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A REVIEW ON PLANT-BASED NANOSPONGES FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Topical drug delivery has emerged as a key strategy for localized and controlled therapeutic interventions. Traditional systems such as ointments and creams often suffer from limitations, including poor skin permeation, uncontrolled drug release, and adverse effects like irritation and dermatitis. Nanosponges (NSs), a novel class of porous, polymeric nanocarriers, offer a promising alternative by enabling enhanced solubility, stability, biocompatibility, and sustained release of both hydrophilic and hydrophobic drugs. Various preparation methods—such as solvent methods, emulsion solvent diffusion, ultrasound-assisted synthesis, and melt techniques—allow flexible design of nanosponge systems tailored to specific therapeutic needs. Particularly, plant-derived bioactive compounds encapsulated into nanosponge carriers have shown improved bioavailability, stability, and therapeutic efficacy, addressing challenges of poor solubility and low absorption. Studies highlight successful applications of nanosponge formulations in antifungal, anticancer, antimicrobial, antidiabetic, anti-psoriatic, and wound-healing therapies. Despite their potential, nanosponge systems face limitations such as dose dumping, scalability issues, and inability to encapsulate larger biomolecules. This review explores the fundamentals of nanosponge technology, preparation methods, characterization, and applications, with special emphasis on plant-based nanosponge formulations. Future prospects include integrating green nanotechnology, targeted drug delivery, and clinical translation for improved therapeutic outcomes.

Keywords: Topical drug delivery, nanotechnology, nanosponges, emulsion solvent diffusion, ultrasound-assisted synthesis, bioactive compounds, bioavailability, targeted drug delivery etc

Introduction

Topical drug administration is a localized drug delivery system anywhere in the body through

ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system **(Bhowmik, 2012).** Nanomedicine brings about the revolutionary and development in the medical sciences, applying nanotechnology in the medicines by employing nanoscale materials could be useful to monitor, control, construct and repair the biological systems **(Ventola et al., 2010).** In recent years, pharmaceutical scientists have explored nanotechnology for temporal and targeted drug delivery systems **(Radaic et al., 2020).** There have been various nanocarriers systems including metallic, polymeric-nanoparticles, nano-suspension, nano-tubes, nanofibers and nanosponges (NS) extensively used for the effective treatment of infectious diseases, besides the commercial application in the consumer products. Reports have shown that apremilast loaded nanoparticles increased drug solubility, bioavailability and efficacy in the treatment of psoriasis **(Anwer et al., 2019).** Smart hand-wash prepared by *Azadirachta indica*, silver nanoparticles was found effective against the pathogenic microbes contrary to commercial hand sanitizers **(Ahmed et al., 2019).** Nanoparticle matrix of chitosan showed potential antifungal activity against fungal pathogens **(Bautista-Baños et al., 2017).** Nanoemulsion of olive oil showed a marked enhancement in permeability and efficacy of amphotericin B **(Hussain et al., 2016).** Nanosponges (NS) prepared by β-cyclodextrin proclaimed to enhance the solubility of BCS class II and IV drugs **(Kang et al., 2019).** Nanosponges (NS) have been tested to deliver drugs, biocatalysts and gases, adsorption of toxic materials **(Varan et al., 2020).** Recently an increase in interest towards the development of nanosponges based drug delivery system was observed in order to improve the solubility and bioavailability of poorly soluble drugs.

Nanosponges in Drug Delivery

Nanosponges are tiny mesh-like structures **(Figure 1)** in which a large variety of substances can be encapsulated **(Trotta et al., 2012)**. They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior **(Swaminathan et al., 2013)**. Nanosponges have recently been developed and proposed for drug delivery. Nanosponges can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability. Nanosponges are able to load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility **(Swaminathan et al., 2013)**. Nanosponges are more like a three dimensional network or scaffold. The backbone is a long length of polyester which is mixed in solution with small molecules called crosslinkers that act like tiny grappling hooks to fasten different parts of the polymer together **(Shinde et al., 2011).**

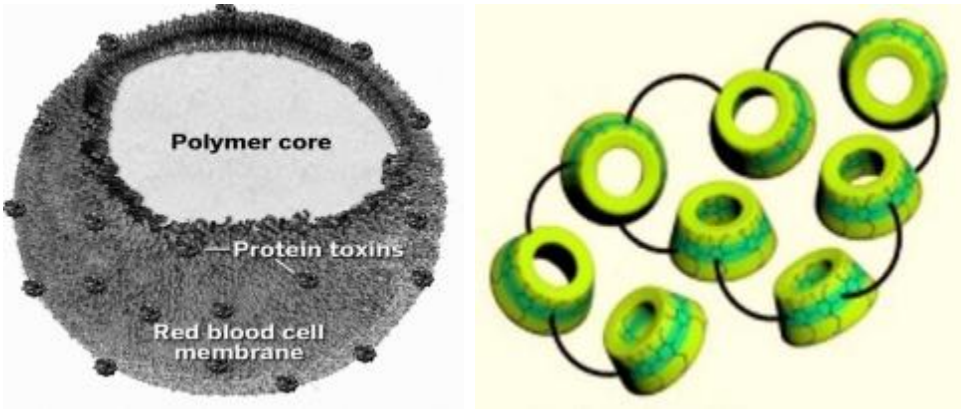

Figure 1: Nanosponge (Polymer and Beta-cyclodextrin)

Properties of Nanosponges:

- This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility.
- The nanosponges are capable of carrying both lipophilic and hydrophilic drugs.
- Efficacy and shelf life of drugs can be prolonged if compared to the non-complexes from by using nanosponges as drug delivery system, higher therapeutic activities are observed being the concentration of the active molecules the same.
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- Nanosponges are non-irritating and non-mutagenic, non- allergic and nontoxic.
- Nanosponges can disperse at molecules level, highly insoluble principles, stabilizing and protecting their structures, from chemicals, light, oxygen etc.
- Extended release –continuous release up to 12th allows incorporation of immiscible liquid improves material processing –liquid can be converted to powders. They can be formed in a sub microns spherical particle. They can be obtained in a wide range of dimensions of the particle **(Singh et al., 2022).**

Chemicals used in Nanosponges Preparation

Polymer: The type of polymer used will affect the formation and performance of the nanosponge. For complexation, the cavity size of the nanosponge should be suitable for accommodating drug molecules of a specific size. The ability of the polymer to crosslink depends on functional groups and reactive groups to be substituted. The choice of the polymer depends on the desired release and the drug to be encapsulated. Ex- Hyper crosslinked polystyrenes, cyclodextrin and its derivatives like Alkyloxy carbonyl cyclodextrin, Methyl βCyclodextrin, 2-Hydroxy Propyl β-Cyclodextrins.

Co-polymers: Poly (Valerol-actone-allylvalerolactone), Poly (Valerolactone-allylvalerolactone oxepanedione), ethylcellulose, polyvinyl alcohol.

Cross-linkers: The choice of crosslinking agent depends on the structure of the polymer and the drug to be formulated. Ex: Carbonyl diimidazoles, Carboxylic acid dianhydrides, Diphenyl Carbonate, Diaryl carbonates, Diisocyanates, Pyromellitic anhydride, Carbonyl diimidazoles, Epichloridrine, Glutaraldehyde, 2, 2-bis (acrylamido) Acetic acid, and dichloromethane.

Method of Nanosponges Preparations

1. Solvent Method:

The polymer is mixed with a suitable solvent, especially in polar aprotic solvents such as dimethylformamide, dimethyl sulfoxide. This mixture is then added to an excess of crosslinkers, preferably with a crosslinker/polymer molar ratio of 1:4. The reaction is carried out at a temperature from 100 °C to the reflux temperature of the solvent and the time is 1 to 48 h. The preferred cross-linking agents are carbonyl compounds (dimethyl carbonate and carbonyl diimidazole). After the reaction is complete, let the solution cool at room temperature, then add the product to a large amount of excess double-distilled water, vacuum filter to recover the product, and then extend the Soxhlet purification **(Panda et al., 2015).**

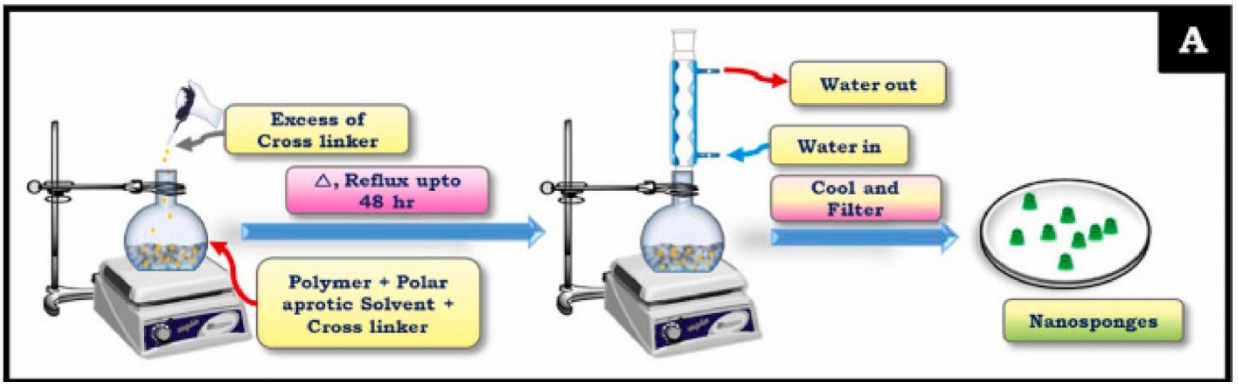

Figure 2: Solvent Method

2. Emulsion Solvent Diffusion Method:

Nanosponges can be prepared using ethyl cellulose and polyvinyl alcohol in different concentrations. Different ratios of drug to the polymer are used to improve drug loading and obtain tailored release. The dispersed phase containing the drug and polymer dissolved in 20 ml of dichloromethane is slowly added to a certain amount of polyvinyl alcohol in 100 ml of aqueous external phase, and a magnetic or mechanical stirrer is used at a stirring speed of 1000-1500 rpm for 3-5 h. The formed nanosponges are collected by filtration and dried in an oven at 40 °C for 24 h and packaged in a container **(Kapileshwari et al., 2020)**.

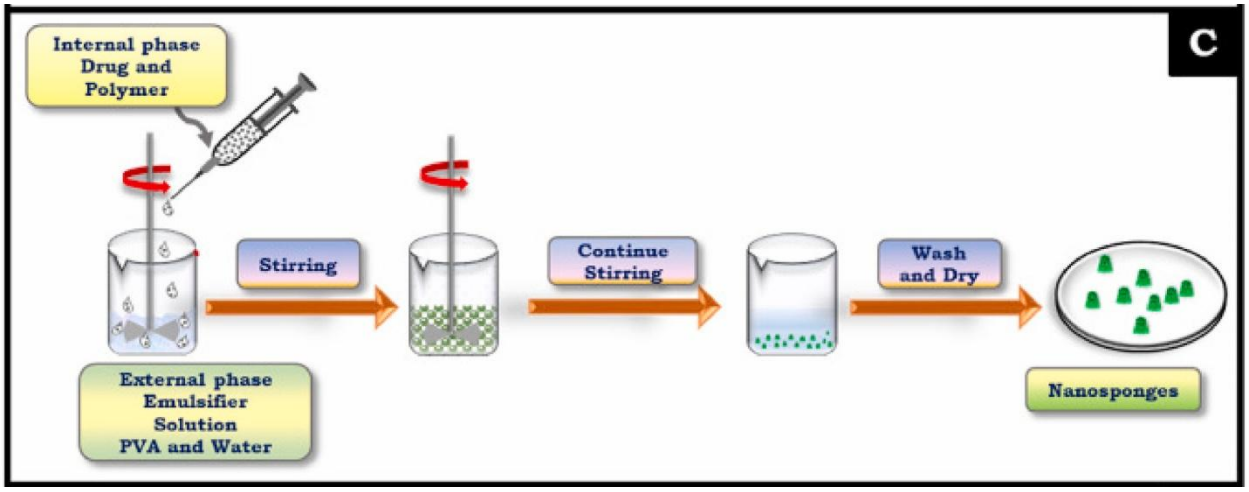

Figure 3: Emulsion Solvent Diffusion Method

3. Ultrasound-assisted Synthesis:

In this method, the polymer reacts with the cross-linking agent under solvent-free and ultrasonic treatment. Here, the polymer and cross-linking agents are mixed in the flask. Place the flask in an ultrasonic bath filled with water, heat it to 90 ºC and sonicate it for 5 h. Let it cool and wash with water to remove unreacted polymer. Purification was performed by prolonged Soxhlet extraction with ethanol. Dry the product under vacuum and store at 25 ºC **(Jyoti et al., 2016)**.

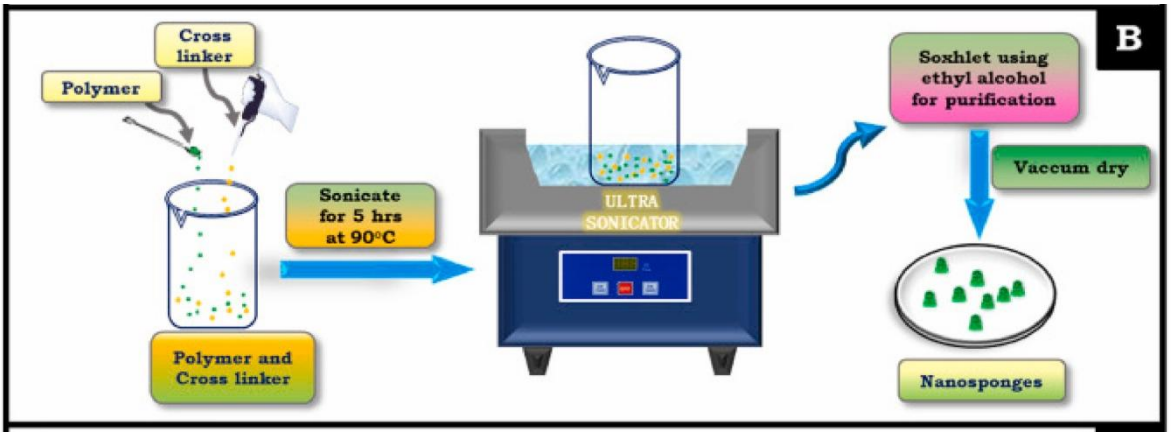

Figure 4: Ultrasound-assisted Synthesis

4. Quasi-Emulsion Solvent Diffusion:

Nanosponges can also be prepared by the quasi-emulsion solvent diffusion method using different polymer amounts. To prepare the internal phase, eudragit RS100 is dissolved in a suitable solvent. Then, the drug can be added to the solution and dissolved under ultrasound at 35 °C. Pour the inner phase into the PVA aqueous solution (outer phase) and stir for 1 h and then filter the mixture to separate the nanosponges. The nanosponge is dried in a 40 ºC air heating oven for 12 h **(Darandale et al., 2013)**.

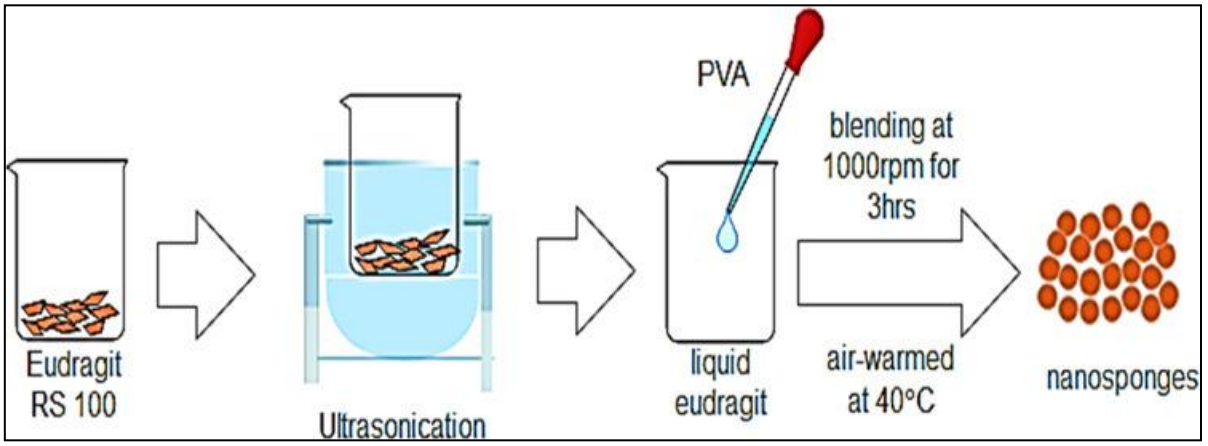

Figure 5: Quasi emulsion solvent method

5. Melt method

The crosslinker and the polymer are melted together in the melting process. All the ingredients were finely homogenized. NSs were collected by washing the acquired product repeatedly with a suitable liquid. Cleaning the product, extracts the waste polymer and reagents which are unreacted and divides the product into the form of NSs **(Rao and Bhingole, 2015).** Such blank NSs were further exposed to the encapsulating of narcotics.

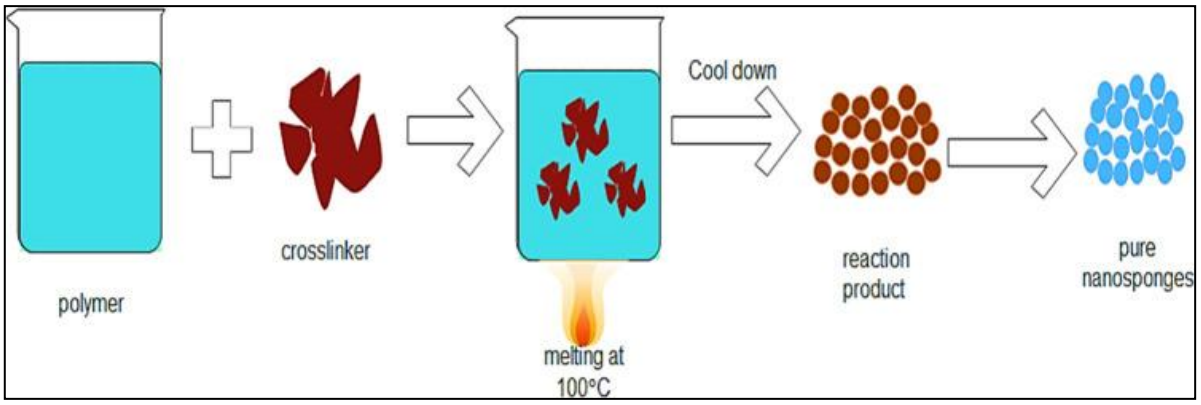

Figure 6: Melt method

Characterization of Nanosponges:

- **Zeta potential:** Surface charge is measured by adding an electrode. Equipment for measuring particle size can be used (Zeta Sizer).
- **Thin Layer Chromatography:** The Rf values of a drug molecule significantly decrease in thin layer chromatography, which aids in recognising the complex formation between the drug and nanosponge.
- **Infra-Red spectroscopy:** Infrared spectroscopy can be used to evaluate how medicinal molecules interact with nano sponges in the solid state. When a compound is formed, nano sponge bands frequently only change significantly. The presence of hydrogen in different functional groups is shown by infrared spectral investigations **(Ramnik et al., 2010; Duchěne et al., 1986).**

- **Single Crystal X-ray Structure Analysis:** Additionally, the inclusion structure and its interactions may be studied using this method. A precise relationship can be established by determining how host and outside molecules interact.
- **X-ray Diffractometry:** Utilizing powder X-ray diffractometry, inclusion complexes in solid state are found. If we take liquid into consideration, it has no unique diffraction pattern and completely varies from a complex Nano sponge. A physical mixture's diffraction pattern is produced by the fusion of two elements. They result in various peaks for a mixture and are helpful in figuring out chemical breakdown and complicated creation.
- **Thermo-analytical methods:** It can be determined using thermo-analytical techniques whether the drug substance changes as a result of the heat breakdown of the Nano sponge. It is possible to see changes in the thermogram produced by DTA and DSC, such as broadening, shifting, the development of additional peaks, or the elimination of particular peaks. The creation of inclusion complexes can also be supported by changes in weight loss **(Vavia et al., 2006).**
- **Porosity:** This evaluation parameter gives the extent voids, of the NSs. For the study of porosity, helium pycnometer is used since the gas can flow between and through the channel mediums present in NSs. The material's true volume is calculated by helium displacement **(Donato and Lazzara, 2012).**

$$\% \text{ Porosity} = \frac{bulk\ volume - true\ volume \times 100}{bulk\ volume}$$

- **Swell Index:** The Brunauer–Emmett–Teller NS testing was performed using the N_2 adsorption micrometric ASAP analyzer. Pre-heat treatment was given to the samples at 120 °C for 2 h before carrying out the study. At optimum temperature and after achieving equilibrium, a steady quantity of dehydrated NS sample (W_d) was added to the bath. The exterior surface was then dehydrated and then measured using filter paper (W_h). The procedure was performed three times, and an average W_h value was calculated **(Sherje et al., 2017).**

$$\textbf{Swelling ratio} = W_h/W_d$$

- **Nuclear magnetic resonance (NMR) spectroscopy:** NMR techniques like 13C,1H, 2D NMR, high-resolution Magic Angle spinning techniques help in understanding the structure of CD crosslinked polymers. The shift in chemical shift values (δ) indicates transfer of proton among species in reaction and hence ascertains structure of the NSs **(Martínez-Richa and Silvestri, 2012).**

Factors influencing nanosponge formation

- **Type of polymer**

Type of polymer used can influence the formation as well as the performance of Nanosponges. for complexation, the cavity size of nanosponge should be suitable to accommodate a drug

molecule of particular size **(Singh et al., 2016).**

- **Type of drugs**

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below **(Singh et al., 2016).**

- Molecular weight of drug should be in between 100 to 400 Daltons.
- Drug molecule consists of less than five condensed rings.
- Solubility in water should be less than 10mg/ml.
- Melting point of the substance should be less than 250°C.

- **Temperature**

Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature **(Challa et al., 2005).**

- **Method of preparation**

The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases freeze drying was found to be most effective for drug complexation **(Challa et al., 2005).**

- **Degree of substitution**

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule **(Singh et al., 2016)**.

Applications of nanosponges in topical delivery

Conventional topical systems such as ointments and creams are often less effective in achieving skin permeation due to their poor efficiency and association with side effects such as burning, contact dermatitis, and stinging sensations, which arise from the uncontrolled release of drugs **(Nor et al., 2017; Butani et al., 2014).** Therefore, nanotechnology-based approaches have become major areas of interest over the past few decades.

One such novel nanocarrier system, particularly effective when formulated as a hydrogel, is the nanosponge (NS) delivery system **(Batheja et al., 2011)**. Nanosponges are porous, spongy, spherical, and small-sized polymeric structures that release drugs in a controlled and predictable manner **(Bolmal et al., 2013).** They are free-flowing, self-sterilizing, cost-effective, and stable across a wide pH range (1–11) and at temperatures up to 130 °C.

The multiple advantages of nanosponges, such as improved safety, enhanced product stability, better aesthetic characteristics, and non-irritancy, make them a suitable approach for the development of topical preparations **(Aldawsari et al., 2015).** A wide range of topical agents can be safely incorporated into nanosponges for controlled release **(Sharma and Pathak, 2011).**

Local anesthetics, antifungals, and anti-acne agents are among the potential categories of drugs that can be effectively delivered through topical nanosponge formulations.

Plant -Based nanosponges

Exploring the principles of ancient Indian medicine, particularly Ayurveda, reveals a promising path forward. Nature appears to hold a treasure trove of potent compounds with diverse therapeutic properties **(Choudhari et al., 2020).** Natural products exhibit remarkable chemical versatility and biological specificity, along with reduced toxicity, making them valuable candidates for the development of new and innovative medications.

The modern pharmaceutical market increasingly favors bioactive compounds derived from natural sources, especially due to concerns over the side effects of conventional drugs. Phytochemicals, valued for their nutritional benefits, not only play a role in preventive healthcare but also show promise in cancer treatment. However, many phytochemicals face challenges related to their hydrophilic nature, high molecular weight, and limited absorption across lipid cell membranes, which results in low bioavailability and reduced efficacy.

Currently, pharmacotherapy largely relies on traditional dosage forms, which provide therapeutic benefits only to a limited extent, posing significant challenges in the effective treatment of diseases. As research progresses, the exploration of natural compounds offers renewed optimism in the ongoing battle against these formidable health challenges **(Amol Dombe and Jaykumar Shirote, 2023).**

Table 1: Plant based Nanosponge and their applications

S. No.	Drug	Carrier	Results	Reference
1.	Ferulic acid	Cyclodextrin nanosponges	Improved antibacterial activity and storage stability	Amani et al., 2022
2.	Quercitrin	Cyclodextrin nanosponges	Enhanced release; improved activity against SARS-CoV-2 and A549 cells	Abou Taleb et al., 2022
3.	*Wrightia tinctoria* extract	Cyclodextrin nanosponges	Sustained drug release with significant anti-psoriatic effect.	Iriventi and Gupta, 2020
4.	Curcumin	β-Cyclodextrin and Cyclodextrin-based nanosponge	Controlled release; effect dependent on cross-linking density	Mashaqbeh et al., 2021
5.	Babchi (*Psoralea corylifolia*)	β-cyclodextrin nanosponges	Improved solubility, photostability, and safety	Kumar et al., 2018

	oil			
6.	Withaferin-A (WFA)	Ethyl cellulose nanosponges	Increased anticancer efficacy of natural product	Shah et al., 2021
7.	Fisetin	B-Cyclodextrin Nanosponges	NSs showed strong anti-breast cancer potential	Aboushanab et al., 2025
8.	Cinnamon essential oil (CEO)	Ethyl cellulose nanosponges	Significant antimicrobial activity without skin irritation	Kaur et al., 2020
9.	Terpenoids-rich Boswellia Carterri ethyl acetate extract	Binary cyclodextrin based nanosponges	Displayed promising therapeutic effects	Ibrahim et al., 2024
10.	Ellagic acid (EA)	Cyclodextrin-based nanosponge	Improved oral bioavailability (↑AUC)	Mady et al., 2018
11.	Nanosponge (NS) based topical gel of curcumin (CUR) and caffeine (CFN) combination	Beta-cyclodextrin based nanosponge	Enhanced anti-psoriatic efficacy; faster onset	Iriventi et al., 2020
12.	α-Mangostin Loaded Nanosponges	Ethyl cellulose nanosponges	Prolonged antidiabetic response with improved compliance	Usman et al.,2021
13.	NSs alpha-amyrin (AMY) and higenamine (HGN)	Curdlan-based nanosponges	Synergistic anticancer effect with sustained release	Dombe and Shirote, 2025
14.	Lemon grass oil	Ethyl cellulose nanosponges	Exhibited antibacterial, antifungal, antitumor, and neuroprotective effects	Ahuja et al., 2020
15.	Ellagic acid	Cyclodextrin	Enhanced solubility,	Sharma et

	(EA)	nanosponges	photostability, and antioxidant activity	al., 2022
16.	Quercetin, curcumin and phenethyl caffeate	Cyclodextrin nanosponges	Protected antioxidants and enabled controlled release	Guernelli et al., 2020
17.	Murraya koenigii extract	Eudragit RS 100 - nanosponges	Showed significant burn wound healing activity	Jadhav et al., 2019
18.	Ferulic acid	Cyclodextrin nanosponges	Suitable system for poorly soluble bioactives	Rezaei et al., 2019

Limitations

- **Encapsulation size restriction**: Nanosponges are primarily suited for small molecules and may not efficiently deliver large biomolecules such as proteins or nucleic acids.
- **Dose dumping risk**: Uncontrolled release may occur under certain physiological conditions.
- **Scalability and reproducibility**: Industrial-scale production with uniform size and morphology remains challenging.
- **Incomplete toxicity data**: Long-term safety, biodegradation, and accumulation risks are still under investigation.
- **Formulation challenges**: Stability during storage, potential drug–polymer interactions, and regulatory approval remain significant barriers **(Singh et al., 2016)**.

Future prospective:

Plant-based nanosponges hold immense potential in the development of novel topical drug delivery systems due to their biocompatibility, controlled release profile, stability, and ability to enhance drug solubility. Future research should focus on large-scale, cost-effective production methods and standardization of preparation techniques to ensure reproducibility and safety. Incorporating advanced characterization tools and in vivo studies will be essential to establish their pharmacokinetic and pharmacodynamic profiles. Moreover, integrating plant-derived nanosponges with emerging technologies such as stimuli-responsive delivery, personalized medicine, and green synthesis approaches may further expand their therapeutic applications. Clinical trials will play a crucial role in translating laboratory findings into practical healthcare solutions, particularly for chronic skin conditions, infections, and cancer therapy. With continuous advancements, plant-based nanosponges are expected to evolve as a promising, sustainable, and patient-friendly platform for future topical drug delivery innovations.

Conclusion

Nanosponges represent a significant advancement in topical drug delivery, offering controlled release, enhanced stability, and improved patient compliance compared to conventional systems. Their ability to encapsulate a wide range of bioactive compounds—including plant-derived phytoconstituents—makes them especially valuable in addressing global health challenges such as cancer, infections, and inflammatory diseases. Plant-based nanosponge formulations have shown remarkable therapeutic promise by overcoming barriers of solubility, stability, and bioavailability. Collectively, nanosponge technology bridges modern nanomedicine with traditional plant-based therapeutics, opening avenues for novel, safe, and effective treatments.

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