REVIEW ARTICLE

Nanoguard: Revolutionizing Skin Care with Topical Nanosponges – A Novel Approach to Combat Skin Infections

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Abstract

Nanosponges are an innovative technique for dermatological formulations that offer controlled release and enhanced efficacy of active substances. This review investigates novel interactions between synthetic and natural components in nanosponge formulations with the goal of revolutionizing dermatological applications. Skin infections are mostly occurring on the skin's surface, mostly in the epidermis's upper layers. An effective barrier against external chemicals, including drugs, is provided by the stratum corneum (SC), the outermost layer of the epidermis. This review focuses on novel techniques to deliver the drug to the target size with accuracy and avoid any negative side effects. The novel formulations combine the therapeutic properties of herbal extracts with the precision of synthetic ingredients to offer enhanced therapeutic effects and a broader variety of applications that might revolutionize the treatment of skin infections. This abstract explores the collaborative potential of merging herbal and synthetic compounds to harness synergies for enhanced therapeutic outcomes.

Keywords: Nanosponges, Skin infection, Herbal extract, Dermatological formulation, Controlled Release, Topical Delivery.
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INTRODUCTION

The majority of dermatologists deal with warts on a regular basis, particularly those who treat young patients.[1] Wart treatments are expensive both directly, due to the expense of pharmaceuticals, over-the-counter items, and health care delivery, as well as indirectly, because they need time away from work or other activities to deal with the health care system. Our first-line wart treatment options are also far from optimum.[2] While many warts react effectively to in-office cryotherapy or over-the-counter salicylic acid preparations, there are some scenarios when these conventional therapies are ineffective or inapplicable. Thankfully, there are several treatment options available for warts, and no dermatologist should have to give up on a wart that is difficult to treat.[3] When warts are surgically removed in regions that are sensitive to appearance or in individuals with darker skin types, the risk of scarring or hypo- or hyperpigmentation may be significantly higher.[4] Noncompliance might be an important barrier since, particularly for young patients, receiving painful treatments repeatedly can be difficult to accept.[5,6]Acne is a highly prevalent disorder, especially in young adults and teenagers. Propionibacterium acnes is the main bacteria linked to acne. This bacterium normally resides in the epidermis, especially in the follicles that hold hair. Because it is anaerobic and gram-positive, it does well in conditions with low oxygen levels.[7]

Applying topical medications decreases systemic side effects and restricts the therapeutic effect on the affected region, making it a good approach for treating skin conditions. An effective barrier against external chemicals, including drugs, is provided by the stratum corneum (SC), the outermost layer of skin.[8] The elimination of this barrier is necessary to give therapeutically acceptable medicine concentrations in various skin layers, which poses a significant challenge to formulation scientists due to the inherent feature of stratum corneum.[9,10]

The use of novel drug delivery system can overcome this barrier. The NDDS for treating skin infections has the potential to completely transform the dermatological industry. This novel approach, in contrast with traditional techniques, focuses on enhancing the accuracy, effectiveness, and patient experience while treating a range of skin problems.[11] Targeted and localized treatment is one of the innovative medication delivery system's main characteristics. The technique makes sure that drugs are precisely delivered to the skin regions that are affected by the disease by encasing therapeutic substances in specific carriers or nanoparticles. By minimizing the amount of unwanted drugs that is exposed to healthy tissues, this focused strategy reduces the possibility of adverse effects while simultaneously improving the therapeutic efficacy.[12,13]

Nanosponges as a Vehicle for Topical Drug Delivery

Targeting drug delivery techniques has long been an aim in order to achieve the desired result. Initially, the nanosponges drug delivery method was solely intended for topical

application, but in the 21st century, oral and intravenous (IV) administration of nanosponges is now possible.[14,15]

The main goal of the NDDS is to rapidly attain and subsequently sustain the targeted drug concentration by administering a therapeutic dosage of medicine to the appropriate site in the body. During a given treatment period, the drug delivery system should administer the medication at a rate that is regulated by the body's needs.[16,17] The core of these structures contains a wide range of pharmaceutical compounds. The standard diameter is smaller than 1-µm, making them the size of a virus. When compared to other nanocarriers, nanosponges are more potent drug transporters with greater drug-loading capabilities. The polyester nanosponges are a three-dimensional network that is capable of breaking down naturally. To create nanosponges, these polyesters are combined with a crosslinker in a solution. In this case, the polyester dissolves significantly in the body because it is often biodegradable. When the nanosponges scaffold disintegrates, the drug molecules that are loaded in a detrimental manner are released.[18]

New drug delivery and drug targeting systems are now being developed in an effort to reduce medication loss and degradation, avoid negative side effects, boost drug bioavailability, and raise the amount of the drug accumulated in the desired zone. A wide range of compounds can be encapsulated or suspended in nanosponges, which are small mesh-like nanoporous specific structures that can then be integrated into a dosage form.[19] Because of their inclusion and non-inclusion behaviors, nanosponges have an outstanding solubilization capacity for pharmaceuticals that are weakly soluble, despite their shown spherical colloidal structure. Drugs with weak water solubility can be dissolved using nanosponges, which can prolong the drug's release and increase its bioavailability. Because of their outer hydrophilic branching and inner hydrophobic cavities, nanosponges may load both hydrophilic and hydrophobic drugs, providing remarkable flexibility.[20,21,22]

Advantages of Nanosponges[23,24]

- Nanosponges enhance the aqueous solubility of weakly water-soluble substances..
- Nanosponges minimize the frequency of dose.
- Nanosponges can deliver drug molecules in a predictable manner.
- Bacteria are unable to penetrate the nanosponges due to their microscopic 0.25 µm small pore size, which causes them to function as self-sterilizers.
- The drug delivery systems utilizing nanosponges that do not cause mutagenesis, toxicity, or irritation.
- The adverse effects are minimized with nanosponges.
- Nanosponges formulations show better patient compliance.
- Complexes of nanosponges are stable at temperatures of 130 °C and throughout a broad pH range of 1 to 11.
- Easy to scale up for commercial production.
- Immiscible liquids can be incorporated.
- Protects APIs from degradation and provides stability.
- Unpleasant flavor can be masked.
- Drug release profiles can be varied from rapid, to medium to delay release, according to dose requirement.
- Nanosponges are free-flowing and are cost-effective.

Disadvantages of Nanosponges[24]

- Chances of dose dumping are possible.
- Only small molecules can be encapsulated not large molecules.
- Chances of retarded release are possible.
- They can affect the degree of crystallization of drugs.

Synthetic Compounds used for Treatment of Skin Infections[25]

Salicylic acid

Salicylic acid, which is benzoic acid with an ortho hydroxy group, is a monohydroxy benzoic acid. A substance that may be synthesized synthetically or by combining the leaves of wintergreen with white willow bark. An odorless white to light brown solid, salicylic acid has no color, and sinks slowly when combined with water. It has fungicidal, bacteriostatic and keratolytic agent. *Escherichia coli* produces a metabolite that is salicylic acid. It works by destroying keratin, a protein that plays a role in the development of the skin.

Silver nitrate

In order to treat pyogenic and umbilical granulomas, epistaxis, corns, and warts, epithelial tissues have been chemically cauterized with silver nitrate. Currently, wart treatment is more common in the UK as 95% silver nitrate caustic applicator pencils are easily accessible without a prescription.

Cantharidin

Cantharidin interacts with mitochondria to produce acantholysis, clinical blister development, and epidermal cell death helpful for the treatment of warts.

Erythromycin

Erythromycin an antibiotic that is used for the treatment of skin infections caused by bacteria. In sensitive bacteria, erythromycin binds with the 23S ribosomal RNA molecule located in the 50S subunit of ribosomes to prevent the synthesis of new proteins. It is used to treat severe acne, burns and minor cuts.

Adapalene

It is used to treat acne vulgaris. It also decreases the number of severities of acne pimples and promotes quick healing of pimples that do develop. It works by affecting the growth of cells and decreases swelling and inflammation.

Herbal Compounds in Dermatological Nanosponges

Drug candidates investigated for use in dermatological and

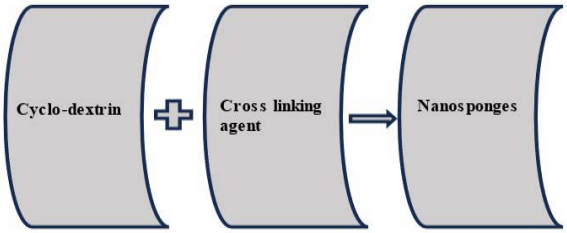

Figure1: Formation of nanosponges

cosmetic applications utilising nanosponge delivery systems is shown in Table 1.

Lemongrass oil

The emulsion solvent evaporation approach was employed to successfully incorporate Lemongrass oil into an ethyl cellulose nanosponge, which was subsequently incorporated into Carbopol hydrogel. Based on its controlled release profile and particle size, the F9 formulation—one of the nine hydrogels integrated with nanosponges loaded with lemongrass—was selected for further research. When F9 was placed in the hydrogel, the nanosponge structure's integrity remained unchanged. The spongy structure with tiny holes was observed using scanning and transmission electron microscopy surface inspection. The *in-vivo* antifungal activity and skin irritation were not observed from the male albino rats treated with the selected combination. With the potential advantage of reducing the risks associated with its use, these results may be positive for the actual execution of lemongrass oil acceptance in pharmaceutical manufacturing.[26]

Cinnamon oil

The volatile oil of cinnamon essential oil (CEO) is derived from *Cinnamomum zeylanicum* and is recognized as one of the most important natural oils due to its antibacterial properties. The nanosponges were manufactured using the solvent emulsion diffusion method, and the efficacy was evaluated by fourier transform infrared spectroscopy (FTIR), particle size, field emission scanning electron microscopy (FE-SEM), *in-vitro* dissolution, *in-vitro* antibacterial, agar diffusion method, *in-vivo* antibacterial activity, skin irritation, and stability studies. Essential oils could possibly be integrated into topical gels for easy administration, and nanosponge carriers may be a more therapeutically effective way to deliver essential oils.[27]

Table 1: Drug candidates investigated for use in dermatological and cosmetic applications utilising nanosponge delivery systems [25-46]

S.No.	*Drug candidate*	*Formulation*	*Application*	*References*
1.	Fluconazole	Hydrogel	Anti-fungal	25
2.	Lemongrass oil	Hydrogel	Antifungal	26
3.	Cinnamon oil	Gel	Anti-microbial	27
4.	Benzoyl peroxide	Gel	Acne	28
5.	Econazole nitrate	Lacquers	Anti-fungal	29
6.	*Butenafine	Gel	Antifungal	30
7.	Clobetasol propionate	Hydrogel	Psoriasis Treatment	31
8.	Curcumin and Caffeine	Gel	Psoriasis Treatment	32
9.	Itraconazole	Gel	Antifungal	33
10.	Dithranol	Hydrogel	Psoriasis Treatment	34
11.	Bifonazole	Hydrogel	Anti-fungal	35
12.	Quercetin	Gel	Anti-inflammation	36
13.	Ketoconazole	Hydrogel	Antifungal	37
14.	Isoniazid	Gel	Treatment of skin infections	38
15.	Imiquimod	Hydrogel	Treatment of skin infections	39
16.	Butenafine Hydrochloride	Gel	Antifungal	40
17.	Clindamycin	Hydrogel	Treatment of Flesh-Eating Disease- Necrotizing Fasciitis	41
18.	Sertaconazole Nitrate	Hydrogel	Antifungal	42
19.	Terbinafine Hydrochloride	Hydro-gel	Anti-fungal	43
20.	Nystatin	Hydro-gel	Treatment of candidiasis	44
21.	Voriconazole	Hydrogel	Anti-fungal	45
22.	Metronidazole	Hydrogel	Anti-microbial	46

Figure 2: Acne marks reduction kit[52]

Figure 3: Cucumber & turmeric anti-acne skin repair face gel[53]

Figure 4: Acne facewash neam & aloe vera[54]

Figure 5: USTRAA anti acne spot gel[55]

Figure 6: Acne eraser night cream[56]

Figure 7: Anti acne cleansing foam[57]

Figure 8: ARATA refreshing face wash[58]

Figure 9: Anti acne gel[59]

Figure 10: Phyto gel with centella asiatica horsetail extract [60]

Curcumin, caffeine

Curcumin and caffeine-loaded nanosponges gels are the polyherbal extracts. They are successfully obtained as an active ingredient for nanosponges formulation with variations in the drug ratio using the hot melt method and incorporated into topical gels. To examine all nine possible experimental runs, a completely randomized factorial design (32) was constructed. The gels were made by adjusting the concentration of the polymer guar gum (X2) and gelling agent carbopol-934 (X1). These two independent factors were examined for their influence on the formulated gels' viscosity (Y1) and *in-vitro* % drug release (Y2). Further evaluations of NS and nanogels were carried out. To improve the formulation, *in-vivo* animal tests have been performed using a mouse model of imiquimod-induced psoriasis.[33]

Azelaic acid

For the treatment of acne and hyperpigmentation disorder, azelaic acid is a promising agent with side effects like skin irritations, rashes, dryness and burning. Its limited solubility

makes it difficult to formulate a suitable formulation. Cyclodextrin nanosponges were prepared by the melt technique, using β-cyclodextrin (β-CD) as the polymer and diphenyl carbonate (DPC) as the crosslinker (Figure 1). Based on the results of each investigation carried out, encapsulating azelaic acid in nanosponges improved the drug solubility, release, and safety while maintaining sufficient antibacterial, antioxidant, and anti-tyrosinase action.[48]

Silymarin

Silymarin-loaded nanosponges were fabricated hot melt method for skin cancer application. Based to the study, nanosponges have the capacity to modify the potential of SLY related to skin cancer. However, the benefits of the research and delivery system will be enhanced and broadened by loading the nano-formulation into an appropriate topical formulation and carrying out an in-depth investigation into the anti-melanoma mechanistic study.[49]

Murraya koenigii

Murraya Koenigii extract nanosponges were synthesized by the quasi-emulsion solvent diffusion method. Based on the study, formulated nanosponges have the capacity to burn wound healing. *In-vivo* studies indicate that *M. Koenigii* nanosponges have cured the burn wound and show nearly no side effects.[50]

Babchi oil

Cyclodextrin base babchi oil nanosponges were synthesized by a solvent evaporation method. Then, babchi oil nanosponges were formulated as a hydrogel. Because there was no erythema or irritation in the *in-vitro* irritation potential of BONS-HG, the produced hydrogel formulation seems to be safe for topical use. Targeting BO to the dermis and epidermis was recommended by CLSM research. The produced BONS-HG demonstrated a strong antipsoriatic activity ($p < 0.001$) in addition to histological evaluation and assessment of oxidative stress indicators. It was seen from the study that there were no side effects of BONS-HG and they are a safe and effective alternative for psoriasis.[51]

Role of nanosponges formulations in the skin infections treatments:

Skin is considered as the most important part of the body when it comes to infections caused by viruses, bacteria, fungus and other types of microorganisms because skin covers the whole body of the person. Skin is highly prone to viruses, bacteria and fungi. Human papillomavirus (HPV) infection is the main cause of warts. Warts are a typical cutaneous viral infection. The virus affects the epidermis, the top layer of skin, and produces an excessive quantity of keratin, a hard protein. The additional keratin gives a wart its rough, hard texture. Warts mainly occur in the top layers of the skin and wart viruses are communicable and can be shared by touching the wart or anything that has come into contact with it. Bacteria and viruses cause acne, pigmentation, and warts. A wide range of compounds can be encapsulated or suspended in nanosponges, which are small mesh-like nanoporous specific structures that can be integrated into a dosage form (Table 2). Because of their inclusion and non-inclusion behaviors, nanosponges possess an extremely high solubilization capacity for pharmaceuticals that are weakly soluble despite their shown spherical colloidal structure. Drugs with weak water solubility can be dissolved using nanosponges, which can prolong the drug's release and increase its bioavailability. Because of their outer hydrophilic

Table 2: Some herbal marketed formulations[52-60]

S.No.	*Marketed product*	*Herbs used*	*Brand*	*Reference*
1	Acne Marks Reduction Kit Fights Acne & Pimples Controls Excess Oil (Figure 2)	Apple Cider Vinegar, Niacinamide, Neem, Glycerin	Mamaearth	52
2	Cucumber & turmeric Anti-Acne Skin Repair Face Gel (Figure 3)	Turmeric (*Curcuma longa*) Manjistha (*Rubia cardifolia*), Cucumber (*Cucumis sativus*), Aqua, Triethanolamine, carbomer, disodium EDTA, *C. sativus* oil, phenoxyethanol, potassium sorbate, glycerine	Mantra Authentic ayurveda	53
3	Acne Facewash Neam & Aloe vera (Figure 4)	Neam, aloe vera, rose water, lavender oil	Vyom india	54
4	USTRAA Anti Acne Spot Gel (Figure 5)	Neem, salicylic acid	Ustraa	55
5	Acne Eraser Night Cream (Figure 6)	Tea tree, basil, neem, cocoa, hyaluronic, niacinamide.	inveda natural ayurveda	56
6	Anti Acne Cleansing Foam (Figure 7)	Tea tree, tulsi, neem, wintergreen.	Kama ayurveda	57
7	ARATA Refreshing Face Wash (Figure 8)	Apricot seed powder, lemon, coconut oil, organic flax seed, peppermint leaf extract	Arata	58
8	Anti Acne gel (Figure 9)	Willow bark extract, pear extract, mint, aloe vera, soyabean extract, jojoba ester	Satthwa	59
9	Phyto gel with centella asiatica horsetail extract (Figure 10)	*Centella asiatica,* Horsetail extract	Earth-rhythm	60

Table 3: Patents filed on nanosponges[61]

S.no.	*Patent number*	*Patent name*
1	JP6100762B2	Nanoparticles encapsulated in membranes and methods of use
2	W02009149883A1	Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies.
3	201821029366	Reconstituable hydrogel powder of dapsone nanosponges useful in the treatment of acne
4	W02006002814A1	Ultrasound assisted synthesis of cyclodextrin-based nanosponges.
5	WO2006121870A3	Silicon nanosponge particles
6	WO2021053039A1	Process of preparing of nanosponges
7	202121024881	Anti-fungal preparation with curcumin and luliconazole nanosponges
8	US1164205B1	Buccal formulation of avanafil with enhanced bioavailability and prolonged duration
9	WO2023133517A1	Subdermal implant for sustained drug delivery
10	US10632070B2	Hydrogel toxin-absorbing or binding nanoparticles
11	2071/MUM/2014	Starch nanosponges
12	202021008717	A method of producing stable lithium silicate nanosponges for capturing CO_2

branching and inner hydrophobic cavities, nanosponges may load both hydrophilic and hydrophobic drugs, providing remarkable flexibility. Patents filed on nanosponges is shown in Table 3.

Herbal drugs can be used in treating of skin infections combined with synthetic compounds and to increase the efficacy, solubility and duration of action of the drugs, they can be incorporated into the nanosponges. Nanosponges are very useful in cases where the drug needs to be delivered in the dermis layer of the skin rather than in the deeper layers. Herbal drugs like *Mahonia aquifolium, Cuscuta reflexa, Beberis vulgaris, Chelidonium majus, Rheum Ribes, Hypericum perforatum, and Hibiscus sabdariffa* and *H. perforatum* has shown good activity for the viruses and bacteria that cause skin infection. Standard drugs like salicylic acid can be used in combined with such plants for the synergistic effects for the cure of warts. Nanospongeformulation of the drugs can show effective results for the treatment of warts and other skin diseases. Nanosponge formulations like gel, hydrogel, serum, cream can be formulated for treating warts and other skin infections.

Synergistic effect of herbal and synthetic compounds

the synergistic effect of herbal and synthetic compounds represents a promising avenue in drug discovery and therapeutic interventions. Across numerous cultures, herbal therapies have been utilized over years, exhibiting a rich pharmacopeia of bioactive chemicals. Herbal extracts have a variety of pharmacological properties because they are frequently intricate blends of phytochemicals. These compounds could interact with different biological targets, offering a comprehensive approach to well-being. However, difficulties, including uniformity and bioavailability, have hindered their use in contemporary practice. However, synthetic molecules solve some of these issues by providing precise dosing and structure. A synergistic effect can be achieved by combining the beneficial characteristics of each, optimizing therapeutic benefits while minimizing drawbacks. The complementary effects of synthetic and natural chemicals combine to provide a synergistic impact that is larger than the sum of their separate contributions. By working together, we can overcome resistance mechanisms, minimize adverse effects, and increase efficacy. To enhance their bioavailability or extend their duration of action, synthetic chemicals can be incorporated to some herbal extracts to boost their anti-inflammatory, antibacterial, and antifungal activities.

Future perspective

the field of medical research is experiencing an evolution as a result of the utilization of nanoscale technologies. Reduced toxicity of drugs when a controlled customized medication release method is applied because it is possible to have better therapy results. Through integrating synthetic and natural substances, nanosponges have the potential to transform cure of skin disorders in the quickly evolving field of dermatological advances. By the incorporation of the herbal drug with synthetic drugs, a synergistic effect can be attained. Responsive and customized release mechanisms that are triggered by factors specific to the skin or the surroundings can begin the new era of smart nanosponges. Real-time monitoring and dynamic therapy adaptations may be achievable with digital health technology, and the legitimacy of these innovative formulations will be strengthened by rigorous clinical validation and regulatory advancements. Warts and other skin problems can be effectively treated in the future by combining synthetic and natural substances in an effective manner to provide comprehensive, personalized, and long-lasting dermatological care solutions. The goals of research should be to ensure safety profiles, optimize dosing

regimens, and elucidate the molecular mechanisms behind these synergistic effects.

CONCLUSION

In conclusion, the combination of synthetic and natural substances can work synergistically to advance treatment techniques. The combined strategy utilizes the accuracy and optimization provided by synthetic chemicals in addition to the many pharmacological characteristics of plant extracts. Nano size and porous characteristics of the nanosponges help them to easily penetrate the skin. Drugs incorporated inside the nanosponges have good skin penetration and avoid negative side effects. By combining herbal drugs with synthetic compounds, the synergistic effect can be achieved and the cure of warts and other skin diseases becomes easy. Herbal plants and standard drugs like salicylic acid can work synergistically to heal warts. For the treatment of skin infections, the nanosponge formulation has shown promising results. Treatments for warts and other skin infections can be achieved through the development of nanosponge formulations in the forms of gel, hydrogel, serum, and cream.

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CONFLICT OF INTEREST

Nil

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