https://doi.org/10.48047/AFJBS.6.7.2024.957-985

THE NEW INSIGHT OF NANOSPONGES IN TOPICAL DRUG DELIVERY

Poonam.P. Patil [1] *, Dr. Sunil J. Aher [2], Dr. Indrayani D. Raut [3], Dr. Sandip Bandgar[4], Pallavi S. Ghule [2]

[1] Department of Pharmaceutical Chemistry, Sanjivani College of Pharmaceutical Education and Research, At Sahajanandnagar, Post-Shinganapur, Tal-Kopargaon, Dist-Ahmednagar, Maharashtra 423603, India.

[2] Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, At Sahajanandnagar, Post-Shinganapur, Tal-Kopargaon, Dist-Ahmednagar, Maharashtra
423603, India

[3] Department of Pharmaceutics, Rajarambapu College of Pharmacy, Kasegaon, Taluka - Walwa, Sangli, Maharashtra 415409

[4] Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth Vadgaon, Maharashtra 416112

***Corresponding Author*:**
Prof. Poonam Prakash Patil
Assistant Professor, HOD Department of Pharmaceutical Chemistry,
SRES's Sanjivani College of Pharmaceutical Education and Research Kopargaon, Maharashtra, India-423603.
Email: poonamprakashpatil4174@gmail.com

Mobile No: 09689942854

Orcid ID: https://orcid.org/0000-0001-5778-3091

Volume 6, Issue 7, June 2024

Received: 25 April 2024

Accepted: 03 june 2024

Published: 20 June 2024 doi:

10.48047/AFJBS.6.7.2024.957-985

ABSTRACT

Skin-related diseases are a leading cause of illness and require precise treatment without harming the body. There are a variety of treatments available that have various side effects. Nanotechnology offers advantages like higher therapeutic efficiency, property of drug targeting, and reduction in toxicity. Nanosponges involve porous, spongelike surfaces, and colloidal sizes less than 1 µm in diameter which allows for high loading capacity. Nanosponges are simple to alter the pharmaceutical release contour and enhance formulation stability while reducing the drug's adverse effects. The ability of Nanosponges to self-sterilize is their most notable feature. They are used as anti-allergic, non-mutagenic, and non-irritant in many investigations. In this review, the collection of NSs, with preparation and characterization parameters and applications in various fields is included. This review will be quite useful in the future in exploring the Nanosponge delivery system in different areas.

Keywords: Nanosponge, cancer therapy, cyclodextrin, solvent methods, optimization of nanosponges.

1. Background

Skin covers approximately 2 m^2 of the human body.[1] Skin-related diseases are a third-leading cause of illness and one of the top ten causes of disability.[2] Skin-related diseases involve Acne, Atopic Dermatitis, Psoriasis, Impetigo, Scleroderma, and Vitiligo caused by fungal or bacterial infections, allergens, or genetic factors. Antibiotics, medicated creams, ointments, or gels, laser treatment, steroid pills, and surgical procedures are among the treatment options available. However, they have numerous drawbacks that render them ineffective in treating skin infections. Local anaesthesia was required for the majority of skin surgery.[3] Vehicles, creams, and solutions have drawbacks because the of quick evaporation of water/alcohol, that is measured as cooling, affects spreading on skin, resulting in an inconsistent topical dosage form.[4] Steroids may lead to melanocyte inhibition and stellate scarring-like adverse effects.[5] To prevent this type of adverse effects we have to use the nanotechnology offering advantages like higher therapeutic efficiency, the property of drug targeting, lower toxicity, and bitter taste masking.[6]

2. Main text

2.1. Nanoparticles in the Treatment of skin diseases

NPs are the smallest particles, usually between 10 to 1000 nm in size.[7] Large number of drug molecules can entrap in NPs because of their small size and high surface area.[8] Different types of NPs such as metal and metal oxides, liposomes, fullerenes, nanoemulsion, polymeric NPs, solid–lipid NPs, polylactide-co-glycoside NPs, and so on, with varying physical and chemical properties, are shown in figure 1[9]. After appropriate surface modifications, NPs can extend circulation half-life and used to target specific diseases.[10] NPs can also include imaging and theragnostic agents. [11,12]

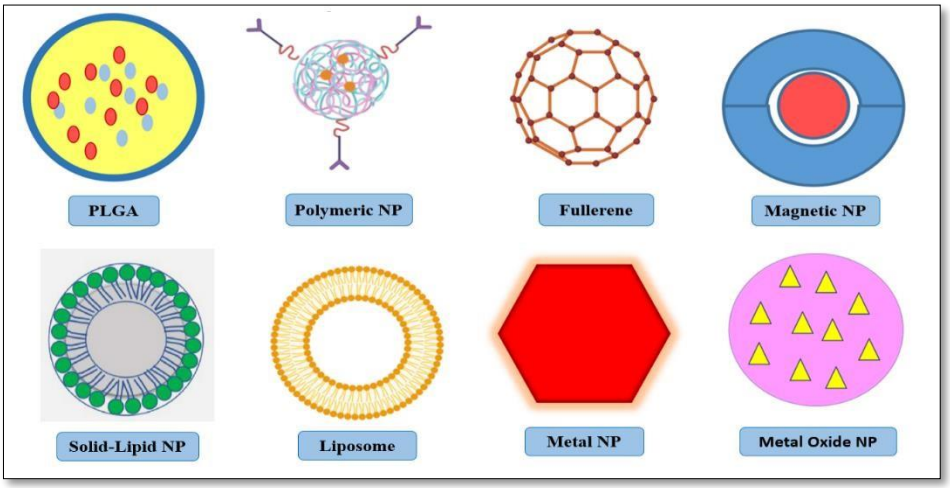

Figure 1: Different types of Nanoparticles

2.2. Drug delivery in skin

Barriers of skin penetration involve:

1) Stratum Corneum: The high concentration of lipids in SC's intracellular matrix, results in a hydrophobic lamellar structure that considerably enhances the barrier capabilities of SC.[13,14] 2) A broad dermal layer is divided into two layers of connective tissue. The superior and inferior papillary and reticular dermis. Numerous supporting elements, including hair follicles, nerves, blood arteries, perspiration and oil glands, are found in the dermis. The third one is hypodermis, that involve Blood vessels, nerves, and hair follicles. Its high fatty layer serves as an energy reservoir, it isolates the body and tolerate pressure by acting as cushions. [15-18] Beyond this barrier, efficient drug delivery systems are required. Nanotechnology used to modify drug penetration by controlling their release and lengthening the period of permanence by ensuring direct contact with the SC. When there is a trauma or swelling the barrier is partially disrupted. This may facilitate the penetration of NPs. NPs have the potential to improve drug particularity, bioavailability, and efficacy while also improve patient acceptance [19] **2.3. Introduction to Nanosponges**

NSs are networks of sphere-shaped porous particles less than 1 μm in diameter that are arranged in three dimensions [20] that serve as frames for drug molecules. Different NSs along with drugs are tabulated in **Table 1**.

Properties of NSs [20, 42-45] includes site-specific drug delivery with targeting and high carrier capacity. Along with swelling properties they are effectively used for low soluble drugs. NSs can trap both hydrophilic and hydrophobic moieties. They are nonlethal, porous, and stable up to temperatures of around 300°C. The nature of NSs can be either crystalline or para-crystalline and they start the controlled release of the medicine at a specified target spot [41].

2.3.2. Advantages and disadvantages of NSs

2.3.2.1. Advantages[46,45,47,48]

Due to the use of biocompatible ingredients, NSs are non-toxic, non-allergenic, or nonmutagenic. Because NSs have a diameter smaller than a bacterium (the average size of the pore is 0.25nm), the formulation is self-sterile. NSs remain stable between pH values of 1 and 11 and also aid in masking the unpleasant taste of the drug. It shows extended release for up to 12-24 hours. It is possible to convert liquids to powders that reduce drug irritability while maintaining efficacy. It is proposed to help minimize adverse effects, better stability, more elegance, and more formulation flexibility. [49]

2.3.2.2. Disadvantages [50,51]

NSs include only small drug molecules. The number of crosslinking influences loading capacity of drug. There is a chance of dose dumping because the crosslinker dissolves so quickly. The particulate nature of NSs designed for topical use and the inconvenience associated with their direct application over the skin, are significant limitations.

Type of nanosponge	Material	Active Ingredient	Synthesis Method	Route of delivery	Therapeutic Use	Purpose	Year of Study	References
Polymer	β-cyclodextrin	Piroxicam	Melt Method	Oral	Analgesic activity	For improved internal solubility and analgesic activity	2023	21
Polymer	β-cyclodextrin	Vitamin D_3	Mechanochemical method	Oral	Supplement material	To increase the chemical and biological properties of Vitamin D_3.	2023	22
Polymer	β-cyclodextrin	Domperidone	Microwaveassisted approach	Oral	Antiemetic activity	For enhancing the target drug Domperidone solubility	2023	23
Biomaterial/ Metal	RNA/ ascorbic acid	Platinum, Paladinum NP	Green Synthesis	-	Hydrogen evolution reactions	Improved catalytic performance	2023	24
Biomaterial	Platelet membrane	Plateletmimicking perfluorocarbon	Ultrasonic emulsification and coextrusion	Oral	Antiplatelet activity	To solve issues of Rapid functional reversal of Antiplatelet Agents	2023	25
Polymer	β-cyclodextrin	Dithranol	Solvent evaporation and Melt method	Topical	Antipsoriatic activity	To improve poor stability and solubility	2023	26
Polymer	Ethyl cellulose	Ribociclib	Ultrasonication	Oral	Anticancer activity	Enhance Ribociclib effectiveness in the treatment of breast cancer.	2022	27

Polymer	Ethyl cellulose	Abemaciclib	Solvent evaporation	Oral	Anticancer activity	For sustained cytotoxicity against human breast cancer cells lines	2022	28

Polymer	β-cyclodextrin	Quercetin	Ultrasound Synthesis method	Oral/ Parenteral	Anticancer activity	Increase its activity against SARS-CoV-2 virus and lung cancer	2022	29
Polymer	Ethyl Cellulose	Hespertin	Quasi-emulsion solvent diffusion	Topical	Antiinflammatory activity	Sustained anti-inflammatory effect	2022	30
Polymer	β-cyclodextrin	Limonene	Melting Method	Oral	Antibacterial activity	Solubility enhancement and stability improvement	2021	31
Polymer	β-cyclodextrin	Curcumin	Melting Method	Oral/ Topical/ parenteral	Pharmaceutical application	Examined curcumin's complexation stability	2021	32
Polymer	Ethyl cellulose	Butenafine	Solvent emulsification technology	Topical	Antifungal activity	To treat the skin infections of fungi.	2021	33
Polymer	β-cyclodextrin	Clobetasol Propionate	Melting Method	Topical	Anti-psoriatic activity	Avoid skin related side effects	2021	28
Polymer	β-cyclodextrin	Griseofulvin	Ultrasonication method	Oral	Antifungal activity	For enhancing bioavailability and masking bitter taste	2020	20

Polymer	β-cyclodextrin	Curcumin and caffiene	Melt Method	Topical	Anti-psoriatic activity	Gel is acts as a useful system for the treatment of psoriasis.	2020	34
Polymer	β-cyclodextrin	5 Fluorouracil	Ultrasound Assisted Method.	Oral	Anticancer activity	To enhance its retention in gastric tumors and to reduce its systemic side effects	2020	35
Polymer	Ethyl cellulose	Brigatinib	emulsion solvent evaporation technique	Oral	Anticancer activity	Sustained delivery for non-small lung cancer	2020	36
Polymer	Ethyl cellulose	Fluconazole	Emulsion-solvent diffusion method	Topical	Antifungal activity	To increase drug permeation through skin	2019	37
Polymer	β-cyclodextrin	Curcumin	Melting method	Oral	Anticancer activity	Study the effect on drug stability, solubility, and cytotoxicity.	2018	38
Polymer	β-cyclodextrin	Rilpivirine Hydrochloride	Microwave assisted synthesis	Oral	Anti-HIV activity	For enhancing oral bioavailability of Rilpivirine hydrochloride.	2017	39
Polymer	β-cyclodextrin	5 Flourouracil	Melting method	Oral	Anticancer activity	Enhanced anticancer activity makes medicines more soluble and limits their release.	2021	40
Polymer	Ethyl cellulose	Lornoxicam	Emulsion solvent diffusion method	Topical	NSAID activity	To reduce side effects orally and develop topical delivery	2022	41

Table 1: Drugs encapsulated in NSs

2.3.3. Types of NSs

There are different types (figure 2) of NS that can be designed and formulated depending on the polymer used.

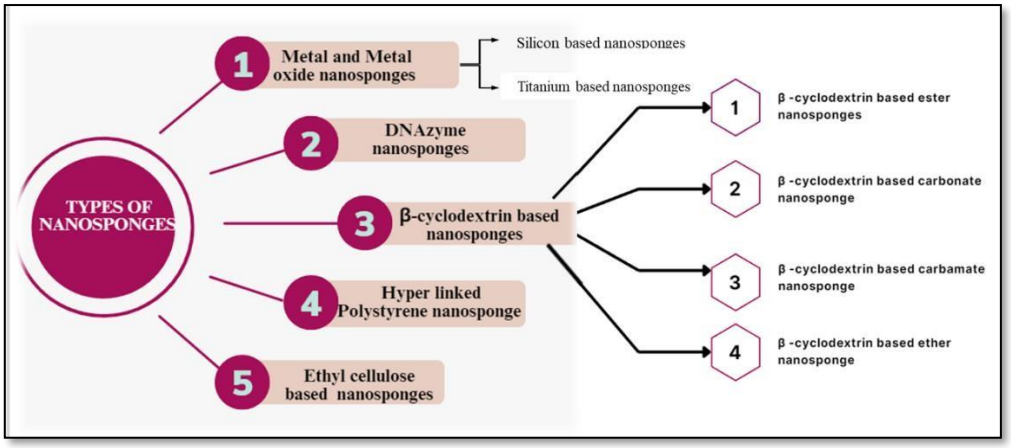

Figure 2: Types of NSs

2.3.3.1. Metal and metal oxide NSs

Metallic NSs formed by combining two or more metals and are preferable to those made of a single metal because of their porous nature. [46] It has a small particle size, a high surface area, and higher stability. ***2.3.4.2. Silicon-based NSs***

Silicon NS particles are made from silicon powder of metallurgical grade. Silicon NS with high porosity is used as a sensor, drug carrier material, catalyst, photosensitizer, adsorbent material, explosive material, and fuel cell electrodes. It is also used as a precursor for high surface area ceramic materials such as SiNa and SiC.[10]

2.3.4.3. Titanium-based NSs

They are prepared from a closely organized TiO_2 network, having higher specific area. Polystyrene microspheres coated with titanium-based NSs are constructed of polymerizable surfactants that have been copolymerized with styrene. [47]

2.3.4.4. DNAzyme NSs

DNAzymes have ease of synthesis, high selectivity, cheap cost, and high catalyst effectiveness. They can be formulated to attach and cleave a complementary target mRNA. [52]

2.3.4.5. Cyclodextrin-based NSs (CDNSs)

Cyclodextrins (CDs) are produced by enzymatic reactions on starch with Bacillus macerans amylase. The types of natural CDs (α, β, and γ), each with glucose units of 6,7, and 8 respectively.[25] CDNSs are obtained by covalently bonding CDs to a crosslinker. The CD structure is a bifunctional conical cylinder with a lipophilic hole and an outer hydrophilic layer.

[53] Based on the type of crosslinker used CDNS divided into various types as per Table 2. Table 2: Types of CDNSs

Sr. No.	Types of CDNS	Crosslinker used	Property	Reference
1	CD-based ether NSs	Epichlorohydrin, bisphenol A diglycidyl ether, ethylene glycol diglycidyl ether, 1,4-butanediol diglycidyl ether, E-51 epoxy resin	- A high level of chemical resistance -variable swelling ability	54,55
2	CD-based carbonate NSs	1,1'- Carbonyl Diimidazole, triphosgene, Dimethyl carbonate, and Diphenyl carbonate	- Less prone to swelling, - Stable in mildly alkaline and acidic liquids. - Small surface area	56,57
3	CD-based ester NSs	dianhydrides, Epiclon-B-4400; citric acid, and 2,6-naphthalene dicarboxylic acid (NDCA).	- Easily hydrolyzed in aqueous media	58-61
4	CD-based urethane/ carbamate NSs	Diisocyanates like, methylene diphenyl diisocyanate	- A rigid structure, -Resistant to chemical deterioration -Negligible swelling	62,63

2.3.4.6. Hyper-linked polystyrene-based NSs

Large amounts of stiff intramolecular structures were added when certain polystyrene coils were suspended in diluted solvents, leading these coils to strongly constrict and form spherical NSs. In the presence of linear polystyrene non solvent, these NSs showed enhanced swelling and a rise in surface area. [10] ***2.3.4.7. Ethyl cellulose NSs***

Ethyl cellulose-based NSs involved main sustained release polymer ethyl cellulose and different crosslinkers prepared generally by an emulsion-solvent diffusion method [28] and an ultrasonicated emulsion solvent evaporation method. [64]

2.3.5. FACTORS AFFECTING NS FORMATION

***2.3.5.1. Type of polymer and crosslinker*:**

Whether the NS is soluble in water or any other solvent depends on the type of crosslinker that is utilised [65]. The cavity size of the NS must be sufficient to fit a particular drug molecule in order for complexation to occur. [66]

2.3.5.2. Degree of substitution

The capability of the parent polymer to form NS is influenced by the substituent's location, kind, and number. [59] If there are more substituents greater degree of crosslinking occurs thus resulting highly porous NSs. [67] ***2.3.5.3. Drug's characteristics*** [68]

The characteristics of drugs molecules that will come into contact with NSs involve Molecular weight should be in the range of 100 to 400 Dalton. The drug structure should be less than five stacked rings. Water solubility and melting point should be less than 10mg/ml and 250°C. 50[29]

2.3.5.4. Complexation nature

It is probable that decrease in drug/NS interaction forces, such as van der Waal and hydrophobic with a rise in temperature, is the cause of the apparent stability constant of the drug NS complex decreasing with temperature.[69]

2.3.6. Loading of Drugs into NSs

Drug loading mechanism into NSs is categorized into three types. Encapsulation involves drug particles are enclosed inside the polymer. Another type involve the drug and polymers are complexed together with the aid of electrostatic charges. Conjugation includes conjugation by forming a covalent bond. [70] For drug loading, Plain NSs and the drug were dissolved in ultrapure water, mixed for 24 hours in the dark at a steady room temperature, and then centrifuged at 2000 rpm for a predetermined amount of time. The supernatants were then freeze-dried for 72 hours as given in Figure 3. [32] Then lastly collect the product and stored in well closed container.

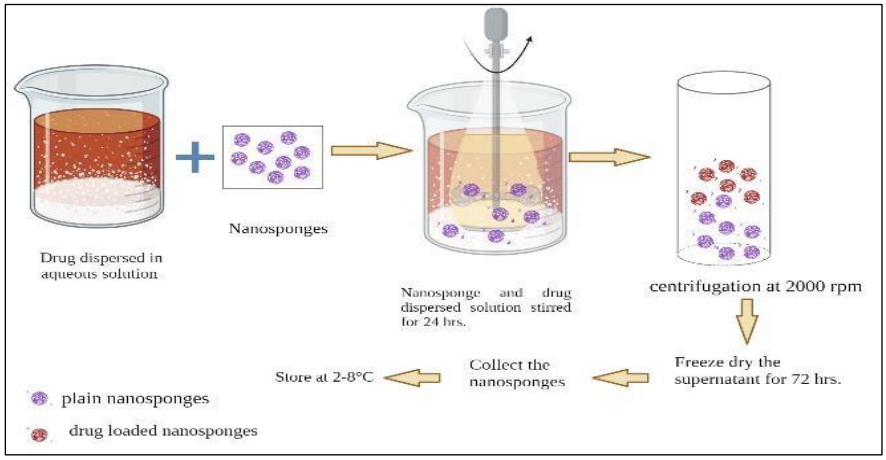

Figure 3: Drug Loading Method

2.3.7. Optimization of NSs

Optimization entails determining the best starting materials to create a formula that produces the required results. NSs can be easily optimized due to their simple composition, as evidenced by the examples in the table 3.[46]

Table 3: Examples of optimized NSs

Optimization Model	Variables	Results	Reference
4^2 factor design	Drug: polymer ratios Volume of solvent, PVA concentrations stirring time % yield, drug content EE	The % yield increases as the drug-polymer ratio increases. Solvent volume and drug content have inverse relation.	30
Design of Expert	Polymer amount (mg) Concentration of PVA Phase evaporation rate Particle size Entrapment efficiency	Low amounts of polymer and higher levels of PVA concentration and evaporation rate could produce the lowest particle sizes. Increased polymer content provides improving drug encapsulation.	71
3_2 Factorial design	EC: PVA ratio (w/w) sonication time (min) Particle size Entrapment efficiency Zeta potential	Increase in the concentration of PVA, sonication time and stabilizer there is reducton in the particle size, zeta potential and increse in the stability was observed.	72
3^2 factorial full design	Drug: EC ratio Stirring speed Particle size Entrapment efficiency	By increasing the stirring rate Particle size is decreased.	73
Design Expert (Robust model)	EC (mg) % PVA (w/v) Particle size % EE	Particles size increases slowly with increase in drug: polymer ratio, PVA in 0.5%. More EE results from a higher drug to polymer ratio.	74

Plackett–Burman design	Mass of Adsorbent (mg) Sonication time (min) Volume of Eluent Ultrasonic temperature pH Vortexing time (min) Efficacy of extraction	Sorbent mass, sonication time, and eluent volume were the factors that had the greatest impact on the Extraction Recovery (%) of vitamin B3.	75
3_2 factorial full design	EC: PVA ratio Stirring speed (rpm) Particle size % Lemongrass Oil released	The size of the NS is reduced as the stirring rate is increased. decreased porosity and increased oil entrapment in the hydrophilic matrix, which could lead to slower release rates.	76

2.3.8. Preparation Method of NSs

NSs can be prepared using various methods and then loaded with varying amounts of the drug.

The various methods are given in figure.4 and are described in Table 4.

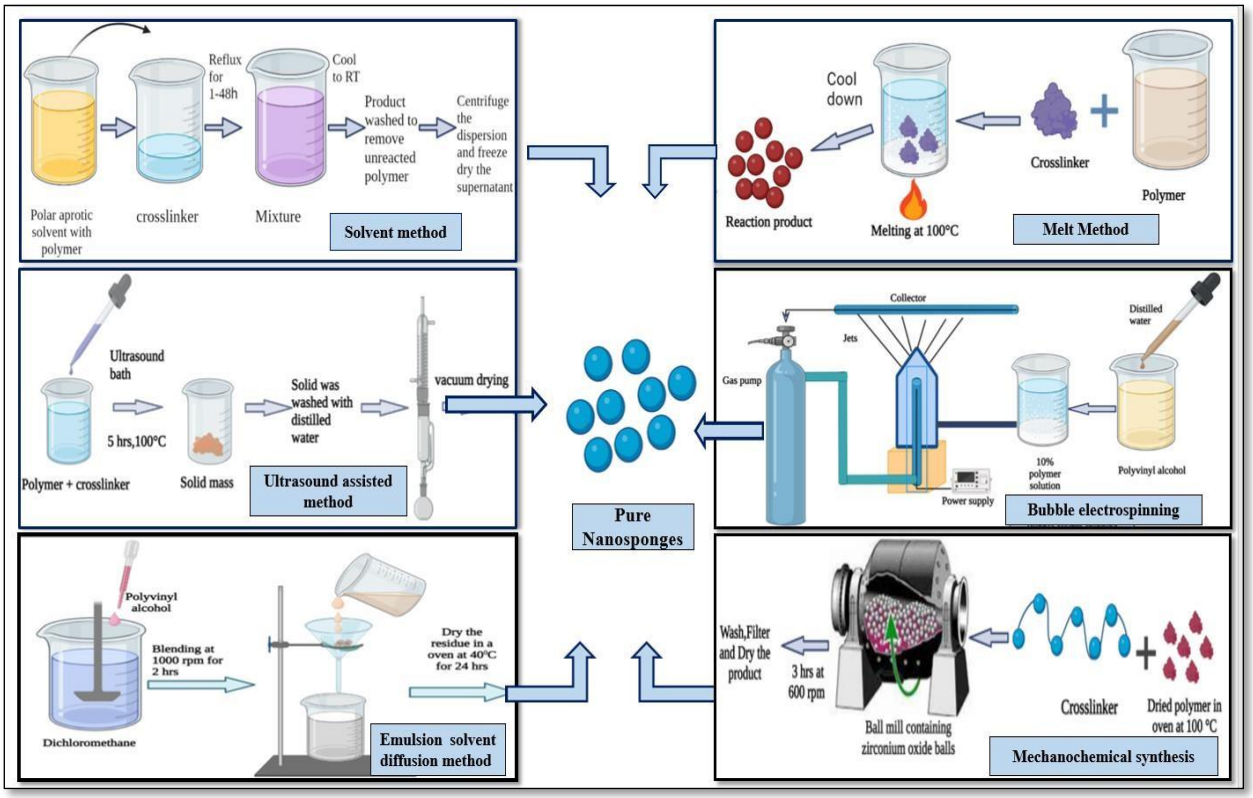

Figure 4: Methods of Preparation of NSs

Table 4: Methods of NS preparation

Method	Properties	Procedure
Ultrasoundassisted technique	Utilizes an ultrasonic water bath. It involves no solvents, making it a procedure that is good for the environment. [77]	Mix ingredients thoroughly before heating for five hours in a water bath to 100 °C. Washing the finished product helped to get rid of unreacted byproducts. [20]
Melt method	Simple, repeatable, and solventfree approach.	Polymer and cross-linker are melted together at 100°C. Using a magnetic stirrer for 5 hours, the product obtained was cooled. Soxhlet may be used to remove impurities. [78]
Synthesis using microwave radiation	Requires less reaction time. [79] Synthesises crystalline NSs. 4 times faster than the melting method.[80]	The drug, cross-linker, and solvent were subjected to microwave irradiation at specific conditions then the solvent was removed by distillation. Soxhlet extracts the Product for 4 hrs.
Solvent method	This method achieves a variable time range by using different temperatures. [77]	Following treatment with a polar aprotic solvent, an excessive amount of the polymer is added to the cross-linking agent solution, refluxing for up to 1 to 48 h. Then cool at RT. [10]
Emulsion solvent diffusion method(ESDM)	This process is based on the emulsification.	The internal phase consisting of a crosslinker and polymer solution, added dropwise into the aqueous solvent, stirred for 1000 rpm for 2 hrs, filtered, and dry in Oven.[81]
Emulsion Solvent evaporation methods	Involves the evaporation of the organic solvent.	Using ultrasonication organic phase (drug+ polymer +cross linker) was emulsified dropwise into the aqueous phase. Stir for 24 hrs, ultracentrifuge, and freeze dry. [33]
Quasi-emulsion solvent diffusion	Requires miscibility of solvents with water.	Emulsification of an organic drug solution that is miscible with water and contains stabilizers. 82[64]
Bubble electrospinning	Process of spinning fibres with the help of electrostatic forces Geometrically observed by the size of the produced bubbles	By using 10% w/v PVA solution, Fibers /sponges were collected using a flat piece of aluminium foil placed 8 cm above the nozzle. Voltages applied ranging from 10 kV to 30 kV. [83]
Mechanochemical synthesis	Absorbing mechanical energy activates chemical bonds, and induces the polymer-crosslinker reaction. [84]	The process occurs in ball mills, with minimal use of solvent or without solvents Synthesis of NSs by mechanochemical approach involves the use of a twin-screw extruder which is capable of fine temperature control. [85]
Chain-Growth Polycondensation Method	polymer end group formed by the monomer reaction becomes greater in reactivity than the monomer itself. [86]	an initiator can be utilized to initiate polymer growth by forming high reactivity points at its tip. [63]

2.3.10. NSs Characterization:

The various evaluation parameters of NSs are tabulated in Table 5 with details of the characterization.

Table 5: Characterization of NSs

Sr. No.	Parameters	Characterization Details
1	*Solubility studies*	Higuchi and Connors demonstrate the use of phase solubility studies.[87] An Erlenmeyer flask is used for sampling and shaken with a mechanical shaker. centrifuged through a 3000 Dalton molecular filter. The solution analysis is done using HPLC to determine the drug concentration. [88]
2	*Morphology study*	Scanning electron microscopy and transmission electron microscopy are used for morphology study.[88]
3	*Particle size, Polydispersity index, and Zeta Potential*	Particle size and the PDI value indicates distribution of particles and ZP indicates particle charge. At 25°C diluted sample is used for evaluation [40]. Negative ZP indicates that NSs are more stable. [89]
4	*Thermoanalytical techniques*	It is used to detect drug substance changes before thermal degradation. It may be due to evaporation and melting-like processes. [90] Analysis is performed in the range of 0 °C to 800 °C at a rate of 10 °C per minute in an air atmosphere with a flow rate of distinct ml/min. [91]
5	*X-ray diffractometry*	It is used for finding the structure and the host-guest interaction of the resulting nano complexes.[92] The crystalline or amorphous nature of the sample can be determined at 5 to 60° in a 2θ scale. [28]
6	*Fourier transform infrared spectroscopy*	To study the drug-excipients interaction and to check the physical stability of the drug. [20] The detection range for the detection of IR is 4000 to 650 cm^{-1}.[72]
7	*Nuclear magnetic resonance spectroscopy*	For understanding the arrangement of polymers. The changes in chemical shift values (δ) implies proton transfer between species in the reaction and thus determines the NSs structure. [93]
8	*Raman spectroscopy*	Raman spectroscopy explains the behavior of NSs as they change from dry to swollen. The intensity and frequency of Raman spectra indicate structural changes. [94]
9	*Entrapment efficiency*	NSs powdered in mortar, then placed in solvent and set aside for 24 hours. Then the solution was filtered and analyzed using a UV spectroscopic method. The formula is for the calculation of % entrapment efficiency. [72] $\%\ \text{Entrapment Efficiency} = \frac{\text{Nanosponges actual drug content}}{\text{Therotical drug content}} \times 100$
10	*Loading efficiency (%)*	For the determination of drugs loaded in NSs.[69]

		After centrifugation, the supernatant was collected and analyzed with an ultraviolet spectrophotometer.[27] $\text{Loading efficiency} = \frac{\text{Total entrapped drug}}{\text{Weight of NSs}} \times 100$
11	*Thin layer Chromatography*	R_f value results in identifying the formation of the complex between the drug and NSs. [90]
12	*Swelling index*	For swelling index determination samples are preheat-treated at 120 °C for 2 hours. The dehydrated NS (W_d) was added to the bath. After that, the outer surface was hydrated, and the weight (W_h) was measured. [95] The formula for calculation: $\text{Swelling index} = \frac{w_h}{w_d}$
13.	*In vitro drug release study*	Used to evaluate the kinetics and type of release of drugs. [27] For this Franz diffusion apparatus is used, consisting of the donor phase with a fixed amount of drug. The receiving phase was made up of phosphate buffer. The drug concentration was monitored using the HPLC method for 48 hours. [96]
14	*Stability determination*	As per ICH guidelines Room temperature (25±2 °C), Freezing temperature (4±2 °C), and accelerated thermal state (60 ±2°C, 75% RH). At specific time intervals (Initial, first, and third months), withdraw samples and tested for stability. [28]

2.3.11. Applications of NSs in the medical field and the atmosphere

2.3.11.1. Cancer Therapy

NS products are crucial in medication delivery, particularly in cancer therapy, as they are up to five times more effective at suppressing tumor development than direct injection of medicines. [10]

2.3.11.2. Topical Agents

NS's application for drug delivery mechanism is a crucial technique for regulating and prolonging the release of skin-retaining medicines. To prevent rashes and other unwanted effects, an NS-based drug delivery system is used. [97] *2.3.11.3. NS as a Biocatalyst and Protein Delivery Carrier*

Preservation of original protein structures and long-term storage are challenges for protein formulation. In the NSs-based technique, proteins are embedded in poly(amidoamine) NSs made of the CD to enhance protein stability.[98]

2.3.11.4. NSs for Enhancement of Solubility

Using a carrier system like NSs, which helps to trap medicinal compounds in a specific pore by enhancing the solubility and bioavailability of therapeutic products in controlled release patterns, can solve the primary problem of solubility. [10] *2.3.11.5. NSs for Removal of Organic Impurities from Water*

A well-known NS, nano porous CD polyurethanes, was employed for removing pollutants from water. The CD polymer can attract a variety of chemical molecules by forming complexes of the guest-host type.[99] The hydrophobic environment provided by the cavity in CD allowed it to enhance its strong attraction for organic molecules at water-solid interfaces. [100] The waterinsoluble CD polymers are effective in removing waste from water gathered at a particular power plant and serve an important function. [101]

2.3.11.6 NS in SARS-CoV-2 Management

Lung type II epithelial cells or macrophage-derived NSs are capable of attracting and then removing the SARS-Cov-2 virus. The same receptors that viruses utilize to enter cells were found in the NSs, and it was believed that coronavirus would be prevented from infecting the cell by connecting with NSs. SARS-CoV-2 is neutralized and loses its capacity to infect cells when it is treated with NSs. NSs make viral mutational changes and obscure viral species. Also, it is able to identify the host cell that still serves as the virus's target and take action to neutralize it (although the quick pace of mutation will provide various difficulties for the establishment of treatments and preventative measures. In a concentration-dependent way, epithelial-NS and Macrophage NS both revealed their ability to neutralize SARS-CoV-2.[102] Cell membranecoated NPs called as cellular NSs. A simple way to improve SARS-CoV-2 inhibition is through surface glycan engineering of host-imitating cellular NSs.[103]

2.3.11.7 Protective Agent against the Photo Degradation

Since gamma-oryzanol has extreme instability and photodegradation it have limited applications. Gamma-oryzanol-based nanosponges provide effective protection against the harmful effects of UV light. Using gamma oryzanol-loaded nanosponges, a gel and an O/W emulsion can be produced. [104]

3. Conclusion

The application of NS for several purposes has created new opportunities for environmental benefits, assessment, and management. For the delivery of medications to the chosen area, the NSs act as both a variable drug transportation medium and a monitored intermediary. NSs also play a role in biosensing to detect a broad range of disease biomarkers and in the improvement of both health and the environment in many ways. Future concepts include the concurrent distribution of multiple molecules and broadening the range of applications from medicinal delivery to drug encapsulation for a variety of applications. Future trends include NSs designed for phase change material storage. Future research should be also focused on the functionalization of NSs to reduce potential toxicity, improve biosafety, and increase specificity/selectivity in biocompatibility and biodistribution. Future research should concentrate on their complex formation performances, structural variability, commercialization, long biosafety evaluations, inexpensive/mass manufacturing, and specific nano-toxicological evaluations.

Acknowledgements:

The management of SRES, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, India, is gratefully acknowledged by the writers for providing all the necessities for the completion of this work.

References

1. Gupta S, Bansal R, Gupta S, Jindal N, Jindal A. Nanocarriers and nanoparticles for skin care and dermatological treatments. Indian Dermatology Online Journal. 2013 ;4(4):267-72. DOI: https://doi.org/10.4103%2F2229-5178.120635.
2. WHO, "Global meeting on skin-related neglected tropical diseases", 2023, accessed on 04/05/2023, https://www.who.int /news-room/events/detail/2023/03/27/defaultcalendar/global-meeting-on-skin-related-neglec ted-tropical-diseases-skin-ntds.
3. Teresa TS, Gary PL, Scott MD. Surgery of the Skin. Mosby, 2005, 39-58. Chapter 3 - Anesthesia and Analgesia. DOI: https://doi.org/10.1016/B978-0-323-02752-6.50008-0.
4. Ivens UI, Steinkjer B, Serup J, Tetens V. Ointment is evenly spread on the skin, in contrast to creams and solutions. The British Journal of Dermatology. 2001; 145(2):264-7. DOI: https://doi.org/10.1046/j.1365-2133.2001.04344.x
5. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. Indian Dermatology Online Journal. 2014 ;5(4):416-25. DOI: https://doi.org/10.4103/2229-5178.142483.

6. Marques MS, Lima LA, Poletto F, Contri RV, Guerreiro ICK. Nanotechnology for the treatment of pediatric diseases: A review. Journal of Drug Delivery Science and Technology. 2022; 75,103628. DOI: http://dx.doi.org/10.1016/j.jddst.2022.103628.

7. Mohanraj VJ, Chen Y. Nanoparticles - A Review. Tropical Journal of Pharmaceutical Research. 2006; 5(1):561-573. DOI: https://doi.org/10.4314/tjpr.v5i1.14634.

8. Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F, Lammers T. Tumor targeting via EPR: Strategies to enhance patient responses. Advanced Drug Delivery Reviews. 2018; 130:17-38. DOI: https://doi.org/10.1016/j.addr.2018.07.007.

9. Ngowi EE, Wang YZ, Qian L, Helmy YA, Anyomi B, Li T. The Application of Nanotechnology for the Diagnosis and Treatment of Brain Diseases and Disorders. Frontiers in Bioengineering and Biotechnology. 2021; 9:629832. DOI: https://doi.org/10.3389/fbioe.2021.629832.

10. Atchaya J, Girigoswami A, Girigoswami K. Versatile Applications of Nanosponges in Biomedical Field: A Glimpse on SARS-CoV-2 Management. Bionanoscience. 2022; 12(3):1018-1031. DOI: https://doi.org/10.1007%2Fs12668-022-01000-1.

11. Haribabu V, Girigoswami K, Girigoswami A. Magneto-silver core–shell nanohybrids for theragnosis. Nano-Structures & Nano-Objects.

2020; 21(10):100636 DOI: http://dx.doi.org/10.1016/j.nanoso.2020.100636.

12. Sharmiladevi P, Girigoswami K, Haribabu V, Girigoswami A. Nano-enabled theranostics for cancer. Materials Advances. 2021: 2(9):2876–2891. DOI: https://doi.org/10.1039/D1MA00069A.

13. Elias PM. Stratum corneum defensive functions: an integrated view. The Journal of Investigative Dermatology. 2005; 125(2):183-200. DOI: https://doi.org/10.1111/j.0022-202x.2005.23668.x.

14. Lin TK, Zhong L, Santiago JL. Anti-Inflammatory and Skin Barrier Repair Effects of Topical Application of Some Plant Oils. International Journal of Molecular Science. 2017; 19(1):70. DOI: https://doi.org/10.3390%2Fijms19010070.

15. Slominski AT, Manna PR, Tuckey RC. On the role of skin in the regulation of local and systemic steroidogenic activities. Steroids. 2015; 103:72-88. DOI: https://doi.org/10.1016%2Fj.steroids.2015.04.006.

16. Chambers ES, Vukmanovic-Stejic M. Skin barrier immunity and aging. Immunology. 2020; 160(2):116-125. DOI: https://doi.org/10.1111/imm.13152.

17. Yousef H, Alhajj M, Sharma S. Anatomy, Skin (Integument), Epidermis. Study Guide from Stat Pearls Publishing. Treasure Island (FL). 2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470464/.

18. Bragazzi NL, Sellami M, Salem I, Conic R, Kimak M, Pigatto PD. Fasting and Its Impact on Skin Anatomy, Physiology, and Physiopathology: A Comprehensive Review of the Literature. Nutrients. 2019; 11(2):249. DOI: https://doi.org/10.3390/nu11020249.

19. Krishnan V and Mitragotri S. Nanoparticles for topical drug delivery: Potential for skin cancer, Advanced Drug Delivery Reviews 2020; 153:87-108 DOI: https://doi.org/10.1016/j.addr.2020.05.011.

20. Omar SM, Ibrahim F, Ismail A. Formulation and evaluation of cyclodextrin-based nanosponges of griseofulvin as a pediatric oral liquid dosage form for enhancing bioavailability and masking bitter taste. Saudi Pharmaceutical Journal. 2020; 28(3): 349-361. DOI: https://doi.org/10.1016/j.jsps.2020.01.016.

21. Gaber DA, Radwan MA, Alzughaibi DA, Alail JA, Aljumah RS, Aloqla RM. Formulation and evaluation of Piroxicam nanosponge for improved internal solubility and analgesic activity. Drug Delivery 2023; 30(1):2174208. DOI: https://doi.org/10.1080%2F10717544.2023.2174208.

22. Trotta F, Pagliaro P, Bisericaru DM, Cavalli R. Developing New Cyclodextrin-Based Nanosponges Complexes to Improve Vitamin D Absorption in an In Vitro Study. International Journal of Molecular Sciences0. 2023; *24*(6), 5322. DOI: https://doi.org/10.3390/ijms24065322.

23. Vij M, Dand N, Kumar L, Wadhwa P, Wani SUD, Mahdi WA. Optimisation of a Greener-

Approach for the Synthesis of Cyclodextrin-Based Nanosponges for the Solubility Enhancement of Domperidone, a BCS Class II Drug. Pharmaceuticals (Basel). 2023 ;16(4):567. DOI: https://doi.org/10.3390/ph16040567.

24. Topuz F, Patil B, Uyar T. Green one-pot synthesis of bimetallic Pd–Pt nanosponges using biomolecules with enhanced catalytic activity for hydrogen evolution. Materials Advances, 2023; (4) 1900–1904. DOI: https://doi.org/10.1039/D2MA01070D.

25. Xu J, Yan N, Wang C, Gao C, Han X, Yang C, Xu J, Wang K, Mitchell M, Zhang Y, et al. Platelet-Mimicking Nanosponges for Functional Reversal of Antiplatelet Agents. Circ Res. 2023; 132(3):339-354. https://doi.org/10.1161/CIRCRESAHA.122.321034.

26. Kadian V, Dalal P, Kumar S, Rao R. Comparative Evaluation of Dithranol-loaded nanosponges fabricated by solvent evaporation technique and melt method. Future Journal of Pharmaceutical Sciences. 2023; 9(13). DOI: https://doi.org/10.1186/s43094023-00461-9.

27. Ahmed MM, Fatima F, Alali A, Kalam MA, Alhazzani K, Bhatia S. Ribociclib-Loaded Ethylcellulose-Based Nanosponges: Formulation, Physicochemical Characterization, and Cytotoxic Potential against Breast Cancer. Hindawi Adsorption Science &

Technology. 2022, Article ID 1922263, 11 pages. DOI: https://doi.org/10.1155/2022/1922263.

28. Anwer MK, Fatima F, Ahmed MM, Aldawsari MF, Alali AS, Kalam MA, Alshamsan A, Alkholief M, Malik A, et al. Abemaciclib-loaded ethylcellulose based nanosponges for sustained cytotoxicity against MCF-7 and MDA-MB-231 human breast cancer cells lines. Saudi Pharmaceutical Journal. 2022; 30(6), 726–734. DOI: https://doi.org/10.1016/j.jsps.2022.03.019.

29. Taleb SA, Moatasim Y, GabAllah M, Asfour MH. Quercitrin loaded cyclodextrin based nanosponge as a promising approach for management of lung cancer and COVID-19. Journal of Drug Delivery Science and Technology. 2022; 77:103921. DOI: https://doi.org/10.1016%2Fj.jddst.2022.103921.

30. Rodrigues K, Nadaf S, Rarokar N, Gurav N, Jagtap P, Mali P, Ayynar M, Kalaskar M, Gurav S. QBD approach for the development of hesperetin-loaded colloidal nanosponges for sustained delivery: In-vitro, ex-vivo, and in-vivo assessment. Open Nano. 2022; 7, 100045. DOI: https://doi.org/10.1016/j.onano.2022.100045.

31. Salehi O, Sami M, Rezaei A. Limonene loaded cyclodextrin nanosponge: Preparation, characterization, antibacterial activity and controlled release. Food Bioscience. 2021; 42, 101193. DOI: https://doi.org/10.1016/j.fbio.2021.101193.

32. Hadeia M, Rana O and Nizar AS. Evaluation and Characterization of CurcuminCyclodextrin and Cyclodextrin-Based Nanosponge Inclusion Complexation. Polymers. 2021, 13, 4073. DOI: https://doi.org/10.3390/polym13234073.

33. Ahmed MM, Fatima F, Anwer MK, Ibnouf EO, Kalam MA, Alshamsan A. Formulation and in vitro evaluation of topical nanosponge-based gel containing butenafine for the treatment of fungal skin infection. Saudi Pharmaceutical Journal. 2021; 29(5), 467-477. DOI: https://doi.org/10.1016/j.jsps.2021.04.010.

34. Iriventi P, Gupta NV, Osmani RAM, Balamuralidhara V. Design & development of nanosponge loaded topical gel of curcumin and caffeine mixture for augmented treatment of psoriasis. Daru. 2020; 28(2):489-506. DOI: https://doi.org/10.1007/s40199-020-00352-x.

35. Jasim IK, Abd Alhammid SN, Abdulrasool AA. Synthesis and Evaluation of βcyclodextrin Based Nanosponges of 5-Fluorouracil Using Ultrasound-Assisted Method. Iraqi Journal of Pharmaceutical Sciences. 2020; 29(2). DOI: https://doi.org/10.31351/vol29iss2pp88-98.

36. Ahmed MM, Fatima F, Anwer MK, Ansari MJ, Das SS, Alshahrani SM. Development and characterization of ethyl cellulose nanosponges for sustained release of brigatinib for the treatment of non-small cell lung cancer. Journal of Polymeric Engineering. 2020; 40(10): 823–832. DOI: http://dx.doi.org/10.1515/polyeng-2019-0365.

37. Abbas N, Parveen K, Hussain A, Latif S, Zaman S, Shah PA, Ahsan M. Nanospongebased hydrogel preparation of fluconazole for improved topical delivery. Tropical Journal of Pharmaceutical Research February 2019; 18 (2): 215-222. DOI: https://doi.org/10.4314/tjpr.v18i2.1.

38. Pushpalatha R, Selvamuthukumar S, Kilimozhi D. Cross-linked, cyclodextrin-based nanosponges for curcumin delivery - Physicochemical characterization, drug release, stability, and cytotoxicity. Journal of Drug Delivery Science and Technology, 2018; 45,45-53. DOI: https://doi.org/10.1016/j.jddst.2018.03.004.

39. Zainuddin R, Zaheer Z, Sangshetti JN, Momin M. Enhancement of oral bioavailability of anti-HIV drug Rilpivirine HCl through nanosponge Formulation. Drug Development and Industrial Pharmacy. 2017; 43(12):2076-2084 DOI: https://doi.org/10.1080/03639045.2017.1371732.

40. Jasim IK, Abdulrasool AA, Abd-Alhammid SN. Nanosponge Based Gastro retentive Drug Delivery System of 5-Fluorouracil for Gastric Cancer Targeting. International Journal Drug Delivery and Technology. 2021; 11(3), 958-963. DOI: 10.25258/ijddt.11.3.52.

41. Shabaraya AR, Sumana G, Vineetha K. Formulation and Evaluation of Nanospongesloaded Gel of Lornoxicam for Topical Delivery. International Journal Drug

Delivery and Technology. 2022; 12 (2):634-639. DOI: http://dx.doi.org/10.25258/ijddt.12.2.29.

42. Momin MM, Zaheer Z, Zainuddin R, Sangshetti RN. Extended release delivery of erlotinib glutathione nanosponge for targeting lung cancer, Artificial Cells, Nanomedicine, and Biotechnology 2018; 46(5):1064-1075. DOI: https://doi.org/10.1080/21691401.2017.1360324.

43. Pushpalatha R, Selvamuthukumar S, Kilimozhi D. Cross-linked, cyclodextrin-based nanosponges for curcumin delivery - Physicochemical characterization, drug release, stability and cytotoxicity. Journal of Drug Delivery Science and Technology. 2018; 45:45-53. DOI: https://doi.org/10.1016/j.jddst.2018.03.004.

44. Taka AL, Pillay K, Mbianda XY. Synthesis and Characterization of a Novel Bio Nanosponge Filter (pMWCNT-CD/TiO2-Ag) as Potential Adsorbent for Water Purification, in: Springer International Publishing AG 2018 P. Ramasami et al. (eds.). Emerging Trends in Chemical Sciences, South Africa. 2018; 313-343. DOI: http://dx.doi.org/10.1007/978-3-319-60408-4_18.

45. Pawar S, Shende P. A Comprehensive Patent Review on β-cyclodextrin Cross-linked Nanosponges for Multiple Applications. Recent Patents on Nanotechnology. 2020; 14(1):75-89. DOI: https://doi.org/10.2174/1872210513666190603083930.

46. Gore K, Bhattacharya S, Prajapati B. Recent Pharmaceutical Developments in the Treatment of Cancer Using Nanosponges [Internet]. Advanced Drug Delivery Systems. Intech Open; 2023. DOI: http://dx.doi.org/10.5772/intechopen.105817.

47. Gursalkar T, Bajaj A, Jain D. Cyclodextrin based nanosponges for pharmaceutical use: A review, Acta Pharmaceutica. 2013; 63(3):335–358. DOI: https://doi.org/10.2478/acph-2013-0021.

48. Srinivas P, Reddy AJ. Formulation and Evaluation of Isoniazid Loaded Nanosponges for Topical Delivery. Pharmaceutical Nanotechnology. 2015; 3(1):68-76. DOI: http://dx.doi.org/10.2174/2211738503666150501003906.

49. Mohammed BS, Fatima J. Preparation of Posaconazole Nanosponges for Improved Topical Delivery System. International Journal of Drug Delivery Technology. 2022; 12(1):8-14. DOI: http://dx.doi.org/10.25258/ijddt.12.1.2.

50. Tiwari K, Bhattacharya S. The ascension of nanosponges as a drug delivery carrier: preparation, characterization, and applications. Journal of Material Science. Material Medicine. 2022; 33(3):28. DOI: https://doi.org/10.1007/s10856-022-06652-9.

51. Kumar S, Prasad M, Rao R. Topical delivery of Clobetasol propionate loaded nanosponge hydrogel for effective treatment of psoriasis: Formulation, physicochemical characterization, antipsoriatic potential and biochemical estimation, Materials Science & Engineering C Materials for biological

applications. 2021; 119:111605. DOI: https://doi.org/10.1016/j.msec.2020.111605.

52. Jin Y, Liang L, Sun X, Yu G, Chen S, Shi S, Liu H, Li Z, Ge K, Liu D, et al. Deoxyribozyme-nanosponges for improved photothermal therapy by overcoming thermoresistance. NPG Asia Materials. 2018; 10:373–384. DOI: https://doi.org/10.1038/s41427-018-0040-7.

53. Mane PT, Wakure BS, Wakte PS. Cyclodextrin Based Nanosponges: A Multidimensional Drug Delivery System and its Biomedical Applications. Current Drug Delivery. DOI: https://doi.org/10.2174/1567201818666210423091250.

54. Rizzi V, Gubitosa J, Signorile R, Fini P, Cecone C, Matencio A, Trotta F, Cosma P. Cyclodextrin nanosponges as adsorbent material to remove hazardous pollutants from water: The case of ciprofloxacin. Chemical Engineering Journal. 2021; 411:128514. DOI: https://doi.org/10.1016/j.cej.2021.128514.

55. Lai X, Zeng X, Li H, Yin C, Zhang H, Liao F. Synergistic Effect of PhosphorusContaining Nanosponges on Intumescent Flame-Retardant Polypropylene. Journal of Applied Polymer Science, 2012; 125:1758–1765. DOI: http://dx.doi.org/10.1002/app.35646.

56. Utzeri G, Matias PMC, Murtinho D, Valente AJM. Cyclodextrin-Based Nanosponges: Overview and Opportunities. Frontiers in chemistry. 2022; 10:859406. DOI: https://doi.org/10.3389/fchem.2022.859406.

57. Caldera F, Tannous M, Cavalli R, Zanetti M, Trotta F. Evolution of Cyclodextrin Nanosponges. International Journal of Pharmaceutics. 2017;531(2). 470-479. DOI: https://doi.org/10.1016/j.ijpharm.2017.06.072.

58. Pedrazzo A, Caldera F, Zanetti M, Appleton SL, Dahkar NK, Trotta F. Mechanochemical green synthesis of hyper-crosslinked cyclodextrin polymers. Beilstein Journal of Organic Chemistry. 2020; 16, 1554–1563. DOI: https://doi.org/10.3762/bjoc.16.127.

59. Ferro M, Castiglione F, Pastori N, Punta C, Melone L, Panzeri W, Rossi B, Trotta F, Mele A. Dynamics and interactions of ibuprofen in cyclodextrin nanosponges by solidstate NMR spectroscopy. Beilstein Journal of Organic Chemistry. 2017; 13:182–194. DOI: https://doi.org/10.3762/bjoc.13.21.

60. Gholibegloo E, Mortezazadeh T, Salehian F, Forootanfar H, Firoozpour L, Foroumadi A, Ramazani A, Khoobi M. Folic acid decorated magnetic nanosponge: An efficient nanosystem for targeted curcumin delivery and magnetic resonance imaging. Journal of Colloid and Interface Science. 2019; 556:128–139. DOI: https://doi.org/10.1016/j.jcis.2019.08.046.

61. Bachir YN, Bachir RN, Zafour AHZ. Nanodispersions Stabilized by β-Cyclodextrin Nanosponges: Application for Simultaneous Enhancement of Bioactivity and Stability of Sage Essential Oil, Drug Development and Industrial Pharmacy. 2018; 45(2):333347.

DOI: https://doi.org/10.1080/03639045.2018.1542705.

62. Appell M, Evans KO, Jackson MA, Compton DL. Determination of ochratoxin A in grape juice and wine using nanosponge solid phase extraction clean-up and liquid chromatography with fluorescence detection. Journal of Liquid Chromatography & Related Technologies. 2019; 41(12):1-6. DOI: http://dx.doi.org/10.1080/10826076.2018.1544148.

63. Krabicová I, Appleton SL, Tannous M, Hoti G, Caldera F, Pedrazzo AR, Cecone C, Cavalli R, Trotta F. History of Cyclodextrin Nanosponges. Polymers. 2020;12,1122. DOI: https://doi.org/10.3390/polym12051122.

64. Shah HS, Nasrullah U, Zaib S, Usman F, Khan A, Gohar U. F, Uddin J, Khan I, AIHarrasi A. Preparation, Characterization, and Pharmacological Investigation of Withaferin-A Loaded Nanosponges for Cancer Therapy; In Vitro, In Vivo and Molecular Docking Studies. Molecules. 2021; 26:6990. DOI: https://doi.org/10.3390/molecules26226990.

65. Khan KA, Bhargav E, Reddy KR, Sowmya C. Nanosponges: A New Approach for Drug Targetting. International Journal of Pharmacy and Pharmaceutical Research. 2016; 7 (3): 381-396.

66. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: A Novel Class of Drug Delivery System – Review, Journal of Pharmaceutical

Pharmaceut Sci.2012;15(1) 103 – 111. DOI: http://dx.doi.org/10.18433/J3K308.

67. Kamble M, Zaheer Z, Mokale S, Zainuddin R. Formulation Optimization and Biopharmaceutical Evaluation of Imatinib Mesylate Loaded β-Cyclodextrin Nanosponges. Pharmaceutical Nanotechnology. 2019; 7, 343-361. DOI: https://doi.org/10.2174/2211738507666190919121445.

68. Mamtha DP, Viresh KC, Shabaraya AR. Nanosponges: An Overview About The Novel Class of Drug Delivery System. World Journal of Pharmacy And Pharmaceutical Sciences. 2021; 10(6):1014-1027. DOI: 10.20959/wjpps20216-19156.

69. Ravi SC, Krishnakumar K and Nair SK. Nano sponges: A targeted drug delivery system and its applications. GSC Biological and Pharmaceutical Sciences. 2019; 07(03):040–047. DOI: https://doi.org/10.30574/gscbps.2019.7.3.0098.

70. Gowda BHJ, Paul K, Ahmed MG. Current Trends in Applications of Nanosponges: A Multifaceted Drug Carrier System, In: An Introduction to Drug Carriers. Editor: Mohammad Ashrafuzzaman. 2021 Nova Science Publishers, Inc. DOI: http://dx.doi.org/10.52305/MZZS5968.

71. Hafiz MA, Abbas N, Bukhari NI. Quality by design approach for formulation development and evaluation of carboplatin loaded ethylcellulose nanosponges. International Journal of Polymeric Materials and Polymeric Biomaterials. 2021; 71(21):1-13. DOI:

http://dx.doi.org/10.1080/00914037.2021.1933978.

72. Poornima, Priya S. Gastroretentive Floating Tablets Enclosing Nanosponge Loaded with Lafutidine for Gastric Ulcer: Formulation and Evaluation. Indian Journal of Pharmaceutical Education and Research. 2021; 55 (1): S100- S111. DOI: 10.5530/ijper.55.1s.41.

73. Amer RI, El-Osaily GH, Gad SS. Design and optimization of topical terbinafine hydrochloride nanosponges: Application of full factorial design, in vitro and in vivo evaluation, Journal of Advanced Pharmaceutical Technology and research. 2020; 11(1):13-19. DOI: https://doi.org/10.4103/japtr.japtr_85_19.

74. Pandya KD, Shah NV, Gohil DY, Seth AK, Aundhia CJ, Patel SS. Development of Risedronate Sodium-loaded Nanosponges by Experimental Design: Optimization and in vitro Characterization, Indian journal of pharmaceutical sciences. 2019 ;81(2):309316. DOI: 10.36468/pharmaceutical-sciences.512.

75. Asfaram A, Ghaedi M, Dashtian K. Ultrasound assisted combined molecularly imprinted polymer for selective extraction of nicotinamide in human urine and milk samples: Spectrophotometric determination and optimization study. Ultrasonics Sonochemistry. 2016; 34:640-650. DOI: https://doi.org/10.1016/j.ultsonch.2016.06.018.

76. Aldawsari HM, Badr-Eldin SM, Labib GS, El-Kamel AH. Design and formulation of a topical hydrogel integrating lemongrass-loaded

nanosponges with an enhanced antifungal effect: in vitro/in vivo evaluation. International Journal of Nanomedicine. 2015; 10:893-902. DOI: https://doi.org/10.2147/ijn.s74771.

77. Ciesielska A, Ciesielski W, Girek B, Girek T, Koziel K, Kulawik D. Biomedical Application of Cyclodextrin Polymers Cross-Linked via Dianhydrides of Carboxylic Acids. Applied Sciences. 2020; 10:8463. DOI: https://doi.org/10.3390/app10238463.

78. Rao MR, Bhingole RC. Nanosponge-based pediatric-controlled release dry suspension of Gabapentin for reconstitution. Drug Development and Industrial Pharmacy. 2015; 41(12):2029-36. DOI: https://doi.org/10.3109/03639045.2015.1044903.

79. Singireddy A, Pedireddi SR, Nimmagadda S, Subramanian S. Beneficial effects of microwave assisted heating versus conventional heating in synthesis of cyclodextrin based nanosponges. Materials Today: Proceedings. 2016; 3(10):3951–3959. DOI: http://dx.doi.org/10.1016/j.matpr.2016.11.055.

80. Singireddy A, Subramanian S. Optimization of microwave-assisted synthesis of cyclodextrin nanosponges using response surface methodology. Journal of Porous Materials.2014;21:1015-1023.DOI: http://dx.doi.org/10.1007%2Fs10934-014-9851-2.

81. Thakre AR, Gholse YN, Kasliwal RH. Nanosponges: A Novel Approach of Drug

Delivery System. Journal of Medical Pharmaceutical and Allied Sciences. 2016; 78-92.

82. Maghsoodi M, Nokhodchi A. Agglomeration of Celecoxib by Quasi Emulsion Solvent Diffusion Method: Effect of Stabilizer. Advanced Pharmaceutical Bulletin. 2016; 6(4):607-616. DOI: https://doi.org/10.15171%2Fapb.2016.075.

83. Yang R, He J, Xu L, Yu J. Bubble-electrospinning for fabricating nanofibers. Polymer. 2009; 50(24):5846–5850. DOI: http://dx.doi.org/10.1016/j.polymer.2009.10.021.

84. Jicsinszky L, Cravotto G. Toward a Greener World—Cyclodextrin Derivatization by Mechanochemistry. Molecules. 2021; 26(17):5193. DOI: https://doi.org/10.3390/molecules26175193.

85. Pedrazzo AR, Trotta F, Hoti G, et al. Sustainable mechanochemical synthesis of βcyclodextrin polymers by twin screw extrusion. Environmental Science and Pollution Research International. 2022; 29(1):251–263. DOI: https://doi.org/10.1007/s11356021-15187-5.

86. Yokozawa T, Ohta Y. Transformation of Step-Growth Polymerization into Living Chain-Growth Polymerization. Chemical Reviews. 2016; 116(4):1950−1968. DOI: https://doi.org/10.1021/acs.chemrev.5b00393.

87. Saokham P, Muankaew C, Jansook P, Loftsson T. Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes. Molecules. 2018; 23(5):1161. DOI: https://doi.org/10.3390/molecules23051161.

88. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, Verma A. Nanosponges: a potential nanocarrier for novel drug delivery-a review. Asian Pacific Journal of Tropical Disease. 2014; 4(Suppl 2): S519-S526. DOI: https://doi.org/10.1016/S22221808(14)60667-8.

89. Penjuri SCB, Ravouru N, Damineni S, Bns2 S, Reddy S poreddy. Formulation and Evaluation of Lansoprazole Loaded Nanosponges. Turkish Journal of Pharmaceutical Sciences. 2016; 13(3): 304-310. DOI: 10.4274/tjps.2016.04.

90. Singh R, Bharti N, Madan J, Hiremath SN. Characterization of Cyclodextrin Inclusion Complexes – A Review. Journal of Pharmaceutical Science and Technology. 2010; 2(3):171-183.

91. Asela I, Donoso-González O, Yutronic N, Sierpe R. β-Cyclodextrin-Based Nanosponges Functionalized with Drugs and Gold Nanoparticles. Pharmaceutics. 2021; 13(4):513. DOI: https://doi.org/10.3390/pharmaceutics13040513.

92. Kumar S, Trotta F and Rao R. Encapsulation of Babchi Oil in Cyclodextrin-Based Nanosponges: Physicochemical Characterization, Photodegradation, and in Vitro Cytotoxicity Studies. Pharmaceutics. 2018; 10(4):169. DOI: https://doi.org/10.3390/pharmaceutics10040169.

93. Richa AM, Silvestri R. Determination of Phase Content in Multiphase Polymers by Solid-State

NMR Techniques. Materials Science Forum. 2012; 714:51-56. DOI: http://dx.doi.org/10.4028/www.scientific.net/MSF.714.51.

94. Mele A, Castiglione F, Malpezzi L, Ganazzoli F, Raffaini G, Trotta F, Rossi B, Fontana A, Giunchi G. HR MASS NMR, powder XRD and Raman spectroscopy study of inclusion phenomena in β-CD nanosponges. Journal of Inclusion Phenomena. 2011; 69:403–409. DOI: http://dx.doi.org/10.1007/s10847-010-9772-x.

95. Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: A critical review. Carbohydrate Polymers. 2017; 173:37–49. DOI: https://doi.org/10.1016/j.carbpol.2017.05.086.

96. Trotta F, Caldera F, Cavalli R, Soster M, Riedo C, Biasizzo M, Baretta G. U, Balzano F, Brunella V. Molecularly imprinted cyclodextrin nanosponges for the controlled delivery of L-DOPA: perspectives for the treatment of Parkinson's disease. Expert Opinion on Drug Delivery. 2016; 13(12):1671-1680. DOI: 10.1080/17425247.2017.1248398.

97. Shivani S, Poladi KK. Nanosponges - Novel Emerging Drug Delivery System: A Review, International Journal of Pharmaceutical Science and Research. 2015; 6(2):529540. DOI: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(2).529-40.

98. Mandan S, Chavan M, Bhadane Y, Kalal C. Nanosponges: A New Drug Delivery System.

Journal of Drug Delivery and Therapeutics. 2019; 8(6-A):141-3. DOI: https://jddtonline.info/index.php/jddt/article/view/2789.

99. Mhlanga SD, Mamba BB, Krause RW, Malefetse TJ. Removal of organic contaminants from water using nanosponge cyclodextrin polyurethanes. Journal of Chemical Technology and Biotechnology. 2007; 82:382–388. DOI: http://dx.doi.org/10.1002/jctb.1681.

100. Li D, Ma M. Nanosponges for water purification. Clean Products and Processes. 2000; 2:112–116. DOI: https://doi.org/10.1007/s100980000061.

101. Mamba BB, Krause RW, Malefetse TJ, Gericke G, Sithole SP. Cyclodextrin nanosponges in the removal of organic matter to produce water for power generation, Water SA. 2008; 34 (5). DOI: http://dx.doi.org/10.4314/wsa.v34i5.180666.

102. Zhang Q, Honko A, Zhou J, Gong H, Downs SN, Vasquez JH, Cellular Nanosponges Inhibit SARS-CoV-2 Infectivity. Nano Letters. 2020; 20 (7):5570-5574. DOI: https://doi.org/10.1021/acs.nanolett.0c02278.

103. Ai X, Wang D, Honko A, Duan Y, Gavrish I, Fang RH, Griffiths A, Gao W, Zhang L. Surface Glycan Modification of Cellular Nanosponges to Promote SARS-CoV-2 Inhibition. Journal of American Chemical Society. 2021; 143(42):17615-17621. DOI: https://doi.org/10.1021/jacs.1c07798.

104. Salunkhe A, More S, Dhole S. Narrative Review on Drug Loaded Nanosponges as a Carrier for Drug Delivery. International Journal of Pharmaceutical Quality Assurance. 2023; 14 (1):244-249. DOI:

10.25258/ijpqa.14.1.42.