diameter that varies from 5 to 300 m, and a typical 25 m sphere can have up to 2,50,000 pores (Fig. 1) and an internal pore structure that is an alternative to 10 ft in length, providing a total pore volume of about 1 ml/g for widespread drug retention and pore volumes that range from 0.1 to 0.3 cm3/g. [32, 33] They can be included into conventional dosage forms such as Creams, Lotions, Gels, Ointments, Tablets and Powders, a broad package of benefits and thus produce formulation flexibility. [34, 35]

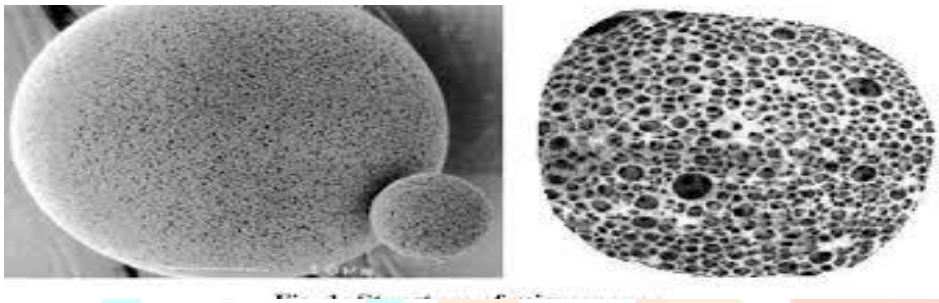


Figure 5: Structure of microsponge

History of Microsponge [36]

The first patents for the microsponge technique were given to advanced polymer systems, inc. by won in 1987. This corporation created several variants of the technology and used them for cosmetic, over-the-counter, and prescription drug items. Currently, Cardinal Health, Inc. holds a licence to exploit this intriguing technology in topical products. When microsponges are applied to the skin, their bioactive ingredient gradually releases on the skin over a predefined period of time in response to stimuli such as rubbing, temperature, or pH.

Characteristics Of Microsponges [37, 38,39]

a. Most vehicles and substances are suitable with microsponge formulations
b. Microsponge formulations are self-sterilizing since bacteria cannot pass through their 0.25 mm average pore size.
c. Microsponge formulations can be economical and have a greater payload (50 to 60%). They are also still free-flowing.

Advantages of microsponge based delivery systems

1. Product stability and shelf life can be increased without the use of preservatives since bacteria are too big to fit within the microsponge. [40]

2. Microsponges have a high internal surface area due to their highly segmented structure; as a result, they have a high pay loading capacity.

3. Unwanted qualities including oiliness and tackiness, as well as an unpleasant smell or feel, can be significantly decreased, making substances appropriate for topical application to skin. [41]

4. The ability to convert liquids into powder that flows freely improves material handling. [41]

5. Microsponges enhance the formulation's elegance. [42]

6. MDS improve the effectiveness of topical medicines and allow for their prolonged release. [43]

7. Microsponges have a wide porous surface and are made of interconnected spaces inside a non-collapsible framework. [44]

8. Stable up to 130 °C and across a broad pH range of 1 to 11.

Ideal Properties of MDS [45]

1. The Microsponges' structure should not disintegrate, i.e., it should keep its structural integrity.

2. It should have a somewhat water-soluble quality.

3. It must maintain its stability while in contact with the polymerization catalyst and when polymerization is occurring.

4. It shouldn't react with the formulation's monomer.

5. During formulation, MDS shouldn't make the mixture more viscous.

6. Microsponges with particle sizes between 10 and 25 m**.**

Suitability of Drug to Dosage Form [46]

1. Skin disorders including ringworm, athlete's foot, candidiasis (yeast infection), sporotrichosis, and viral infections like varicella zoster (chicken pox), herpes simplex virus, and cytomegalovirus are treated with MDS (Epstein bar virus).

2. MDS distributes API in a sustained manner over a long length of time, making it suited for anti-inflammatory drugs.

3. The molecular weight of the API should be very low, or 600 g/mole, so that it may readily penetrate.

4. The t1/2 of the medicine should be less than or equal to 5 hours, which is appropriate for the drug's prolonged effect.

Therapeutically agents utilized for microsponges Approaches [47,48,49]

Skin secretions can be absorbed by microsponges. lowering skin shine and oiliness as a result. These particles, which are incredibly small, inert, and indestructible spheres, cannot penetrate the skin, but they cluster in the tiny crevices of the skin and gradually release the medicine that has been trapped there. Additionally, these formulas can stop an excessive buildup of components in the skin's interior.

Figure 6: Drug Enclosed in microsponges delivery System.

They considerably reduce medication irritability without compromising effectiveness. Retinol, (vitamin A), Fluconazole, (Anti-fungal), Paracetamol (NSAID), Trolamine (Analgesic), Miconazole (Anti-fungal), Lornoxicam (NSAID), Curcumin (anti-Inflammatory) etc.

Formulation Consideration [50]

Limiting the amount of active that can dissolve in the vehicle in order to prevent aesthetic issues, the vehicle will exhaust the microsponges before application. The number of microsponges in the vehicle must not exceed 10 to 12% weight. The microsponges polymer composition and payload must be tuned for the desired release rate throughout the specified period.

Microsponges Advantages over conventional formulations [51]

Traditional topical formulations are only meant to treat localized conditions like cuts, wounds, bleeding on the skin's surface, etc. Because of their quick penetration into the skin and ineffective results, these products have high API Concentrations. By preventing an excessive buildup of components in the epidermis and dermis, microsponges, in comparison to standard formulations, require a significantly lower quantity of API to exert the necessary therapeutic activity. Additionally, Microsponges considerably lessen adverse effects brought on by API buildup on the skin's surface, enhancing patient safety and compliance. It necessitates extra vehicle in the formulation due to uncontrolled API evaporation in many topical preparations and a possible incompatibility.

METHOD OF PREPARATION OF MICROSPONGES:

According to the liquid-liquid suspension polymerization and quasi emulsion solvent diffusion procedures, which are based on the physicochemical parameters of the drug to be loaded, drug loading in microsponges can be done in one step or two steps.

- **Liquid-liquid suspension polymerization** [52,53]

This liquid-liquid suspension polymerization method creates porous microspheres using the liquid-liquid suspension polymerization process. The monomers are prepared by first dissolving them with the active components in a suitable monomer solvent solution, and then dispersing them in an aqueous phase that contains additives (surfactant, suspending agents, etc.) Then, the catalyst is added, the temperature is raised, or irradiation is used to start the polymerization. The various steps involve in the preparation of microsponges are summarized as:

- Selection of monomer or combination of monomers
- Formation of chain monomers as polymerization begins.
- Formations of ladders as a result of cross linking between chain monomers
- Folding of monomer ladder to form spherical particles agglomeration of microspheres, which give rise to formation of bunches of microspheres. Binding of bunches to form microsponges.

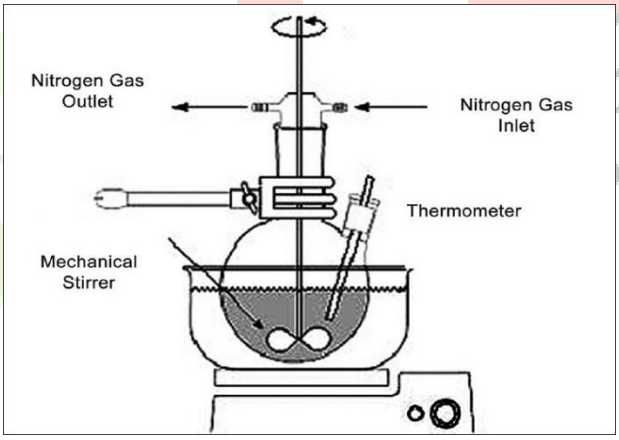


Figure 7: Reaction vessel for microsponge preparation by liquid-liquid suspension polymerization

- **Quasi-emulsion solvent diffusion**

The preparation of the microsponges using the quasi-emulsion solvent diffusion technique in this two-step procedure uses various polymer concentrations. Eudragit RS 100 was dissolved in ethyl alcohol to create the inner phase. The medicine may then be dissolved in the solution by ultrasonically agitating it at 35°C. The water-based PVA solution was then filled with the inner phase (outer phase). The mixture is filtered to separate the microsponges after 60 minutes of stirring. The microsponges are dried for 12 hours at 40 degrees Celsius in an air-heated oven, then weighed to estimate the manufacturing output (PY). [54,55]

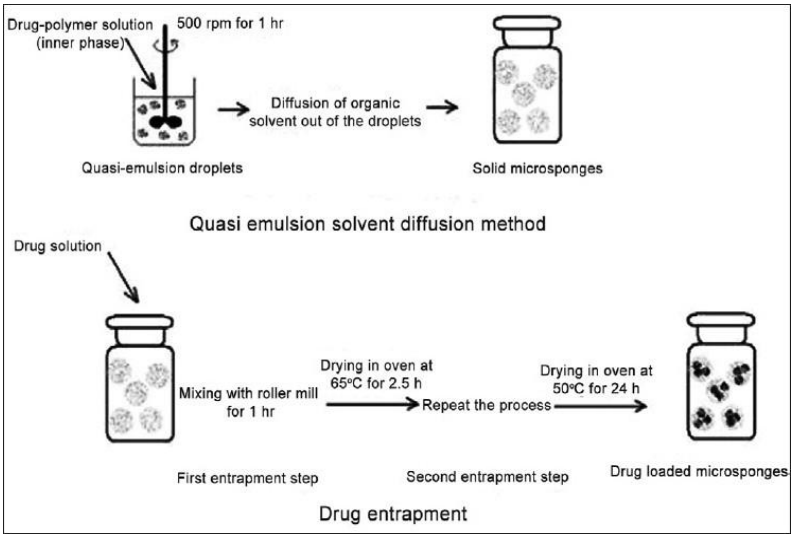


Figure 8: Method of quasi-emulsion solvent diffusion

Table 05: Optimum Values for Microsponge Formulation: [56,57]

Sr. No	Specification	Optimum value
1.	Drug and polymer ratio	1:1, 1:2, 1:3, 2:1, 3:1
2.	Amount of drug (mg)	100 – 300
3.	Polyvinyl alcohol(mg)	100
4.	Inner phase solvent (ml)	Ethyl alcohol
5.	Amount of inner phase solvent	10
6.	Amount of water in outer phase (ml)	100
7.	Temperature of inner phase	25°C
8.	Types of process	Magnetic stirrer &Bath sonicater
9.	Magnetic stirrer speed	100 rpm

- **Oil in oil emulsion solvent diffusion**

The emulsion was created using this procedure because the interior phase is made up of a volatile organic liquid. Dichloromethane is employed as the volatile solvent in the majority of preparations. And polyactide glycolic acid, span 85, is the polymer employed in this. To create the microsponge, the internal phase was gradually introduced to the dispersion medium while being constantly stirred. [58,59]

- **Addition of porogen**

For this, a porogen like hydrogen peroxide or sodium bicarbonate makes up the interior phase. A uniform dispersion system containing the porogen was created in the polymeric solution by dispersing it, and this system was then redispersed in an aqueous phase containing PVA. When hydrogen peroxide is added, interconnecting pores with sizes ranging from 5 to 20 m are created.[60]

- **Lyophilization**

By quickly removing the solvent, the microspheres are transformed into porous microspheres in this process. Utilizing chitosan hydrochloride solution is how it is done. After being incubated in this solution, the microspheres are lyophilized. Due to the fast elimination of the solvent, microparticles may break and/or shrink.[61]

Vibrating orifice aerosol generator method

The synthesis of lipid bilayer mesoporous silica particles was mostly accomplished using the vibrating orifice aerosol generator technique. Tetraethyl orthosilicate, ethanol, water, and diluted hydrochloric acid were refluxed to create the stock solution, which forms the core particle. And after being diluted with a solvent that included a surfactant, the solution started to form monodisperse droplets. The liposomes contain the created microspheres. These are the few techniques documented for the production of microsponge in. [62] The majority of microsponges are made via quasi emulsion solvent diffusion, which has the fewest drawbacks for the finished product compared to the other ways. Each of the aforementioned approaches has a unique method of preparation.

Hypothetical Mechanism of Action: [63]

Due to the active ingredient's low solubility, the vehicle is added to The microsponges are porous in nature and only partially soluble (they lack a continuous membrane). The active component can freely flow between the particles and the vehicle until equilibrium is reached, at which point the vehicle becomes saturated. Due to this, the active that is already in the vehicle will be absorbed into the skin when the Formulated Microsponges are applied to the skin. Due of the vehicle's ability to deliver the first dosage and then maintain release. When the microsponges are introduced to the vehicle, it stops the medication from leaching out when the vehicle is first treated with the medicine. In the end, the rate of active release will be affected by both the concentration gradient between the vehicle and the polymers as well as the partition coefficient of the active component.

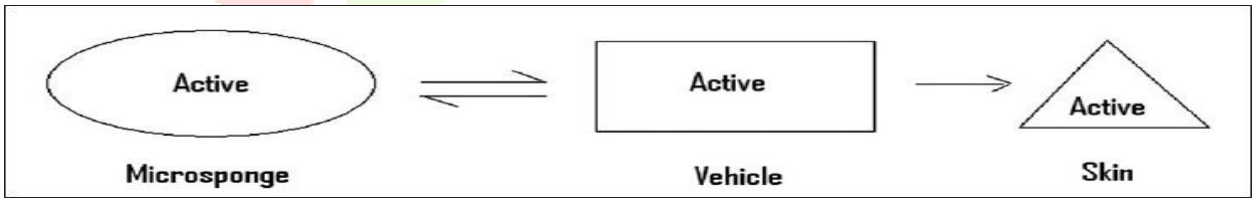


Figure 9: Hypothetical Mechanism

DRUG RELEASE MECHANISMS: [64]

In order to build microsponge delivery systems that release functional substances over time in response to one or more external stimuli, these programmable parameters can be efficiently regulated. The following are the key release methods of this system:

1. **Sustained or Timed Release**

   While pore diameter, volume, and resiliency of the polymer microsponges are assessed for the polymer microsponges to provide the required sustained release effects, various physical and chemical parameters of the entrained active ingredients such as volatility, viscosity, and solubility will be investigated in the development of sustained-release microsponges.

2. **Release on Command**:

   In response to outside stimuli, microsponges can be made to release the specified amounts of active ingredients gradually.

a. **Pressure Release:** When pushed or squeezed, the microsponge system releases the active ingredient, replenishing the amount of entrapped active ingredient on the skin. The stability of the microsponges and the release of the sponge can both affect how much material is discharged**.**

b. **Temperature Release:** Depending on the temperature, the microsponges' ability to release their active components can be triggered. In certain cases, thick active substances that linger a bit at room temperature prevent a rapid passage from the Microsponge to the skin. The flow rate increases and the release also improves when the skin's warmth rises.

c. **pH Release:** By altering the coating of the microsponge, it is possible to facilitate the release of the pH-based active ingredient.

d. Solubility:

Antiseptics and deodorants that are water-soluble, like microsponges, release their contents when there is water present. Diffusion, while taking into account the Material's distribution coefficient between the microsponge and the external system, can also activate the discharge.

EVALUATION OF MICROSPONGES

- **Particle size determination**

By regulating the size of the particles during polymerization, it is possible to produce free-flowing powders with delicate aesthetic characteristics. Laser light diffractometry or any other appropriate technique can be used to analyze the particle size of a loaded and unloaded microsponge. All formulations allow for the expression of the values (d 50). in terms of size range. To explore the impact of particle size on drug release, the cumulative percentage of drug released from microsponges of various particle sizes will be plotted versus time. Particles between 10 and 25 m in size are preferred for use in the final topical formulation because particles larger than 30 m can cause a gritty feeling. [65]

- **Morphology and surface topography of Microsponges**

Prepared microsponges can be coated with gold-palladium under an argon atmosphere at room temperature for morphology and surface topography, and then the surface morphology of the microsponges can be examined by scanning electron microscopy (SEM). The Ultra structure of a fractured microsponge particle can also be seen in the SEM image. [66]

- **Determination of loading efficiency and Production yield**

The following equation may be used to determine the loading efficiency (%) of the Microsponges: By precisely calculating the initial weight of the raw materials and the final weight of the obtained microsponge, it is possible to determine the production yield of the microparticles. [66]

- **Determination of true density**

Utilizing an ultra-pycnometer and helium gas, the real density of microparticles and benzoyl peroxide (BPO) was determined by averaging out many measurements**.**

- **Polymer/ monomer composition**

The features of the active substance that will eventually be trapped and the medium in which it will be spread influence the choice of monomer. To enable flexibility in the release of active substances, polymers with different electrical charges or levels of hydrophobicity or lipophilicity may be created. By examining their drug release profile, several monomer combinations will be evaluated for their compatibility with the medications.

- **Compatibility studies**

Through the use of thin layer chromatography (TLC) and Fourier Transform Infrared spectroscopy, the compatibility of a medicine with reaction adjuncts may be investigated (FT-IR). Powder X-ray diffraction (XRD) and differential scanning colorimetry can be used to investigate the impact of polymerization on the crystallinity of the medication (DSC). For DSC, samples can be precisely weighed into aluminum pans, sealed, and heated at a rate of 15 oC/min throughout a temperature range of 25-430 ºC in nitrogen atmosphere. [67]

The features of the active substance that will eventually be trapped and the medium in which it will be spread influence the choice of monomer. To enable flexibility in the release of active substances, polymers with different electrical charges or levels of hydrophobicity or lipophilicity may be created. By examining their drug release profile, several monomer combinations will be evaluated for their compatibility with the medications.

- **Drug Release**

Utilizing a customised basket made of 5 m stainless steel mesh and the dissolution apparatus USP XXIII, one may examine the dissolution profile of microsponges. 150 rpm is the rotational speed. To achieve sink conditions, the dissolving medium is chosen while taking the solubility of the actives into account. Samples from the dissolving media can be examined at different intervals using an appropriate analytical technique.[68]

- **Resiliency**

According to the demands of the final formulation, microsponges' resilience (viscoelastic characteristics) can be modified to generate bead lets that are either easier to work with or stiffer. Increased cross-linking tends to reduce the rate of medication release. In order to have the best concentration of medicine at the location, the resilience of microsponges is therefore researched and modified according to needs and by taking release into account. Depending on how crosslinking changes over time. [69]

- **Characterization of pore structure**

Pore volume and diameter play a dynamic role in controlling the active ingredient's concentration and duration of activity. The movement of active Ingredients from microsponges into the vehicle is also influenced by pore diameter. The pore width of the microsponges can influence the rate of drug release from them. Numerous porosity metrics of microsponges are being investigated, including total pore surface area, incursion extrusion isotherms, pore size distribution, average pore size diameters, form and morphology of the pores, bulk, and apparent density.[70]

- **Determination of pore diameter**

The pore diameter is determined by B.E.T. nitrogen multipoint analysis and from the measurement of the pore volume using the mercury intrusion method, which is the traditional way of measuring and expressing pore sizes. [71]

APPLICATIONS OF MICROSPONGES:

Topical prescription, over-the-counter, and personal care products can be made safer, more effective, and more aesthetically pleasing by using microsponge delivery methods. There are several applications for microsponges. It is usually used topically; however oral usage has increased recently. Due to its high loading capacity and prolonged release capability, it has been reported in several patents that it may be used as an excipient. It provides the formulator with several alternatives for creating pharmaceutical and cosmetic goods. Microsponges are

created to effectively administer a pharmaceutical active component at the lowest amount possible, as well as to improve stability, lessen adverse effects, and alter drug release. Numerous moisturizers, specialist rejuvenation products, and sunscreens are examples of over-the-counter products that use the microsponge medication delivery method. [72]

- **Microsponge for topical delivery**

The foundation of the microsponge systems is a tiny, polymer-based microsphere that may bind, suspend, or entrap a wide range of substances. The microspheres are then added to a designed product, such a gel, cream, liquid, or powder, to get the desired result. A single microsponge has a diameter of less than one thousandth of an inch and is as small as a talcum powder particle. Each microsphere, like a real sponge, is made up of many interconnected gaps inside a non-collapsible structure that can take in a variety of chemicals. Typically, the outer surface is porous, allowing for the regulated flow of materials into and out of the sphere. To create spheres that are customised for certain product applications, a number of the microsponge system's key properties, or parameters, may be specified throughout the production process. The polymerase has been shown to be non-irritating, non-mutagenic, non-allergenic, non-toxic, and non-biodegradable in extensive safety investigations. The result is that they cannot be broken down or converted into other compounds by the human body. Even though they are minute, these systems, when included in topical medicines, are too big to pass through the stratum corneum. Skin irritation is a frequent adverse effect of benzoyl peroxide (BPO), which is frequently used in topical formulations for the treatment of acne. It has been demonstrated that BPO delivered using a delivery device with controlled release may lessen negative effects while increasing percutaneous absorption. Consequently, an organic internal phase comprising benzoyl peroxide, ethyl cellulose, and water was added to an emulsion solvent diffusion approach to provide microsponge delivery of benzoyl peroxide. [73,74].

- **Microsponge for oral delivery**

By trapping ineffectively water-soluble pharmaceuticals in the pores of the microsponge system, it has been demonstrated that the microsponge system speeds up the rate of solubilization of such medications in oral applications. As a result of the medication being effectively reduced to microscopic particles due to the tiny size of these holes, the rate of solubilization is significantly accelerated by the large increase in surface area. By adjusting the intra particle density of an acrylic polymer called Eudragit RS, one may regulate the oral distribution of ibuprofen microsponges. Using powder-coated microsponges and the dry impact mixing process, a sustained release formulation of chlorpheniramine maleate is created for oral medication administration. After creating controlled oral ketoprofen administration using the quasi-emulsion solvent diffusion technique with Eudragit RS 100, direct compression tablets for microsponges were created. Results showed that, as a result of the plastic deformation of the sponge-like microsponge structure, product in gramme mechanically strong tablets, compressibility was much enhanced. A commercial microsponge 5640 device was used to administer flurbiprofen to the colon in a controlled, targeted manner. According to in vitro studies, the addition of the enzyme caused

compression-coated colon-specific tablet formulations to begin releasing the drug at the eighth hour, which corresponds to the time the proximal colon arrived, in a modified release pattern. In contrast, the drug release from colon-specific formulations made by pore-plugging microsponges increased at the eighth hour, which was the time the enzyme addition was made. [73,74]

- **Microsponge for Bone and Tissue Engineering Bone-substitute**

Pre-polymerized polymethyl methacrylate and liquid methyl methacrylate monomer powders were combined with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyapatite powders to create compounds. The final composites served as microsponges and seemed to be porous. Basic fibroblast growth factor (bFGF), which was included in a collagen sponge sheet, was sustainedly released in the mouse sub-cutis in response to the sponge matrix's biodegradation and displayed local angiogenic activity in a dose-dependent manner. The blood flow in the ischemic hind limb of a mouse was significantly increased after the injection of collagen microsponges containing bFGF, which was not possible with a bolus administration of bFGF. These findings point to the importance and therapeutic value of type I collagen as a bFGF reservoir. [73, 74]

- **Cosmetic technology**

Intriguing applications of microsponge technology may be found in oral cosmetics, such as prolonging the release of volatile compounds to lengthen the duration of the "fresh sensation." Such flammable compounds, such as MDS, can easily include into mouthwashes or dental pastes. MDS can be used to increase the shelf life of a variety of colored cosmetic products by trapping the colour in the microsponges, such as rouge or lipsticks. MDS increases the covering power and helps to break down homogeneity. Consequently, the MDS-produced colourful cosmetics will be very wonderful.[75]

Marketed Formulations of Microsponge: The detail of marketed formulation of microsponge as manufactured by several pharmaceutical companies is enlisted in table.

Table 6: Marketed formulations based on microsponge drug delivery system [76-77]

Name of product	Treatment	Manufacturer
Glycolic Acid Moisturizer w/SPF 15	Anti-wrinkles, soothing	AMCOL Health &Beauty Solution
Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc
Line eliminator dual retinol facial treatment	Anti-wrinkle	Avon
Retinol 15 Night cream	Anti-wrinkle	Sothys
Retinol cream	Helps maintain healthy skin	Bio medic
Epi Quin Micro	Hyper pigmentation	Skin Medica Inc.
Sports cream RS and XS	Anti-inflammatory Embil	Pharmaceutical Co. Ltd.
Salicylic Peel 20	Excellent exfoliation	Biophora
Oil free matte block SPF 20	Sunscreen	Dermalogica
Lactrex™ 12 % Moisturizing Cream	Moisturizer	SDR Pharmaceuticals, Inc
Dermalogica Oil Control Lotion	Skin protectant	John and Ginger Dermalogica Skin
Ultra-guard	Protects baby's skin	Scott Paper Company
Carac Cream, 0.5 %	Treatment of actinic keratoses	Dermik Laboratories, Inc.

FUTURE PROSPECTS

Since it has special qualities like improved product performance and elegance, extended release, improved drug Release profile, reduced irritation, and improved physical, chemical, and thermal stability that make it flexible to develop novel Product forms, microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future. The creation of a delivery method for oral peptide administration using different ratios of polymers will be the main challenge in the future. The safe distribution of the Active material is made possible by the use of bio erodible and biodegradable polymers for medication delivery. As these porous structures have also been explored for drug delivery via the pulmonary route, it is clear that they are capable of releasing drugs effectively even in the absence of dissolving fluid, making the colon a good target for drug release. Additionally, these carriers must be created for other drug delivery methods such parenteral and pulmonary. These particles can be utilized for stem cell culture and cellular regeneration in the body since they can also be used as the medium for cell culture. These carrier systems have been used in cosmetics

because of how elegant they are. These changes made it possible for researchers to use them in other ways. These formulation innovations also provide new opportunities for medication delivery.[78]

CONCULSION:

Dermatologists and cosmetic chemists aim to develop new technologies and specialized commodities. New cosmetic and dermatological formulations can be created with a greater understanding of skin physiology and knowledge of its structure and function. The pharmaceutical formulator has to have a thorough grasp of the physicochemical characteristics of the drugs and polymers used in order to perform this unique approach of drug administration effectively. The medicine's topical active period is extended by microsponges capacity to extend the drug's stay in the skin and allow prolonged drug release for up to 12 hours. These traits support the idea that MDS might serve as a platform for a new generation of dermatological and cosmetic procedures. To completely comprehend the extent of drug distribution in the stratum corneum, epidermis, and dermis layers of skin as well as the mechanism of drug penetration, all of which are still in their infancy, further study is, however, necessary. Due to the unique characteristics of the microsponge drug delivery system, including greater product functionality and elegance, longer release, improved drug release profile, and decreased toxicity, a variety of pharmaceutical applications in the near future might provide a possible possibility.

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