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NANO-SPONGES AS VERSATILE NANOCARRIERS FOR DRUG DELIVERY: ADVANCES, APPLICATIONS AND FUTURE PERSPECTIVES

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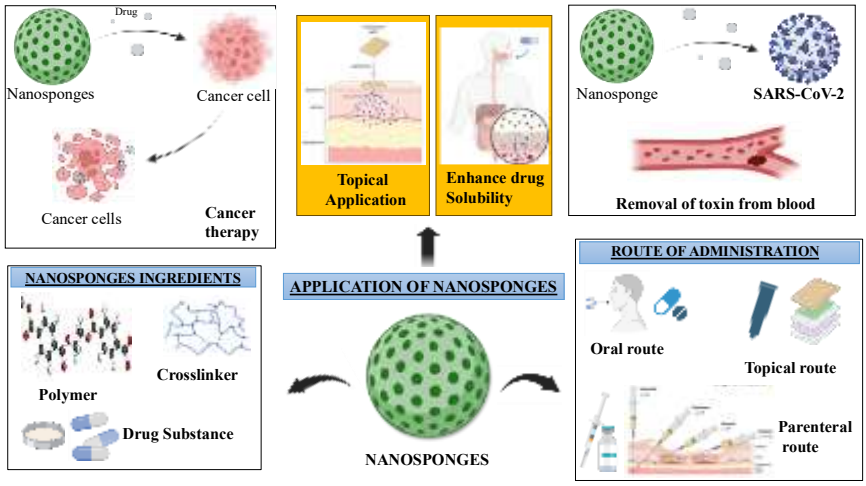
ABSTRACT

The emergence of drug delivery systems has been hindered by the complex chemical processes that can lead to toxicities and improper bioavailability of the drug with uncontrolled drug releases. Nanosponges are designed to increase a drug's solubility, stability, and bioavailability. Effective drug encapsulation and controlled release are made possible by the porous structure, which increases therapeutic efficacy while lowering adverse effects. Nanosponges were recently developed as colloidal nanocarriers with cross-linked polymers that have a three-dimensional porous structure. The nanocarriers have the ability to entrap a variety of drug molecules, ranging from hydrophilic drugs to hydrophobic drugs. The size, shape, method of preparation, type of polymer, and type of drug entrapped determine the size or shape of nanocarriers. Nanosponges have been observed for effective drug loading along with controlled and targeted drug release properties. Regarding conventional drug-delivery systems like nano-carriers, Nanosponges improve drug stability, controlled release mechanisms, and therapeutic potential in various fields such as cancer treatment, SARS-CoV-2 infection management, topical drug delivery, solubility improvement, and removal of toxins. Nanosponges have been found to have significantly enhanced pharmacokinetic/pharmacodynamic properties and increased shelf life as drug formulations, making them a promising area in advanced drug delivery systems.

KEYWORDS: Case studies; Nanosponges; Polymer-based nanocarriers; Solubility enhancement; Topical drug delivery.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Drug delivery technology has received new interest for its ability to revitalize existing drugs by improving their effectiveness. Right now, targeted drug delivery is one of the main challenges that researchers face. Creating drug delivery systems that focus on specific targets to improve treatment success, reduce side effects, and optimize dosing schedules is a key trend in today's medicine [1].

Nanosponges are nanoscale structures that incorporate pores a few nano measuring nanometers, which enable them to carry various drug molecules. These tiny particles can transport hydrophilic as well as lipophilic drugs and can also improve the stability of poorly soluble drugs [2]. Nanosponges are generated by appropriate cross-linking using several organic and inorganic materials. They are used to trap various molecules through inclusion and non-inclusion complexes

[3]. Nanosponges act as encapsulating nanoparticles that surround drug molecules in their inner cavities, allowing for controlled and sustained drug release [4].

At first, Nanosponges were only used for topically administered drug. In the last 20 years, their uses have expanded to oral and intravenous drug delivery systems [5]. For oral administration purposes, Nanosponges-drug complexes can be encapsulated in a matrix consisting of appropriate excipients, diluents, lubricants, and anti-caking materials for the development of capsules or tablets. Furthermore, for parenteral drugs, Nanosponges-drug complexes can be dispersed in an inert sterile water, saline solutions, or other suitable aqueous suspensions. For topical application of the Nanosponges drug delivery system, the Nanosponges can be added to topical hydrogels [6,7]. NS can be prepared from a variety of organic and inorganic materials. Titanium or other metal oxides, silicon particles, and carbon-coated metals are different examples [8]. Metallic Nanosponges including NS based on titanium oxide, silicon NS, and carbon-coated metallic NS [9,10].

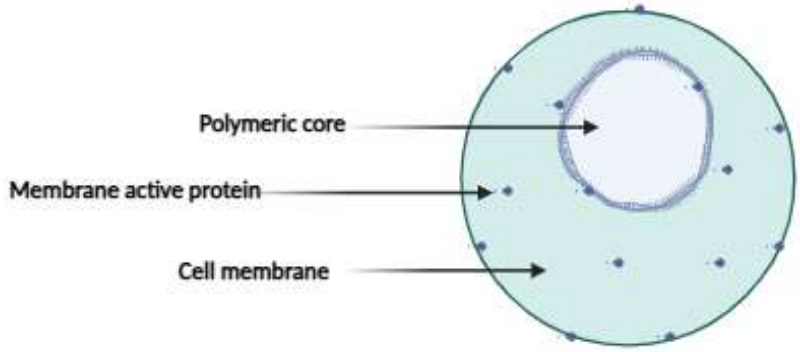


Figure 1. Structure of Nanosponges

Advantages, Disadvantages and Properties of Nanosponges [11-15]

The advantages, disadvantages and Properties of Nanosponges are illustrated in Figure 2.

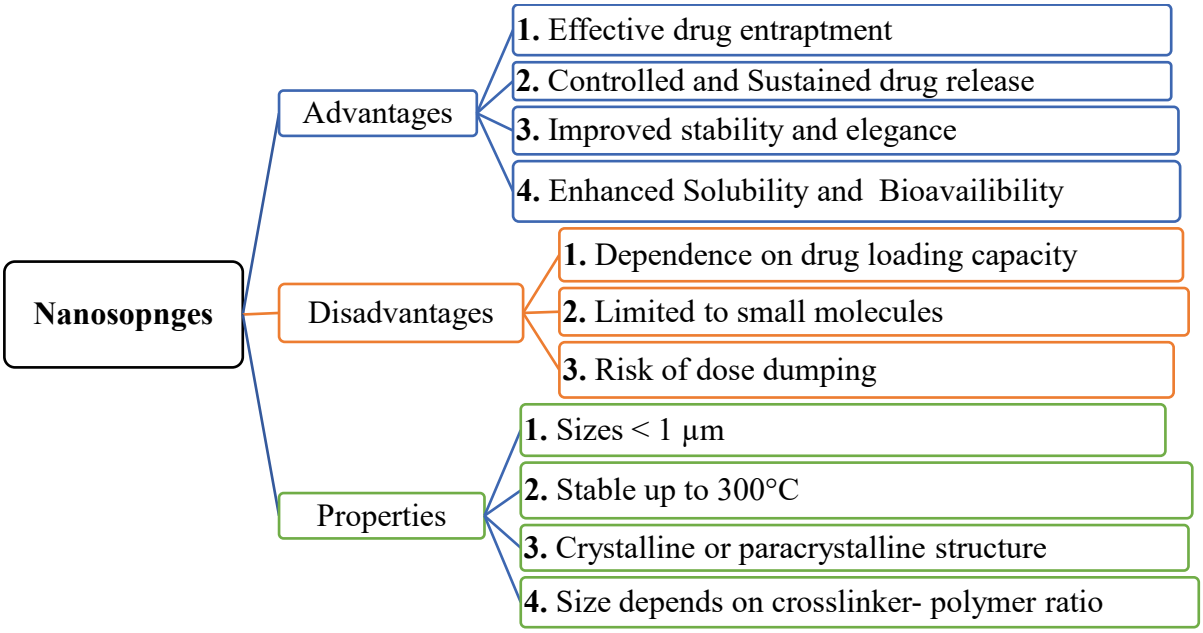


Figure 2. Advantages, Disadvantages and Properties of Nanosponges

2. METHODOLOGY

To gather pertinent data on Nanosponges as adaptable nanocarriers for drug delivery, a comprehensive literature search was undertaken. Relevant literature was sourced from a range of electronic databases, including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. The literature search utilized a variety of keywords, such as "Nanosponges," "drug delivery," "nanocarriers," "cyclodextrin-based Nanosponges," "polymeric Nanosponges," "controlled drug release," and "targeted drug delivery." In addition, Boolean operators, which include "AND" and "OR," were also used to enhance the search results. The inclusion criteria involved original research articles, literature reviews, and relevant book chapters published in the last 10-15 years in the English language, which were focused on the use of Nanosponges in drug delivery. Emphasis was placed on literature on recent developments in Nanosponges in drug delivery, their applications in medicine, and their prospects.

Literature on non-English publications, abstracts presented in conferences without the availability of the complete text, duplicate publications, and literature on unrelated topics to Nanosponges in drug delivery was excluded. Literature with insufficient information and lacking scientific merit was also excluded.

The literature was analysed to present a clear overview on the recent advances in Nanosponges in drug delivery and their future prospects.

3. DISCUSSION

Nanosponges' Ingredients [13, 14]

Polymer

The choice of polymer affects the structure of the Nanosponges, the size of its cavities, and how it releases drugs.

Cross-Linkers

This influences porosity and stability of nanopsonges and their formation.

Drug Substance

The properties of the drug molecule will ultimately exert some influence on the development of the Nanosponges. Generally, considerations made in drug specification are: -

- Molecular weight ranges from 100-400 Daltons.
- Maximum of 5 condensed rings
- Very low solubility in water (< 10 mg/ml)
- Melting point ≤ 250°C

Chemicals used for making Nanosponges [16]

Figure 3 shows the chemicals used in Nanosponges preparation:

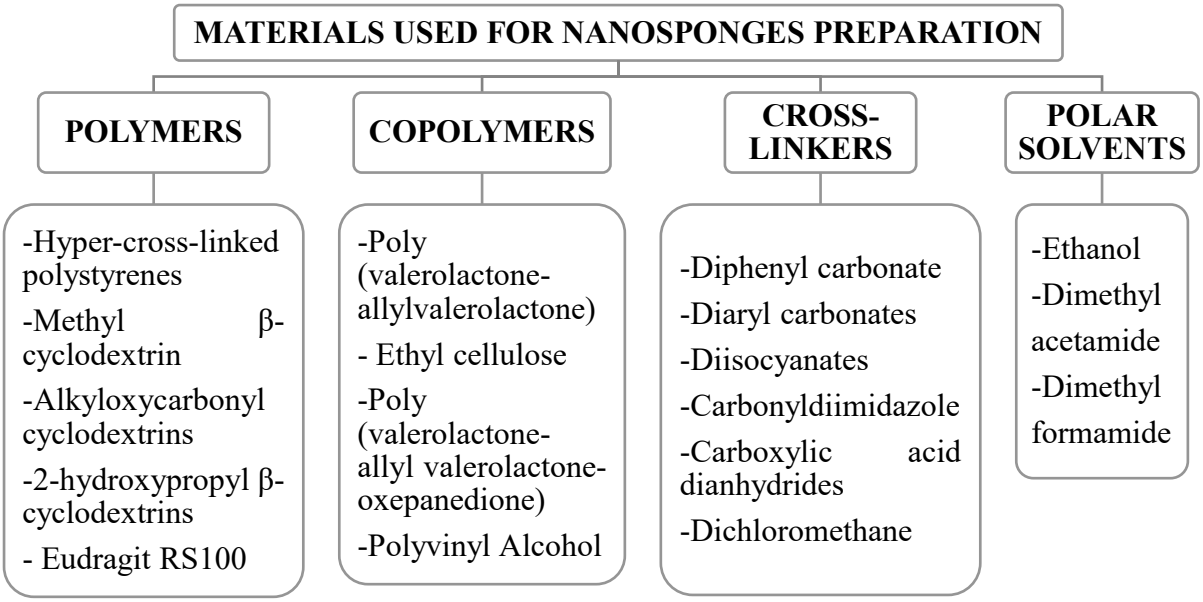


Figure 3. Chemicals used for making Nanosponges

4. CASE STUDIES

1. Case studies showing pharmacodynamic activity of Nanosponges:

Case studies showing pharmacodynamic activity of Nanosponges are presented in Table 1

Drug	Carrier	Objective	Outcome	Route of drug delivery
Tamoxifen [17]	Beta cyclodextrin	Cytotoxic study	The TNC formulation showed higher cytotoxicity than plain Tamoxifen against MCF-7 at both 24 and 48 hours	Oral
Isoniazid [18]	Ethyl cellulose	Anti-tubercular activity	Nanosponges systems showed long-lasting and controlled drug release. making them effective treating cutaneous tuberculosis	Topical
Erlotinib [19]	Beta cyclodextrin	Enhance-ment of apoptotic activity	The ERL-NS increased the apoptotic index significantly in MIA-PaCa-2 cells from 0.37 to 0.79 and in PANC-1 cells from 0.42 to 0.82	Oral
Mupirocin [20]	Ethyl cellulose	In Vivo wound healing study	Mupirocin-NSs gel enhanced the wound healing process in diabetic rats more than MP cream (78%) or ointment (79%), reaching 92%	Topical

			closure, close to the standard Becaplermin gel, which is 96%	
Propolis [21]	Ethyl cellulose, Xanthan gum	Performed zone inhibition study	Nano sponges gel exhibited strong antibacterial action against *C. albicans, S. aureus,* and *E. coli*, which was better than that of marketed gels	Topical
Butenafine Hydrochloride [22]	Ethyl cellulose, Carbopol 934	Anti-fungal activity	Nano sponges and nanogel enhanced BH's antifungal activity against *C. albicans* and *A. Niger*, showing larger zones of inhibition compared to marketed cream and pure drug	Topical
Quercetin [23]	Ethyl cellulose, Carbopol 934, HPMC	Anti-microbial study	Effective antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Proteus vulgaris*, and *Bacillus subtilis.*	Topical

Table 1. Case studies showing pharmacodynamic activity of Nanosponges

2. Case studies showing pharmacokinetic activity of Nanosponges:

The pharmacokinetic activity of Nanosponges is demonstrated through various case studies, as shown in table 2.

Drug	**Carrier**	**Objective**	**Outcome**	**Route of drug delivery**
Tamoxifen [17]	Beta cyclodextrin	Improve AUC and Cmax	The TNC formulation showed 1.44-fold higher AUC and 1.38-fold higher Cmax compared with plain drug	Oral
Erlotinib [19]	Beta cyclodextrin	Improve oral bioavailability	ERL-NS achieved 1.8-fold higher Cmax and ~2-fold higher $AUC_{0-\infty}$ than pure ERL.	Oral
Propolis [21]	Ethyl cellulose,	Ex vivo permeation study	Nanosponges gel exhibited better permeation 79.82%, compared with plain and marketed gels	Topical
Griseofulvin [24]	PVP K30	Improve oral bioavailability	Nanosponges formulation increased Cmax (2.13-fold) and AUC (3.78-fold)	Oral
Mupirocin [20]	Ethyl cellulose	Ex vivo deposition study	MP-NSs gel showed higher deposition, 211.4 µg/cm2, compared to cream (83.57 µg/cm²) and ointment (34.03 µg/cm²), which improved skin residence.	Topical
Piroxicam [25]	Beta cyclodextrin	Improved oral bioavailability	Significant increase in Cmax and AUC compared with commercial tablets	Oral
Imatinib Mesylate [26]	β-Cyclodextrin, Diphenyl Carbonate	Biodistribution study	At 24 hours, free imatinib concentrations were primarily confined to the liver and were greater for the test formulation compared with the Marketed formulation, and were lower in the kidney below quantification.	Oral

Table 2. Case studies showing pharmacokinetic activity of Nanosponges

3. Case studies showing Stability studies with Nanosponges:

Table 3 summarizes case studies highlighting the stability studies of Nanosponges.

Drug	**Nanosponges vehicle**	**Outcome**
Econazole nitrate [27]	β-cyclodextrin, Carbonyl diimidazole	No significant change in pH, viscosity, spread ability, or drug content during 90 days stability study
Ibrutinib [28]	Eudragit RL 30, Polyvinyl Alcohol	Stable under accelerated conditions 40 ± 2 °C/75 ± 5% RH for up to 3 months, presenting slight changes in % drug content (99.89 → 97.09%) and in vitro drug

		release (99.21 → 98.12%), with no significant differences, confirming its stability
Gliclazide [29]	Eudragit S100	No significant changes in drug and release within 60 days
Murraya Koenigii extract [30]	Eudragit RS 100	Over 30 days at room temperature, the colour, pH, and homogeneity of the gel remained unchanged, showing no drug degradation, hence confirming that it is stable.

Table 3. Case studies showing Stability studies with Nanosponges

5. APPLICATION OF NANOSPONGES

a) Nanosponges in Cancer Therapy:

Nanosponges have been demonstrated to be an emerging targeting carrier in drug delivery systems, especially in cancer therapy. These ultrafine sponge-like materials are being designed to encapsulate drugs and deliver them in a controlled manner to the targeted site. Peptide labelled Nanosponges can target receptors overexpressed on tumour cell membranes and release the drug directly into tumour cells [31].

b) Enhancement of Solubility by using Nanosponges:

The solubility of a drug in water is often a critical parameter that generally affects its therapeutic efficacy and formulation design. Nanosponges are worthy carrier systems in which the drug is entrapped within its porous structure; it enhances the solubility and bioavailability and offers controlled drug release.

Cholesterol-linked β-cyclodextrin (β-CD) Nanosponges attracted interest as they enhance the solubility and permeability of hydrophobic drugs without affecting biological lipid membranes [32-35].

c) Topical agent:

The NS delivery system represents a novel technology in the field of controlled and prolonged release of topically acting agents, which can provide extended drug retention within the skin. Classic dermatological and cosmetic preparations usually supply active agents at locally relatively high concentrations, but their duration of action is short. This often results in a cycle of overmedication for short periods and undermedication for long periods.

By contrast, Nanosponges-based drug delivery systems exhibit uniform and sustained rates of drug release. This results in negligible irritation without compromising the therapeutic efficacy. in such a formulation, a wide variety of substances, including gels, lotions, creams, ointments, liquids, and powders, can be incorporated [36-38].

d) Application of Nanosponges as Absorbents in Blood:

Nanosponges have been demonstrated to work as absorbents to remove poisonous substances from the blood, providing an efficient treatment for poisoning. As an intravenous drug, NSs act as artificial red blood cells to attract and bind poisonous substances which can damage biological cells. They effectively neutralize poisonous substances compared to standard antidotes because they "trap" these substances and prevent them from damaging healthy cells. [39-41]

e) Nanotechnology based Strategies for SARS-CoV-2 Management:

Nanosponges, derived from human respiratory epithelial type II cells or macrophages function as decoys by sequestering SARS-CoV-2 and inhibiting infection. They mimic host cell receptors, inactivate the virus in a dose-dependent manner, and remain effective against mutated forms. With a PLGA core, uptake is increased, and macrophages coating absorbs inflammatory cytokines with immunomodulatory properties [42–47].

Chitosan nanoparticles and carbon quantum dots provide controlled pulmonary and intestinal drug delivery and obstruct viral binding. Nanoparticle-based vaccines such as LNPs for mRNA delivery and VLPs, improve antigen stability, multivalent presentation, and co-delivery of adjuvants for rapid and efficient COVID-19 vaccination.

RECENT PATENT DEVELOPMENT IN NANOSPONGES-BASED DRUG DELIVERY SYSTEMS [48]

In recent years, numerous patents have been filed regarding Nanosponges, primarily focusing on improved preparation techniques to enhance their efficiency, as summarized in Table 4.

Patent No.	Authors	Title
US9574136B2 (2017)	Kun Lian	Nanoparticles, Nanosponges, methods of synthesis, and methods of use
US8828485B2 (2014)	Kun Lian, Qinglin Wu	Carbon-encased metal nanoparticles and sponges as wood/plant preservatives or strengthening fillers
WO2021053039A1 (2021)	Francesco Trotta, Alberto RUBIN PEDRAZZO	Process for preparing a Nanosponges
CA2692493A1 (2009)	Sea Marconi, Technologies Di Vander Tumiatti, S.A.S, Francessco Trotta, Vander Tumiatti, Roberta Cavalli, Carlo Mario Roggero, Barbar Mognetti, Giovanni Nicolao Berta	Cyclodextrin-based Nanosponges as a vehicle for antitumoral drugs

Table 4. Recent Patent development in Nanosponges-Based Drug Delivery System

FUTURE DIRECTIONS

Nanosponges represent an advanced nanoscale drug delivery with superior therapeutic efficacy and reduced drug toxicity by means of controlled and targeted release. The particle size, porosity, crystallinity, and degree of crosslinking strongly influence the performance of Nanosponges. The future strategy will be the development of cost-effective and less risky production methods; at the same time, surface functionalization techniques will be pursued to enhance specificity and biosafety [49]. Multifunctional Nanosponges, oral delivery of proteins, and 3D printing are some of the recent approaches that prove the immense prospects for Nanosponges in both clinical and industrial applications [50, 51].

CONCLUSION

Nanosponges are colloidal carrier formulations for drugs and are produced by cross-linking polymers to form a three-dimensional structure with pores. Nanosponges can carry many drugs and will swells with properties of controlled release formulation. In summary, the properties of Nanosponges depend on many factors such as the polymer used to make Nanosponges, size of Nanosponges, drug-Nanosponges interaction, complex formation. Some case studies reveal better stability, effectiveness, and safety of drugs in Nanosponges. As these properties are advantageous, Nanosponges have been explored for their application in treating cancer patients, SARS-CoV-2 infection, topically delivered drugs, increasing the solubility of drugs, and detoxifying blood; this unfolds the potential of Nanosponges in various aspects of pharmacy.

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ABBREVIATIONS

NS: Nanosponges; **NSs:** Nanosponges; **TNC:** Tamoxifen Nanosponges Complex; **MCF-7:** Michigan Cancer Foundation – 7; **ERL-NS:** Erlotinib Nanosponges; **MP:** Mupirocin; **BH:** Butenafine Hydrochloride; **AUC:** Area Under the Curve; **Cmax:** Maximum concentration; **PVP:** Polyvinylpyrrolidone; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2; **PLGA:** Poly (lactic-co-glycolic acid); **LNPs:** Lipid nanoparticles; **VLPs:** Virus-like particles;

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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No financial support or sponsorship was received from public, commercial, or not-for-profit funding agencies for this study.

Author Contributions

All authors contributed to the study design, data analysis, and manuscript preparation.

SUMMARY

Nanosponges are advanced nanocarriers used in the field of nanotechnology. Nanosponges have a porous structure, which makes them efficient in increasing the solubility, stability, and bioavailability of the drugs. Nanosponges have the ability to entrap both hydrophilic and hydrophobic drugs. Nanosponges have a better pharmacokinetic and pharmacodynamic profile compared to the traditional drug delivery systems. Nanosponges have the potential to be used in the treatment of cancer, topical application, solubilization of drugs, and detoxification agents. Nanosponges have a good future in the field of modern drug delivery systems.

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