# Nutraceutical-loaded nanosponges are transforming the treatment of psoriasis: a versatile and focused method for reducing psoriatic skin lesions

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## Abstract

Millions of people worldwide suffer with psoriasis, a chronic inflammatory skin condition characterized by red, itchy, and scaly skin plaques. Despite the availability of various treatment options, there remains a need for more effective and safer therapies. Nanosponges, a new class of polymeric nanoparticles, have emerged as a potential breakthrough in treating psoriasis by specifically targeting the inflammatory cytokines responsible for driving the disease. To enhance the therapeutic potential of nanosponges, the integration of nutraceuticals has garnered attention. Nutraceuticals, or bioactive compounds derived from plants or dietary supplements, are more than simply food; they provide health advantages as well. By incorporating nutraceuticals within nanosponges, their synergistic effects can be harnessed to further alleviate psoriasis symptoms. However, the utilization of nano nutraceuticals within nanosponges presents certain challenges. Achieving optimal loading and controlled release of nutraceuticals, ensuring their stability, and determining appropriate dosing strategies are areas that require further investigation. Additionally, the selection of specific nutraceuticals must be guided by their proven efficacy in ameliorating psoriasis symptoms. Despite these challenges, nanosponges hold significant potential to revolutionize the treatment of psoriasis. Therefore, continued research in this area could lead to the development of a new generation of safe, effective, and targeted treatments for psoriasis.

**Keywords:** Psoriasis, Nanosponge, Nanotechnology, Preclinical study

1. **Overview:**

Psoriasis (PSO) is a prevalent chronic dermatological condition that may impact individuals of various ages, genders, and ethnic backgrounds. Due to the hereditary component of psoriasis, those with a familial history of the condition are at an increased risk of developing it themselves. A scientific study has associated the development of the disease with many genes responsible for skin cell production and immune system regulation. Psoriasis is a complex condition since several variables may either induce or aggravate its symptoms. These include stress, infections, and dermal lesions. Numerous drugs have been linked to the initiation and worsening of psoriasis. The most prominent causes of PSO include beta-blockers, lithium, tetracyclines, antimalarial pharmaceuticals, and non-steroidal anti-inflammatory medicines. Identifying and addressing these triggers may assist in managing the condition. Around the world, 2 to 3 percent of individuals have PSO, and 30 percent of those who have psoriasis go on to develop psoriatic arthritis. The illness commonly initially arises between the ages of 15 and 25, however it may develop at any age. The chronic inflammatory skin disorder psoriasis affects around 2% of the global population. Growing data in recent times has shown the long-standing association between psoriasis and mental disorders. Psoriasis is a skin disorder characterized by the creation of new blood vessels, poor epidermal differentiation, thick inflammatory cell infiltrates, altered lymphatic flow, and widespread cell proliferation[1, 2].

Psoriasis is a substantial risk factor for a wide variety of disorders, including type 2 diabetes[1], cardiovascular disease, and dyslipidemia, among others. Other common symptoms include arthritic pain, severe depression, and restless legs syndrome. Psoriasis can show up anywhere on the body, but the extensor surfaces of the limbs (like the elbows and knees), the scalp, and the lower back are the most common places to find it. The nails can also be affected by psoriasis. Although psoriasis can appear in anyone at any time, it is most common in those between the ages of 15 and 22 [2]. Psoriasis is more likely to appear in females slightly earlier than it does in males, and a woman's family history can also play a significant influence in the disease appearing at a younger age. The condition may only last a few weeks, but it could also go into remission and stay throughout life. There are currently more than 125 million cases of this disease reported all over the world [3]. Even though this illness does not directly cause death, it does reduce the patient's overall quality of life. Additionally, it causes psychological stress, and in some circumstances, people might attempt suicide as a result of it. Psoriasis is a complicated cause, although autoimmune elements are believed to play a significant part in its development along with persistent exposure to UV radiation and other environmental stress factors causes ROS-mediated oxidative stress, which in turn exacerbates psoriasis [4]. As a direct consequence of this, the skin's integrated defense mechanism is rendered ineffective.

NICE in the United Kingdom has issued guidelines that provide an overview of the many treatment options available to people with psoriasis [5]. Treatments such as phototherapy, topical therapy, and systemic treatment are among these alternatives. An improvement in PASI of at least 75 percent or 90 percent (referred to as PASI75 or PASI90) is one of the targets for treatment[6]. This correlates to an absolute PASI score of <4 or <2 depending on which target is fulfilled. First-line treatments include topically applied medications such as vitamin D analogs (calcipotriol) or corticosteroids[7]. Occlusion or combination therapies, such as calcipotriol and betamethasone, are two methods that can be used to boost the effectiveness of topical treatments. Because they discolor the skin and irritate, preparations containing dithranol

and tar are no longer widely used[8]. The second line of therapy consists of traditional systemic medications and phototherapy (psoralen and UVA radiation, also known as NB-UVB and PUVA, respectively). Because of the correlation between prolonged exposure to PUVA and an increased risk of skin cancer, NB-UVB has largely supplanted PUVA [9]. Methotrexate is effective because it inhibits lymphocytes through a variety of mechanisms, including the inhibition of dihydrofolate reductase, the blockage of aminoimidazole carboxamide ribotidetransformylase (AICARTase), and the build-up of adenosine. The suppression of bone marrow activity is the most important unfavorable effect that it has along with nausea, pneumonitis, hepatitis, liver fibrosis, and teratogenicity are some of the other potential concerns that could arise from receiving treatment[10]. Oral methotrexate treatment is typically administered once every seven days.

The formulation that is administered subcutaneously produces fewer gastrointestinal adverse effects and is more effective as a result of better bioavailability. Cyclosporin is a calcineurin inhibitor and has a rapid beginning of action; however, it is associated with an increased risk of hypertension as well as permanent renal damage[11]. Acitretin is a retinoid that may be taken orally and it encourages the development of keratinocytes. Dry skin, hair loss, hyperlipidemia, and hepatotoxicity are some of the potential adverse effects of this medication. Both methotrexate and acitretin should be avoided during pregnancy for safety reasons. Biologic treatments and oral small-molecule inhibitors may be considered for patients whose illness is resistant to methotrexate and/or ciclosporin, or for cases in which second-line medicines are not an appropriate treatment option[12].The monoclonal antibodies or soluble receptors that act as the active ingredients of biological drugs are what are referred to as "biologicals" [13].They have had a significant influence on the outcomes of diseases ranging from moderate to severe. The most common inflammatory mediators like TNF-α and IL inhibitors are recommended for moderate-severe psoriasis. The topical therapy that is currently available for the management of psoriasis is the primary therapeutic option, and it also serves as an adjuvant to the systemic medication that is currently in use to treat this condition. The topical route of delivery enables focused therapeutic activity and assists in the avoidance of systemic adverse effects in the treatment of this condition[14].

The numerous pores in the microsponge's interior structure enable the medicinal ingredient to flow through with ease. Allowing the enclosed moiety to move freely breaks the delicate balance and causes an unsaturated condition, which reduces the drug concentration in the vehicle. Continue doing this until the body has absorbed the complete quantity of medicine. As the liquid is being created, the drug molecule becomes more soluble, which lowers the benefit of its delayed release and makes the drug moiety behave as if it had been administered in its free form rather than its trapped form. When they blend it with water, they utilize the resulting fluid as a transporter. They are handy equipment for hardening liquid material. The chemical linkers may induce the nanosponges to cling to the target in a unique manner. Due to their established safety for both invasive and oral routes, they are a beneficial technique to give drugs. It is feasible to inject nanosponges via the lungs and veins owing to their tiny size. To form capsules or tablets for oral delivery, the complexes may be blended with diluents, lubricants, excipients, and anti-caking agents. The manufacturing process needs this step. To give the drug parenterally, it may be dissolved in saline, sterile water, or any of a variety of different aqueous solutions. Their integration into topical hydrogels may be effective.

These relatively small spaces can accommodate a wide variety of materials because of their drug-loading capacity. These extremely minute particles have the capability of transporting medicinal compounds l lipophilic. In addition to this, they can improve the stability of medicinal compounds or molecules that have a low solubility in water. The nanosponges are composed of a polyester scaffold (backbone) or network that is three-dimensional and has the capability of organically disintegrating[15]. However, further research is needed to optimize the formulation and manufacturing processes of nanosponge-based nutraceuticals, ensuring their safety, stability, and scalability. Additionally, clinical studies are necessary to evaluate their efficacy in managing psoriasis and to determine the optimal dosing regimens. In this review, we are going to discuss the target drug delivery system for the treatment of Psoriasis with the help of nanosponge-based nutraceuticals.

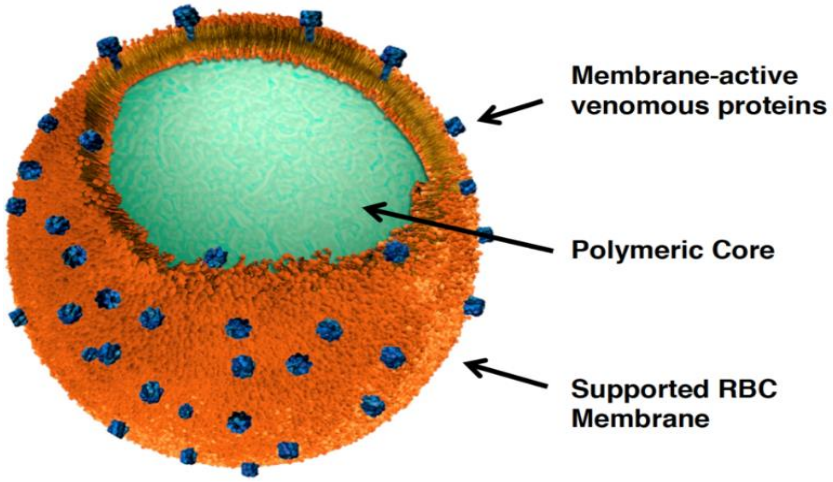


**Figure 1: Structure of nanosponge**

**1.1 Characterization and Pathophysiology of Psoriasis**

Comprising three main layers, the skin is the largest organ in the human body. The outermost layer, or epidermis, is composed mostly of specialised cells known as keratinocytes and is separated into four layers: stratum corneum, stratum spinosum, stratum granulosum, and stratum basale. Fibroblasts and immune cells in the surrounding area produce the fibrous extracellular matrix (ECM), which makes up the majority of the dermis, the next layer. Adipose tissue makes up the majority of the hypodermis, the deepest layer. This essential network of layers serves as the body's main defence against toxins, viruses, UV rays, and physical harm. The skin also regulates the body's temperature and water balance. The physical barrier, which is mostly located in the epidermis, and the immunological barrier, which is present in both the dermis and the epidermis, make up the two main parts of the skin barrier. Together, these two systems maintain the equilibrium of the skin and improve human health in general. Disruption of these processes, however, may result in psoriasis.

As previously mentioned, psoriasis results from a complicated interplay between environmental, immunologic, and genetic variables. Because T cells are activated and migrate to the skin, where they induce inflammation, PSO is regarded as an autoimmune disease even if there is no obvious immunogen. Activated T cells generate proinflammatory cytokines, such as interleukin-17 (IL-17), interleukin-23 (IL-23), and tumour necrosis factor-alpha (TNF-α), which promote the proliferation of keratinocytes in the epidermis. The epidermis attracts

inflammatory cells such as neutrophils and dendritic cells, which cause redness and swelling. One factor contributing to the common PSO plaques and lesions is an elevated immune cell count in the skin. Psoriatic lesions are warmer and redder because the condition also causes the skin to produce more blood vessels, a process known as angiogenesis, to fulfil the higher metabolic demands of rapidly proliferating skin cells. The interaction of cytokines, immune cells, and keratinocytes might result in a self-reinforcing chronic inflammatory cycle, which may explain why PSO is persistent.

As we've discovered more about these pathways, bespoke medications that block particular cytokines in the inflammatory cascade have increased in favour. By interrupting the pathomechanism at distinct periods, these medications strive to more accurately and effectively treat the symptoms of psoriasis. Furthermore, new research is extending our understanding of psoriasis and could lead to the identification of innovative therapy targets and tactics.

Plaque psoriasis (psoriasis vulgaris), the most widespread variety of psoriasis, generally presents as big, raised, red areas with silvery-white scales. Excessive skin cell turnover causes psoriasis vulgaris, which typically affects the elbows, knees, scalp, lower back, and nails, to amass dead skin cells on the surface. Scaling, a hallmark of the condition, derives from this. Inverse psoriasis is a form of psoriasis that is also known as veiled psoriasis or intertriginous psoriasis. It affects the skin folds in the groin or inner thigh area in addition to the breasts, neck, buttocks, and underarms. Because of the increased blood flow and immune cell infiltration, the affected skin typically looks red, shiny, and itchy. Psoriatic lesions may occasionally be unpleasant and bothersome as well. Pitting, ridges, and discoloured nails are probable PSO side effects. Nail detachment may occur under harsh situations. We may consider scalp PSO if the condition affects the forehead, back of the neck, or scalp. "Guttate psoriasis," a form of psoriasis, is distinguished by small, teardrop-shaped papules that frequently occur following a streptococcal throat infection. Children and teens are more prone to encounter this form of PSO. There are two unusual kinds of PSO: pustular and erythrodermic. While the latter creates red, swollen skin that is exceedingly itchy and burning, the former is distinguished by the quick production of blisters filled with pus. It is vital to bear in mind that severity may vary widely and that some persons have several disorders. The sort and severity of the condition dictate the appropriate course of therapy.

### 1.2 Challenges in the Topical Delivery of Anti-Psoriatics

Numerous issues with topical anti-psoriatics affect both patient adherence and the effectiveness of treatment. These challenges include those related to patient-specific factors, pharmaceutical formulation, and skin characteristics.

The stratum corneum, the skin's outermost layer, serves as a barrier to slow the pace at which the active substances penetrate the skin. Typically, psoriasis is characterised by larger, hyperkeratotic plaques that are more difficult for medications to penetrate, reducing the effectiveness of conventional therapies and medication delivery. It is challenging to penetrate the skin's outermost layer using the standard pharmaceutical formulation procedure for topical therapy. Hyperkeratosis and inflammation are two significant signs of the illness that exacerbate this problem. It's possible that psoriasis's elevated cholesterol and decreased ceramide concentration make it more difficult for the active ingredients to penetrate the skin's deeper layers. Furthermore, the lack of adequate skin water and other hydration stimuli

prevents the entry of quite large pharmaceutical dosages. However, the moisture level of the skin is often unpleasant, which limits the anti-psoriatics' ability to penetrate the skin deeply. Additionally, the permeability of the skin varies depending on where the body is located. For instance, the skin of the face and genitalia is more porous than the skin of the palms and soles. Selecting a distribution system requires taking into account the particular characteristics of the impacted area. Tacrolimus, dithranol, and calcipotriene are among the anti-psoriatic drugs classified as Class II by the Biopharmaceutical categorisation System (BCS). This categorisation suggests that the drugs have low water solubility, which may affect their absorption and bioavailability. As a result, formulations that increase the solubility of medications are often required.

Psoriasis topical treatments may need consistent, long-term application. Among the factors that might make patient compliance challenging are the pain of repeated application, the duration of treatment, and the possibility of side effects. As previously mentioned, prolonged use of anti-psoriatics, especially potent corticosteroids, may cause skin irritation, dryness, or itching. This may result in decreased patient adherence and medication withdrawal. Additionally, if a medicine is given topically to large areas of the body or to people whose skin integrity is impaired, it may possibly reach the bloodstream. It could make systemic adverse effects more likely.

## 2. Nanosponges (NSs) for Psoriasis Topical Therapy

By complexing cyclodextrin with crosslinker-like carbonyl diimidazole, nanosponges—hyper-crosslinked cyclodextrin polymers—create nanostructured three-dimensional networks. In their crystal structure, various polymer chains may create distinct microdomains that are ideal for encasing medications with various chemical compositions. Nanosponges are known to dissolve drugs that are poorly soluble in water and provide long-term release. Their exterior hydrophilic branches and interior hydrophobic chambers allow them to transport both hydrophilic and hydrophobic therapeutic substances. In a variety of therapeutic uses, they could possibly improve medication delivery.

Curcumin has a stronger anti-patch impact when taken with anti-inflammatory drugs, such as coffee, than when taken by alone, which means that psoriasis therapy takes less time. In light of these results, scientists tried to create a topical gel based on nanosponge that contains a combination of caffeine and curcumin, which might be a useful therapy for PSO. The NS was created using the hot-melt method and included beta-cyclodextrin as a polymer and dimethyl carbonate as a crosslinker. Topical gels were then used with it. Curcumin plus caffeine reduced the time needed to evaluate anti-psoriasis effectiveness from around 20 days to 10 days, according to the study. Additionally, the nanogel provided a 12-hour continuous release.

Skin shrinkage, acne, hypopigmentation, and associated allergic contact dermatitis are some of the negative side effects of topical corticosteroids, even if they have shown promise in treating psoriasis. One such steroid is clobetasol propionate. To counteract these adverse effects, Kumar et al. created a hydrogel with nanosponges made of diphenyl carbonate and β-cyclodextrin. The drug release value was 86%, and the formulation increased the solubility of pure clobetasol propionate by 45 times. Furthermore, the biocompatibility of nanosponges containing clobetasol propionate was confirmed by in vitro cell survival experiments using a human monocyte cell line (THP-1). The in vivo research found that mice had much less orthokeratosis

than the group that did not get treatment. The study also found a decrease in epidermal thickness and a significant pharmacological effect.

As previously mentioned, dithranol's anti-inflammatory, antiproliferative, and antioxidant properties make it the recommended treatment for psoriasis. Its poor solubility and stability, however, significantly impair its effectiveness and dose calculation. Kadian et al. conducted a comparative study on the effects of the kind of preparation technique in order to solve this issue. They examined the stability, efficacy, and physicochemical characteristics of the dithranol-containing nanosponges produced by the solvent evaporation or melt techniques. Their research revealed that the solvent evaporation procedure was a more efficient means of enhancing the drug's solubility and stability. Their findings showed that the solvent evaporation method of incorporating dithranol into nanosponges prolonged the antioxidant activity of the medication and improved its photostability and solubility. Making and evaluating dithranol nanosponges embedded in carbopol hydrogel was the aim of another investigation. When compared to the untreated control group, the degree of epidermal thickness increased significantly after the administration of these nanosponges containing dithranol (0.5 and 1.0% w/v). The present work provided a prospective model of a multifunctional cyclodextrin nanosponge hydrogel to aid in the development of a feasible topical therapeutic method for psoriasis. This would remove the potential for detrimental systemic side effects while expanding the range of available therapy options. There may soon be new therapeutic developments in commercial dose formulations.

### 2.1 Features of Nanosponges[16, 17]:

a) Nanosponges offer a diversity of diameters that are 1 micrometer or less in size. By adjusting the proportion of crosslinker to the polymer in the synthesis process, one can produce nanosponges of a desired size [16, 17].
b) Depending on the parameters of the process, they can take either the crystalline or the paracrystalline form. During the process of Complexation with medicines, the crystalline structure of nanosponges plays an essential function [16, 17].
c) Drug loading capacity is affected by crystallization degree. The drug-loading capabilities of paracrystalline nanosponges can be demonstrated in several different ways [16, 17].
d) They are insoluble in the great majority of organic solvents, are non-toxic, and can endure temperatures of up to 300 degrees Celsius [16, 17].
e) They are stable between low (1 pH) and high (11 pH) [16, 17].
f) When mixed with water, the resulting suspension is both clear and iridescent [16, 17].
g) It is possible to replicate them using techniques like simple thermal desorption, solvent extraction, microwaves, and ultrasound [16, 17].
h) Their three-dimensional structure allows them to selectively grab, transport, and release a wide range of chemicals. They can join up with a wide range of various functional groups, allowing them to act in a large variety of potential targets [16, 17].
i) Nanosponges can preferentially connect to the target site by the utilization of chemical linkers, which makes this possibility conceivable, and also, they can generate inclusion and non-inclusion complexes depending on the medications they are complexed with [16, 17].
j) Nanosponges can be given magnetic qualities if magnetic particles are included in the reaction mixture. This will cause the nanosponges to take on magnetic properties [16, 17] (Table 1).

**Table 1: Types of Nano-sponges**

| Types | Description | Applications | Ref. |
|---|---|---|---|
| Nanosponges constructed with cyclodextrin | Cyclodextrin nanosponges interact with matrix molecules. Natural α-, β-, &γ-cyclodextrin cross-links form cyclodextrins. B-cyclodextrins are used because of their cavity size and cross-linkable polymers. | In biomedical applications, cyclodextrin-based NS delivers drugs. It is also utilized in cosmetics, agriculture, and water purification. | [18] |
| Titanium nanosponges | Polystyrene microspheres covered with titanium-based nanosponges were produced by copolymerizing styrene with polymerizable surfactants. | Photoelectrochemical photo anodes are TiO2/ZnO hybrid nanostructures. Metallic NS particles like TiO2 and silicon have been used in many applications, including recyclable oil absorbents, photo-catalytic properties like antimicrobial applications, biosensors, and drug delivery. | [19] |
| Nanosponges comprise silicon | A silicon powder of metallurgical grade is used in the preparation of silicon nanosponge particles. Particles measuring between 1 and 4 microns in size are scratched to produce silicon nanosponge particles. | Among the many uses for the very porous silicon NS as a carrier material are fuel cell electrodes, photosensitizers, adsorbents, sensors, catalysts, and pharmaceuticals. The production of silica nitrate and silicon carbide, two building blocks of high-surface-area ceramic compounds, also uses it. | [19] |
| Polystyrene nanosponges | The very porous silicon NS may be a carrier material for a variety of applications, including as fuel cell electrodes, photosensitizers, adsorbents, sensors, catalysts, and medicines. Furthermore, it serves as a precursor in the synthesis of silicon carbide and silica nitrate, two other high-surface-area ceramic compounds. | Use of hyper-cross-linked NS enabled the separation of organic electrolytes by size exclusion chromatography. Tissue scaffolds use NS based on cyclodextrin and hyper-cross-linked polystyrene NS. | [20] |

| | | | |
|---|---|---|---|
| | After individual coils of polystyrene were suspended in weak solvents, massive amounts of stiff intramolecular bridges were added. Consequently, the coils shrunk tightly, forming spherical nanostructures (NSs). The NS solutions diffused fast and had little viscosity, but they also had significant rates of sedimentation. These NSs have a larger inner surface area, and the linear polystyrene nonsolvent has expanded considerably inside them. | | |

**2.2 Pharmacokinetics of Nanosponges:**

Nanosponges are a novel class of drug delivery technology that can improve the solubility, bioavailability, & stability of many medications. They are composed of Crosslinked polymers that form a three-dimensional network with nanosized cavities that can encapsulate drugs of different sizes and properties and can be administered by various routes such as oral, topical, parenteral, and nasal[19]. The creation of nano-drug delivery systems allows for the improvement of chemical and bioactive substance solubility, surface modifications, bioavailability, biocompatibility, and drug-loading efficacy in many areas of life[29-30].

**Table 2: Pharmacokinetics of Nanosponges**

| Nutraceutical | Nanosponge | Pharmacokinetics | Ref. |
|---|---|---|---|
| Resveratrol | Cyclodextrin-based nanosponges | Increased bioavailability and prolonged half-life | [21] |
| Curcumin | Poly(lactic-co-glycolic acid)-based nanosponges | Enhanced solubility and cellular uptake | [22] |
| EGG | Chitosan-based nanosponges | Improved oral bioavailability and reduced toxicity | [23] |
| Quercetin | PLGA-based nanosponges | Increased cellular uptake and anti-inflammatory activity | [23] |
| Lutein | β-Cyclodextrin-based nanosponges | Enhanced bioavailability and protection from oxidation | [24] |
| Zeaxanthin | β-Cyclodextrin-based nanosponges | Increased bioavailability and protection from oxidation | [25] |

## 3. Methods of preparation of nanosponges:

### 3.1 Solvent evaporation method

The solvent approach for making nanosponges is heating a mixture of the polymers and a polar aprotic solvent like dimethyl sulphoxide (DMSO) or dimethyl formamide (DMF). The mixture is then Crosslinked at the suggested 1:4 ratio by adding a cross-linker. The above reaction should be conducted at a temperature of 10 degrees Celsius for one to forty-eight hours or until the solvent temperature begins to reflux. The solution is cooled to room temperature once the reaction is complete. The next step is to mix in some twice-distilled water to the final product. The product is recovered through a series of processes beginning with vacuum filtration, moving on to soxhlet extraction with ethanol refinement, and ending with drying [26].

A study employed assisted-emulsion solvent evaporation and ultrasonication to produce NS. Enhancing the anticancer capabilities of nanosponges is the active component withaferin-A (WFA) from Withania somnifera [27]. Another study found that the emulsion-solvent evaporation method worked well for producing OLM-loaded nanosponges made of ethylcellulose (ONS1–ONS4) [28].

### 3.2 Ultra-sound assisted synthesis

Ultrasound-assisted synthesis is a versatile and efficient technique that can be used to synthesize a wide variety of nanosponges. In this technique, the polymers are prepared for their eventual reaction in a flask with the cross linkers while the solvent is omitted from the process. After that, the flask is put into an ultrasonic bath that has been preheated to a temperature of ninety degrees Celsius, and the water in the bath is filled with it. The combination is then subjected to sonication for a total of five hours. The finished product is broken up into smaller pieces before being packaged, and this step occurs after the mixture has been allowed to cool back down to room temperature. Finally, the non-reacting polymer is removed from the product by washing it with water, and the ethanol-containing soxhlet apparatus is used to create nanosponges [29, 30].

**Table 3: Examples of Ultra-sound assisted Method**

| Materials | Nanosponge properties | Applications | References |
|---|---|---|---|
| Poly(lactic-co-glycolic acid) (PLGA) | Hollow, porous, and biocompatible | Drug delivery | [31] |
| Chitosan | Hydrophilic, biodegradable, and non-toxic | Gene delivery | [32] |
| Graphene | Highly porous, conductive, and stable | Water purification | [33] |
| Dendrimers | Multifunctional, stimuli-responsive, and biocompatible | Cancer therapy | [34] |
| Nanocellulose | Biocompatible, biodegradable, and sustainable | Tissue engineering | [35] |
| Poly(ethylene glycol) (PEG) | Non-toxic, biocompatible, and versatile | Drug delivery, gene delivery, and tissue engineering | [36] |

| | | | |
|---|---|---|---|
| Gold nanoparticles | Highly stable, biocompatible, and fluorescent | Cancer therapy and bio-imaging | [37] |
| Carbon nanotubes | Highly conductive, durable, and stable | Energy storage and catalysis | [38] |
| Quantum dots | Highly fluorescent, tunable, and stable | Bioimaging and sensing | [39] |

### 3.3 Emulsion solvent diffusion method

To generate nanosponges using this method, ethyl cellulose and polyvinyl alcohol are mixed in several different proportions or percentages. The result is the nanosponges. This strategy is broken up into not just one but two distinct stages: the scattered and the continuous. The dispersion phase consists of the medication and ethyl cellulose being mixed. Following the dissolution of the medication in 20 ml of dichloromethane, a certain quantity of polyvinyl alcohol (PVA) is added to an amount of the continuous phase that is 150 ml in volume. After that, the dispersed phase is in a usable state (aqueous). After that, the mixture is stirred at a rate of one thousand revolutions per minute for approximately two hours (rpm). Filtration is the method that is utilized to collect the products, which in this instance are the nanosponges. In the final stage of production, the product undergoes the drying process in an oven at a temperature of 400 degrees Celsius [40],[41].

**Table 4: Emulsion solvent diffusion method**

| Materials | Nanosponge properties | Applications | References |
|---|---|---|---|
| Poly(vinyl alcohol) (PVA) | Hollow, porous, and biocompatible | Drug delivery | [42] |
| Chitosan | Hydrophilic, biodegradable, and non-toxic | Gene delivery | [43] |
| Graphene | Highly porous, conductive, and stable | Water purification | [44] |
| Gold nanoparticles | Responsive, fluorescent, and stable | Cancer therapy | [45] |
| Dendrimers | Multifunctional, stimuli-responsive, and biocompatible | Drug delivery and imaging | [46] |
| Carbon nanotubes | Highly porous, conductive, and stable | Energy storage and catalysis | [47] |
| Metal-organic frameworks | Highly porous, tunable, and stable | Gas storage and separation | [48] |
| Quantum dots | Luminescent, stable, and biocompatible | Bioimaging and biosensing | [49] |
| Nanocarriers | Multifunctional, targeted, and controlled release | Drug delivery and therapy | [50] |

### 3.4 Microwave irradiation method

In order to conduct out microwave reactions, the scientific microwave system owned by Cata was utilised. Additionally, a fiber-optic probe was inserted into the reaction vessel in order to measure the temperature of the reaction mixture while the reactions were being carried out. For the purpose of crosslinking, diphenyl carbonate was utilized, and diphenyl formamide was used as the solvent in the production of cyclodextrin-based nanosponges. After that, a mixture of cyclodextrin and diphenyl carbonate in dimethyl formamide was taken in a set proportion and subjected to microwave irradiation for a specific duration of time under specific conditions. After the period of time that had been permitted had elapsed, the solvent was removed, and after the solvent had been removed entirely, the remaining residue was examined[51]. The study showed that the aqueous solubility of Lopinavir (LPO), an Antiretroviral (ART) drug by preparing solid dispersion (SD) through the microwave irradiation (MWI) technique was improved [52]

## 4. Transfer of drug to nanosponges

In order to reach a mean particle size of less than 500 nm, the nanosponges that are going to be used in the drug delivery process need to go through pre-treatment as shown in (Figure 2). After dispersing the nanosponges in water and sonicating them to limit the chance of aggregation formation, the suspension was centrifuged in order to remove the colloidal component. This was done so that the nanosponges could be used in further research. After removing the supernatant, the sample was freeze-dried in order to remove excess moisture and complete the drying process. First, an aqueous suspension of nanosponges was created, and this was followed by dispersion of the nanosponges in an excessive amount of the drug. After that, the suspension was kept for the required amount of time for the Complexation while being continually stirred. The uncomplexed (undissolved) drug that was created as a by product of the Complexation process was separated from the complexed drug through the use of centrifugation. At that precise time, the solid crystal of nanosponges was formed either by evaporating the solvent or by freeze drying the solution. The Complexation of the drug with the nanosponge involves the crystalline structure of the nanosponge, which plays an important function.

## 5. Applications of nanosponges:

The pharmaceutical sector is increasingly making use of nanosponges because of the biocompatibility and flexibility of these microscopic sponges. Applications can be found for these nanosponges in a wide variety of fields. Nanosponges have the potential to be used in the formulation of a wide variety of dosage forms in the pharmaceutical industry; it is possible to encapsulate pharmacological molecules that are either lipophilic or hydrophilic in nature. This indicates that nanosponges can contain medications that are categorised as BCS-class II by the biopharmaceutical classification system in addition to medications that have a low solubility in water. This is because nanosponges have a high surface area to volume ratio. Here, some of the applications of nanosponges are discussed

### 5.1 Solubility enhancement

Nanosponges have the ability to increase the wetting and water solubility of molecules that normally have very low water solubility [19]. In order to skip the phase of dissolving the medications first, they can be molecularly disseminated inside the structure of the nanosponge, and subsequently they can be released as molecules. As a direct consequence of this, the perceived solubility of the drug may be enhanced. The solubility and dissolving rate of a substance can be significantly improved by using nanosponges, which can also significantly improve the drug's bioavailability. This can help solve a number of formulation and bioavailability issues[55].

### 5.2 Nanosponges for drug delivery

The goal of pre treatment is to reduce the mean particle size of drug delivery nanosponges to less than 500 nm. To prevent aggregates, submerge the nanosponges in water, sonicate them, and then centrifuge the mixture to separate the colloidal fraction. After draining the supernatant, freeze-dry the sample. Distribute the extra medication equally throughout the complexation process, and use the watery Nanosponges suspension to frequently stir the mixture. Use centrifugation to separate the complexed drug from the uncomplexed (undissolved) medication after complexation.

The drug is not dissolved by water, but it could be transported thanks to the nanoscale porosity structure of the nanosponges. When it comes to the medicine dissolving more quickly, the permeability and solubility of the drug nanosponge complexes are of utmost importance. According to studies, cyclodextrin nanosponges are three to five times more effective than conventional techniques in delivering medication to the intended site.[56]. There are a number of ways to give solid-consistency nanopowders, including oral, parenteral, topical, and inhalation. Before the complexes of the nanosponge are utilized to make tablets and capsules for oral administration, they are dissolved in an appropriate excipient, such as a lubricant, diluent, or anti-cracking agent. This facilitates the process of integrating the details into the final output. Nanosponges are very versatile materials that might enhance a product's functionality and aesthetic appeal. Enhanced product adaptability and solubility, lower skin irritation, regulated and progressive release, and increased product solubility are a few of these characteristics. [57].

### 5.3 Nanosponges for cancer therapy

One of the most challenging challenges currently faced by the pharmaceutical industry is anticancer medication distribution. These drugs are hard to dissolve in water, making this process one of the most challenging aspects of the industry. When it comes to preventing the development of tumors, the authors of the study assert, in one of the articles that they have written, that a nanosponge complex is an approach that is three times more successful than direct injection [58]. Nanosponge-based delivery systems have been employed in cancer therapy because to its superior selectivity, biocompatibility, degradability, and delayed release behavior. Drug loading into nanosponges is influenced in this instance by the degree of crystallization. The drug makes up the bulk of the nanosponges payload, and by exposing a targeting peptide, the nanosponge is better able to anchor itself to the tumour receptor, which has been pushed to the surface by radiation. Nanosponges are able to attach to the surface of

cancer cells and then release drug molecules when exposed to them. When cancer cells come into contact with nanosponges, this process begins [59]. One of the potential benefits of targeted drug distribution is the possibility of achieving a greater therapeutic effect with a lower dose and fewer adverse effects [60].

**5.4 Protein distribution using nanosponges**

Researchers looked at the ability of β-cyclodextrin-based nanosponges to encapsulate substances. In recent years, cyclodextrin-based nanosponges, or CD-NSs, have gained relevance in the area of drug administration due to their versatility and simplicity of manufacture. The increasing use of proteins in business and health presents an intriguing opportunity for CD-NS to study the various beneficial effects proteins have on small and large molecules. Using protein-coated CDs as artificial chaperons, which stop proteins from crystallizing into amorphous stabilizers or from clumping after freezing, is one example of this using PAA-NS10 and AA-NS11 poly (amidoamine) nanosponges as a protein model to simulate the complexing of bovine serum albumin (BSA) [17]. Both PAA-NS10 and PAA-NS11 exhibit encapsulation effectiveness of 90% and 92%, respectively, and differ structurally from the previous generation of carbonated NSs. Encapsulation efficiency values rose in direct proportion to the quantity of PAA-NS added; the largest gain in encapsulation efficiency, of 0.3%, was achieved by increasing the amount of PAA-NS from 0% to 1% w/v. It seems that the small differences in encapsulation effectiveness were caused by either the additional nitrogen atoms or the modified crosslinked structure. In the end, the in vitro release showed that both NSs released at a much slower pace when they were in the opposite direction of the β-CD/BSA complexes. [71–73]

**5.5 Nanosponges as a tool for combating yeast infections**

One of the deadliest diseases that can manifest anywhere in the world is a fungal infection of the skin. Because of its many advantages, topical therapy is increasingly being seen as a viable option for treating coetaneous infections. These advantages include localising medication application and minimising systemic side effects. Athlete's foot, ringworm, tinea versicolor, jock itch, and vaginal thrush can all be treated topically with the pharmaceutical fungicide econazole nitrate [61]. An infection with a fungus is the root cause of many disorders. There are several different formulations of econazole nitrate that are available to buy from different sellers on the market. The topical application of econazole nitrate does not result in a significant increase in the amount of the drug that is absorbed by the skin. However, in order for the therapy to be successful, it is required to combine a high concentration of active agents. Following this, the econazole nitrate nanosponges were placed into a hydrogel as a topical administration method in order to achieve a sustained release of the medication. Itraconazole is yet another antifungal medicine, and according to the biopharmaceutical classification system, it is categorised as a class II substance. Both the pace at which this medicine dissolves and its bioavailability are quite poor. As a result, the objective of this study was to enhance the solubility of itraconazole in the interest of finding a solution to the problem with the drug's bioavailability. If itraconazole is included in nanosponges that also contain -cyclodextrin, which acts as a cross-linking agent with carbonate bonds, then the solubility of itraconazole can be boosted [62].

### 5.6 As an absorbent for the treatment of toxins in the blood

By absorbing the toxic chemical, nanosponges are able to purge it from our bloodstream, so preventing further damage. If we inject nanosponges into the bloodstream, rather than employing antidotes, the nanosponges will be able to remove the poisons from the bloodstream [63]. In the bloodstream, the nanosponge takes on the appearance of a red blood cell, which fools harmful substances into attacking it so that it may subsequently absorb them. It is dependent on the specific poison as to how many molecules of toxin each nanosponge is capable of absorbing[64].

## 6. Nanosponges for Psoriasis Treatment

Nanosponges are a novel class of nanomaterials that can be used for various biomedical applications, including topical and systemic treatments. Nanosponges are composed of cross-linked polymers such as cyclodextrins or polycarbonates, that form a three-dimensional network with nanosized cavities[65].

### 6.1 **Nanosponge-Based Topical Treatments for Psoriasis**

Nanocarriers are more visible in topical delivery systems because they are more soluble and passively aggregate at the target site. Creating liquid, solid, or semisolid dosage forms for topical drug delivery systems (TDDS) is a simple process. Providing the skin or mucosal layers with a therapeutically suitable medication concentration is their primary goal. It is possible for the nanosponges in the topical formulation to penetrate skin and aggregate in the dermis and epidermis [79-83]

### 6.2 Nanosponge-Based Systemic Treatments for Psoriasis

Nanosponge-based systemic Treatments can enhance the drug bioavailability reducing the frequency of dose. These possibilities make them a suitable option for systemic treatment.
Nanosponge-based systemic treatment for breast cancer has been a recent advancement. The nanosponge was coated with folic acid that binds with folate receptors. This study expressed that nanosponge-based treatment has higher antitumor activity.**[84-86]**

## 7. Mechanism of action of nanosponges in the treatment of psoriasis

Psoriasis is a skin condition that causes the skin to release inflammatory cytokines such as TNF-alpha, IL-6, and IL-17 (IL-17). Inflammation from these cytokines causes red, scaly, and itchy skin plaques. Due to the porous nature of nanosponges, the active ingredient must be packaged separately and then added to the delivery system. There is no restriction on the movement of the encapsulated substance from the particles into the vehicle until saturation and equilibrium have been reached. When applied to the skin, the active component vehicle becomes unsaturated, disrupting homeostasis[66]. When applied to the epidermis, nanosponge particles soak up and release their active chemicals into the vehicle, where they remain until the skin absorbs or dries them[67, 68].

## 7. Animal studies

a) The drug activity of the DTHNS-HG treated group was significantly higher than that of the control group in in-vivo antipsoriatic experiments performed on mouse tails. Oxidative stress in keratinocytes can be effectively managed by manufactured formulations, as shown by the measurement of oxidative stress markers such as MDA and NO levels [69].
b) In vivo validation of the anti-psoriatic potential of the produced nanoformulations was accomplished with the assistance of the mouse tail model. The findings of the histological and biochemical examinations suggested that the manufactured nanogel possessed significant anti-psoriatic activity [65].
c) The nanosponge formulations were incorporated into a model carbopol gel formulation, and both the in-vivo animal investigations and the formulations' stability were evaluated. In Test 2, the inflammatory process that was caused by IMQ was significantly less severe, as evidenced by the lack of parakeratosis and a decrease in acanthosis [70].
d) The mouse model of imiquimod-induced psoriasis was used in the in-vivo animal investigations that were conducted for the purpose of optimising the formulation. The increased ability of NS based gel to successfully relieve psoriasis has been inveterately proven by the encouraging outcomes of experiments conducted in vivo. Therefore, the CD-NS-based topical gel that was developed could be recommended as a potentially useful carrier for a successful local therapy of psoriasis[71].
e) In vivo testing was performed on an imiquimod-induced psoriasis mouse model to evaluate the effectiveness of the nano hydrogel. In addition to an analysis of the histopathology, an examination of the oxidative stress indicators showed that the produced BONS-HG had considerable antipsoriatic activity ($p < 0.001$)[72].

### 7.1 In- vitro studies:

a) In vitro testing revealed that it was effective against THP1 cells, exhibiting both anti-inflammatory and immune-modulatory properties. The carbopol hydrogel was given additional benefits for topical application as a result of the incorporation of CP nanosponges [65].
b) When tazarotene was included in nanosponges, the time-course of the in-vitro skin penetration showed that its concentration in SC was considerably enhanced after 3 hours, 6 hours, 9 hours, and 12 hours after application ($P < 0.05$). Additionally, the concentration of tazarotene in the [E + D] was considerably increased after three hours, six hours, nine hours, and twelve hours ($P < 0.05$)[70].
c) Research on the capacity of the THP1 cell lines to sustain their vitality has been carried out as part of cytocompatibility testing. Research on the capacity of the THP1 cell lines to sustain their vitality has been carried out as part of cytocompatibility testing. The BONS-irritancy HG's potential was evaluated using the Hen's Egg Chorioallantoic Membrane Test (HET-CAM), and in vivo imaging of cutaneous uptake was performed using the Confocal Laser Scanning Microscopy (CLSM) technique. Rabbits were used in both of these tests that were carried out. Because the in vitro irritation potential of BONS-HG did not demonstrate any evidence of erythema or irritation, this indicates that the generated hydrogel can be utilised safely as a topical formulation[72].
d) There have been a number of investigations into the use of nanosponges as a possible treatment for psoriasis. For instance, a topical hydrogel that treats psoriasis effectively by containing

nanosponges loaded with clobetasol propionate and containing clobetasol. Clobetasol propionate is a powerful corticosteroid that can suppress the immune system and reduce inflammation, but it also has the potential to cause skin atrophy, acne, hypo pigmentation, and allergic contact dermatitis. In both in vitro and in vivo testing, the antipsoriatic activity of clobetasol propionate was improved thanks to the nanosponge hydrogel's increased solubility, entrapment efficiency, and release profile [65]. The nanosponge hydrogel also reduced the skin irritation and histopathological changes induced by clobetasol propionate.

e) Another study showed that a topical gel containing curcumin and cefdinir-loaded nanosponges for psoriasis treatment. Curcumin is a natural polyphenol that has anti-inflammatory, antioxidant, antimicrobial, and antiproliferative properties, but it has poor solubility and bioavailability. Cefdinir is an antibiotic that can inhibit the growth of Staphylococcus aureus, a common pathogen associated with psoriasis. The nanosponge gel enhanced the solubility, permeability, stability, and synergistic effect of curcumin and cefdinir. The nanosponge gel also showed significant anti-psoriatic activity in vivo by reducing the epidermal thickness, inflammation, and scaling of psoriatic lesions[73].
f) Recent examined the conventional treatments, recent efforts, and potential future applications of lipid-based nanoparticles for the treatment of psoriasis[74]. Another form of nanocarriers known as lipid-based nanoparticles has the ability to encapsulate pharmaceuticals that are either lipophilic or hydrophilic within their lipid core or bilayer. In addition, they have the capability of increasing the medication's ability to pass through the stratum corneum, which is the outermost layer of the skin and acts as a barrier for the delivery of drugs. In the review, a number of different kinds of lipid-based nanoparticles, such as solid lipid nanoparticles, nanostructured lipid carriers, nanovesicles, and nanoemulsions, as well as their most recent attempts at developing nanoformulated psoriasis treatments, were discussed.
g) Curcumin and caffeine nanosponges were shown to have enhanced anti-inflammatory and anti-proliferative effects on psoriatic skin lesions in mice, compared to free drugs or conventional gels[71].
h) Clobetasol propionate (CP), a potent corticosteroid, was loaded into cyclodextrin nanosponges and formulated into a hydrogel for topical delivery. The CP nanosponge hydrogel showed improved anti-inflammatory and anti-proliferative effects in a mouse tail model of psoriasis, compared to the conventional CP cream.
i) Dithranol (DTH), a well-known antipsoriatic drug, was also incorporated into β-cyclodextrin nanosponges and integrated into a Carbopol hydrogel. The DTH nanosponge hydrogel demonstrated superior anti-psoriatic efficacy and reduced skin irritation in a mouse tail model of psoriasis, compared to the conventional DTH ointment[75].
j) These studies suggest that nanosponges are promising nanocarriers for psoriasis treatment, as they can improve the delivery and performance of various drugs. Nanosponges can also offer advantages such as easy preparation, biocompatibility, biodegradability, and versatility. However, in order to validate the safety and efficacy of nanosponge-based formulations for the treatment of psoriasis in humans, additional clinical trials will need to be conducted.

## 8. Conclusion/ Future direction:

Hyperproliferation of cells is the hallmark of psoriasis, a skin disorder with several known causes, including hereditary and environmental ones. Topical, systemic nonbiologic, systemic biologic and phototherapy are some of the available treatments for psoriasis. Despite the wide range of antipsoriatic medicines available, each with a distinct mechanism of action, topical therapy remains the most practical approach of delivering pharmaceuticals over the skin barrier. As cutting-edge nano-delivery techniques to improve API distribution at the targeted area, lipid-based nanoparticles hold a lot of promise. Recent research found that although several APIs may be encapsulated into different lipid nanocarriers, liposomes and nanoemulsions have been the mainstay of successful nano-based psoriasis therapy. Combining lipid-based nanoparticles with antipsoriatic medications improves skin penetration and lessens psoriasis symptoms. By increasing skin penetration, retention, and delayed release, the treatments also show extremely favorable outcomes in relieving psoriasis lesions due to their large surface area at the nanoscale level. To fully explore their tremendous potential in the topical dispersion of antipsoriatic applications, further research and opportunities including several lipid-based nanocarrier forms, such as liposomes, transfersomes, and ethosomes, are needed. Making drugs into nanoparticles is often expensive in the pharmaceutical industry. Resolving worries over safety and cytotoxicity associated with the production of pharmaceuticals, including nanoparticles, may be aided by a thorough understanding of their interactions with the body. Recent research that used lipid-based nanocarriers for API found that these treatments performed better in terms of drug penetration and bioavailability than the control group, which received traditional therapy without the use of nanocarriers. Thus, the synthesis of nanodrugs is certain to be effective if best practices are followed in nanomedicine applications.

As the area progresses, we are seeing an astounding number of uses of nanotechnology in medicine. This is the reason why nanoparticles will be used in future nanotechnology-based drug delivery systems; the market is predicted to grow six times over to US$334 billion by 2025 from less than a billion dollars the year before. Excellent research in nanomedicine will progress during the next two decades as the importance of material design becomes more apparent due to clinical needs. This novel therapeutic strategy has led to the emergence of a new paradigm in the treatment of psoriasis.

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