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Review Article

Cyclodextrin Based Nanosponges: A Novel Approach For Targeted Drug Delivery

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ABSTRACT

Solid cross-linked porous nanoscale polymeric structures are known as nanosponges. This broad idea includes hydrogels and metal organic frameworks. This manuscript focuses on nanosponges, their types and details related to its crucial type cyclodextrin based nanosponges, their methods of preparation and applications. Cyclodextrins are starch-derived cyclic oligomers of glucose. Cyclodextrins have the rare capacity to form inclusion host-guest complexes with numerous hydrophobic substances due to the unique structure created by the combination of the outward hydrophilicity and the inside hydrophobic surface. These complexes might improve the solubility of the guest molecules and stabilize the molecule without causing any other alterations in their favorable properties. These characteristics along with the flexibility to use various crosslinkers and the high polymeric surface, make these sponges particularly well-suited for a wide variety of applications.

INTRODUCTION

Innovative medication delivery systems called nanosponges are minuscule sponge-like structures with cavities. These cavities can be filled with drugs and have pores between 1 and 2 nanometers in size.(1) Nanosponges have a sponge-like morphology and are very small in size. These are tiny, mesh- like structures that may enclose a wide range of different substances. They have a demonstrated spherical colloidal nature and are said to have a high capacity for solubilization.(2) Drugs that are poorly soluble in water can be solubilized using nanosponges, which also give extended release and increase drug bioavailability. Due to their internal hydrophobic chambers and exterior hydrophilic branching, nanosponges have unmatched flexibility and can load both hydrophilic and hydrophobic medicinal molecules.(3)

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Components of Nanosponges

Table1: The major components used in formulation of nanosponges

Components	Examples
Polymer	• Cyclodextrins (β, α, γ) • Titanium dioxide • Ethyl cellulose Polyvinyl alcohol • Copolyvidonum(4)
Cross- linking agents	• Carbonyl diimidazole • Hexamethylene diisocyanate • Pyromellitic dianhydride • Dichloromethane • Diphenyl carbonate(5)
Solvent	• DMF (Dimethyl formamide) • DMSO (Dimethyl sulphoxide)(2)
Drug moiety	• Molecular weight between 100 and 400 Daltons(5)

Types of Nanosponges

Table2: Categorization of nanosponges into various generations based on their evolution.(6)

Generation	Category	Subcategory
First	Plain Nano sponges	• Cyclodextrin based ether Nano sponges • Cyclodextrin based urethane Nano sponges • Cyclodextrin based carbonate Nano sponges • Cyclodextrin based ester Nano sponges
Second	Modified Nano sponges	• Electrically charged cyclodextrin Nano sponges • Hydrophobic Nano sponges • Fluorescent carbonate Nano sponges
Third	Stimuli Nano sponges	• Amino cyclodextrin Nano sponges • Glutathione-responsive Nano sponges
Fourth	Molecularly imprinted Nano sponges	• Molecular imprinted polymer-based CD Nano sponges

- **First generation {Plain nanosponges}**

Cyclodextrin based ether nanosponges

By reacting CDs with cross-likers containing epoxide groups such as epichlorohydrin, bisphenol A diglycidyl ether, ethylene glycol diglycidyl ether, etc., CD-based ether NSs are frequently created. This particular class of NSs demonstrates strong chemical resistance and variable swelling capabilities.(7)

Cyclodextrin based urethane nanosponges

Diisocyanates are primarily used in the synthesis of urethane (or carbamate) CD-NSs. Their robust structure, great resistance to chemical deterioration and little swelling extent in both aqueous and organic conditions serve as distinguishing features. Li and Ma created the first carbamate CD-NSs which are utilized to remediate wastewater by reacting CD with hexamethylene diisocyanate and toluene-2,4-diisocyanate.(8) These NSs outperformed activated carbons in the elimination of several organic compounds such as p-nitrophenol which was reduced to ppb levels even at low concentrations.(9)

Cyclodextrin based carbonate nanosponges

Active carbonyl chemicals including as 1,1'-carbonyldiimidazole, Tri-phosgene, and diphenyl

carbonate are used in the synthesis of CD-based carbonate NSs. Short cross-linking bridges decreased swelling ability, strong stability to acidic and mildly alkaline solutions are all characteristics of these NSs.(10) Carbonate NSs exhibit a limited surface area (about 2 m2/g) and a strong attraction for some organic compounds just like urethane NSs do.(11)

Cyclodextrin based ester nanosponges

Ester NS is typically created by combining CDs with dianhydrides or di/ poly carboxylic acids such citric acid, ethylenediamine-tetra acetic dianhydride (EDTA dianhydride), butane tetracarboxylic dianhydride and pyro melic dianhydride.(12)

- **Second generation {Modified nanosponges}**

The extension of the previously mentioned CD polymers range of application and the emergence of a new generation of NSs were made possible by the incorporation of desired functionalities. There are three ways to introduce certain moieties: Functionalization of an NS after cross-linking but before cross-linking CD functionalization or simultaneous addition of a functionalizing agent and a cross-linking agent step.(13)

- **Third generation {Stimuli nanosponges}**

Stimuli-sensitive polymers adapt to changes in their environment by changing their structure, permeability or color. The morphology, supramolecular processes and molecular processes that are stimuli sensitive are what enable an organism to perceive a stimulus and respond to it. (14) Stimuli-sensitive nano-carriers are renowned for their potential to boost therapeutic efficiency with a minimum of adverse effects, as well as their controlled target release upon initiation by stimulating signals or particular transport routes.(15)

- **Fourth generation {Molecularly imprinted nanosponges}**

When a template molecule is present during the synthesis of a polymer, a technique called molecular imprinting can be used to provide three-dimensional polymers molecular recognition properties.(16)

Cyclodextrin-Based Nanosponges

A family of molecular cages known as cyclic 1,4-linked oligosaccharides with hydrophilic exterior surfaces and a lipophilic inside is known as cyclodextrins (CDs). When creating nanosponges, cyclodextrins (CDs) have been the most often used materials.(17,18) Early in the 1950s, physicochemical characteristics of CD were found and ever since, the pharmacological and physicochemical qualities such as stability, solubility and bioavailability of active moieties have then been improved.(19) It has been noted that cyclodextrin complexes made with biocompatible hydrophilic polymers can improve the solubility of encapsulated classes in aqueous conditions.(20) A novel hyper-crosslinked nanostructured material can be created by reacting cyclodextrins with crosslinkers called "nanosponges".(21)

Components of Cyclodextrin Based Nanosponges

Table3: Components of cyclodextrin based nanosponges

Components	Examples
Polymer(22)	• Cyclodextrin-α (6 membered sugar ring molecule) • Cyclodextrin-β (7 membered sugar ring molecule) • Cyclodextrin-γ (8 membered sugar ring molecule)
Cross-linkers(5)	• Carbonyl diimidazole • Diphenyl carbonate • Diaryl carbonate • Glutaraldehyde • Dichloromethane

Solvent(2)	• DMF (Dimethyl formamide) • DMSO (Dimethyl sulphoxide)
Co-polymers (23)	• Ethyl cellulose • Polyvinyl alcohol

Characteristics

1. Cross-linked cyclodextrin polymers are known as CD-NS.(24)
2. CD-NS are 3-D structures that allow for the selective capture, transport and release of a wide range of chemicals. They can be coupled with several functional groups which enables them to be targeted to various places.(25)
3. Highly porous nanoparticles are CD-NS.
4. They are capable of forming complexes with many lipophilic and hydrophilic molecule types.(26,27)
5. They are biodegradable and safe for biological use.
6. Even at high temperatures up to 300 degrees Celsius, these are still stable.(28)
7. They can exist in both crystalline and Para crystalline forms.(29)

Types of Cyclodextrin Based Nanosponges

Table4: Classification of cyclodextrin based nanosponges Based On Polymer Used(30)

1.	β– cyclodextrin based Nano sponges
2.	α– cyclodextrin based Nano sponges
3.	γ– cyclodextrin based Nano sponges

Based On Functional Groups(6,31)

1.	Cyclodextrin based carbamate Nano sponges
2.	Cyclodextrin based carbonate Nano sponges
3.	Cyclodextrin based ester Nano sponges
4.	Cyclodextrin based polyamidoamine Nano sponges (32)
5.	Modified Nano sponges

Methods of Preparation

1. Solvent evaporation technique

In the solvent evaporation approach, the fusing step is skipped and the cross-linking agent is instead solubilized using solvents like DMSO or DMF.(33) The polymer is combined with a polar aprotic solvent and the resulting combination is added to a cross-linker solution and refluxed for one to forty-eight hours. The end result is produced by mixing a substantial amount of distilled water with cold solution. Finally, filtration is used to recover the finished product and Soxhlet extraction is used to purify it over an extended period of time.(34) By either a non-inclusional or an inclusional process, spherical, solid nanostructures with high water solubility are produced. High pressure homogenization involves homogenizing prepared nanosponges in water at continuous speed for 10 minutes minimizes the size of NS.(25)

2. Ultrasound-assisted technique

In the initial step of ultrasound-assisted manufacturing, cyclodextrins and cross-linking agents are combined without the need of solvents.(35) Anhydrous -CD and DPC are taken in a vial, placed in an ultrasonic bath with water that has been pre-heated to 90°C and then sonicated for five hours. Additionally, the solvent evaporation and melt technique's crystallization and purification procedures are the identical.(36)

3. Microwave-assisted technique

Microwave irradiation is the easiest way for synthesizing CDNS and it considerably slows down reaction time. The NS that is produced has more crystallization.(37) Microwave aided manufacturing showed a four-fold reduction in reaction time compared to typical melt technique. The procedure produced crystallinity and a homogenous distribution of the particle size.(38)

4. Melt method

In this method, the cross-linking agent is melted with a CD and all of the ingredients are homogenized before being heated at 100°C for five hours while being stirred magnetically. The

above matrix is then given time to cool. To get rid of by-products and unreacted components.(6,39)

Drug Loading in Blank Nanosponges

The drug loading capabilities of NS are different for para-crystalline and crystalline forms. When compared to para-crystalline NS, crystalline NS results in a larger drug pay load. Due to the hydrophobic CD channels that are surrounded by hydrophilic nanocavities in the polymeric matrix, these nanosponges have a variety of mesh polarities, enabling strong interactions with drugs of different lipophilicities and structural types.(40,41) The drug or herbal extract is dissolved in ethanol or suitable solvent with uniform agitation for 15 minutes and then keeping the mixture undisturbed for 24 hours. Then the resultant is centrifugated and supernatant of the mixture is lyophilized.(42)

The loading capacity of the nanosponges is calculated using formula(43):

$$Loading\ Capacity = \frac{Weight\ of\ drug\ in\ \beta\text{–CDNS}}{\text{Weight of }\beta\text{CD in }\beta\text{–CDNS}} \times 100$$

Characteristic Evaluation of Nanosponges

1. Production yield

Calculating the initial or beginning weights of raw materials and the end weight of nanosponges will produce the production yield (PY).

Yield of production = [Actual mass of nanosponges/Theoretical mass (drug + polymer)] × 100

Different batches percentage yieldswere calculated using weighing the dried nanosponges.(44,45)

2. Spectroscopic Technique

- **Fourier-transformation infrared spectroscopy**

The FTIR spectra of optimized loaded NS and Blank NS were captured and analyzed for potential chemical interactions. The translucent pellets of these samples were generated by mixing these compounds with potassium bromide. FTIR spectra was acquired in the area of 4000–400 cm−1(46)

- RAMAN spectroscopy
- Ultraviolet- visible spectroscopy
- Nuclear magnetic resonance

3. Measurement of Zeta-Potential

The stability and durability of the Nanosponges was estimated using a zeta potential study. Zeta potential is a metric for electrostatic charge impact. This fundamental force is what separates nearby particles from one another. Depending on the strength of both forces, the overall effects can be either attraction or repulsion.(47)

4. Drug entrapment efficacy

In a volumetric flask, correctly weighed nanosponges (10 mg) were added to 5 ml of methanolic HCl (HCl: Methanol-10:1) to determine the entrapment efficiency. The flask was shaken with a vortex mixer for one minute.(48) The Methanolic HCl was used to create a volume up to 10 ml. After that, the mixture was diluted, filtered and the Spectrometric analysis was used to determine the drug concentration at 295nm.(49)

$$\text{Capture Efficiency} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \times 100$$

5. In-vitro drug release-Dissolution Study:

The prepared formulation was subjected to a 12-hour in vitro drug release study utilizing an Electrolab model dissolution tester USP Type-2 apparatus (rotating paddle) set at 100 rpm and a formulation with a temperature of 37±0.5°C was added to the 900ml medium.(50) To maintain a constant volume, 10 ml samples were taken out of the dissolving medium at predetermined intervals and replaced with new medium. Using a UV-visible spectrophotometer, the sample solution's absorbance was measured at 231 nm to determine whether the model drug was present.(51,52)

6. X-Ray Diffraction Technique

7. Porosity or swelling index(53)
8. Differential Scanning Calorimetry
9. Microscopic Technique
10. Photodegradation studies (54)

ROLE IN DRUG DELIVERY

1. Targeted and controlled release drug delivery

When drugs are delivered by nanosponges, they are only released at the targeted spot hence preventing their circulation throughout the body.(55)

Table5: Various applications of cyclodextrin based nanosponges in targeted and controlled release drug delivery

Drug Candidate	Category	Target Site	Reference
Strigolactones	Anticancer	Prostate	(56,57)
Meloxicam	Anti-inflammatory and analgesic	Controlled release	(58)
Acetylsalicylic acid	Analgesic	Controlled release	(59)
Lansoprazole	Antiulcer	Prolonged release	(25)

2. Improve stability

Drug compounds that are prone to deterioration when exposed to water, oxygen (air), heat or radiation can be stopped from degrading by using cyclodextrin nanosponges.(60) Nanosponges are being used in numerous studies on these interactions. The nanosponges prevent oxidation, hydrolysis, racemization, polymerization and enzyme hydrolysis from happening to the drug molecules.(61)

Table6: Various applications of cyclodextrin based nanosponges in improving stability.

Drug Candidate	Category	Route pf Administration	**Remarks**	Reference
Gamma-oryzanol	Antioxidant	Topical	Improved photostability	(62)
Quercetin	Antioxidant	-	Enhanced photostability	(25)
Babchi oil	Anti-psoriatic	Topical	Enhanced photostability	(63,64)

3. Enhanced solubility

Poor solubility of BCS (Biopharmaceutical Classification System) class II medications possesses a challenge in their preparation.(65) However, these medications can be more effectively integrated into cyclodextrin nanosponges. By increasing their wetting and solubility in water, these nanocarriers increase their aqueous solubility through the formation of inclusion complexes.

Table7: Various applications of cyclodextrin based nanosponges in enhancing solubility:

Drug Candidate	Category	Route of Administration	Remarks	Reference
Doxorubicin	Antineoplastic	Parenteral	Increase aqueous solubility	(25)
Dexamethasone	Anti- inflammatory	Oral, Parenteral	Enhanced aqueous solubility	(66)

Telmisartan	Anti- hypertensive	Oral	Improved intrinsic solubility	(67)
Flurbiprofen	Anti- inflammatory	Oral	Increase aqueous solubility	(25)
Repaglinide	Hypoglycemic	Oral	Improved aqueous solubility	(25,68)

4. Oral drug delivery

An established route of administration with good patient compliance is oral medication delivery. Due to poor solubility, ineffective intestinal permeability, and pre-systemic activation, delivering molecules via oral route presents difficulties. Nanosponges made from cyclodextrin have shown promise as oral delivery without sacrificing any safety concerns.(69)

5. Topical drug delivery

For topical drug delivery, nanosponges may be included in creams and gels. Although they haven't been extensively studied, nanosponges could be a very effective method for treating skin conditions. If successfully entrapped, nanosponges enhanced drug delivery via topical gel in addition to drug targeting.(70,71)

6. Pulmonary drug delivery

The pulmonary route is a substitute for parenteral drug delivery but the drug has to be in the form of aerosol to be delivered by this route. The advantage of the nanosponges is their lower interparticle forces of attraction and improved flow properties. Additionally, they have a small, thin and low bulk density. Their increased deposition in the lower pulmonary area is the result of their dynamic diameter.(72)

CONCLUSION

Nanosponges are innovative crosslinked carriers which are used to deliver variety of drugs to targeted sites and plays vital role in increasing their bioavailability. Drugs that are either lipophilic or hydrophilic can be incorporated into the nanosponges which release them in a regulated and predictable way at the target location. It can be modulated by adjusting the polymer to water ratio, the release rate, particle size, and cross-linker. Nanosponges permit the insoluble medications and safeguard the active components from controlled physicochemical deterioration. Due to their diminutive size and spherical shaping, they can be created in a variety of ways or dose types/ forms like aerosol, topical, parenteral, capsules and pills. Cyclodextrin nanosponges are a rapidly growing area of nanotechnology with numerous uses in medicine delivery, research and targeting among other elements due to their distinct size-dependent characteristics and porous nature. They offer the potential to create novel therapeutic approaches. Their capacity to seize drugs and exercise control releasing features provide a novel method of medication delivery that raises the level of the drug targeting. Consequently, cyclodextrin nanosponges hold out a lot of hope for achieving the site-specific and regulated delivery objectives which can also provide fresh viewpoints in the near future in the treatment of difficult disorders.

ABBREVIATIONS

NSs	Nano sponges
CD	Cyclodextrin
CDNS	Cyclodextrin based Nano sponges
DMSO	Dimethyl sulphoxide
DMF	Dimethyl formamide
DPC	Diphenyl carbazide

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