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Cyclodextrin Nanosponges: A Promising Approach for Modulating Drug Delivery

Sunil Kumar, Pooja Dalal and Rekha Rao

Abstract

Nanotechnology showed great promise and impact on administration of therapeutic agents owing to its advantages over contemporary delivery systems. Nanoscale carriers like nanosponges represent a novel category of hyper cross-linked polymer structures with nanosized cavities which can be filled with variety of active moieties (hydrophilic as well as hydrophobic). These nanocarriers can circulate around the body until they found the specific target site and adhere on the surface and release the active moiety in a predictable and controlled manner, resulting in more effective delivery of a given dosage. Nanosponge technology helps to reduce drug associated side effects, improve stability, increase elegance and improve the flexibility of formulations, administered orally, parenterally and topically. Among nanosponges, *cyclodextrin-based nanosponges (CDNS)* are smart versatile carriers studied widely for drug delivery applications. Statistically, it have presented that approximately 40% of active moieties marketed currently and about 90% of active moieties in their preliminary phase confront problems regarding to solubility. In the past decade, the number of studies describing CDNS has dramatically increased. In the present chapter, scientists working in arena of nanotechnology can get an idea of fabrication, characterization and therapeutic utilities of nanosponges.

Keywords: drug targeting, solubility enhancement, porosity, nanocarrier, controlled release

1. Introduction

The development of new active moiety is very expensive and time consuming. Currently, it is estimated the bringing a new portion of active moiety through discovery, development, clinical trials and regulatory approval will take a decade and cost approximately \$120 million. Therefore, an attempt has been made to improve the safety efficacy relationship of established drugs using a variety of methods, such as individualized drug therapy, therapeutic drug monitoring and dose titration. The delivery of active moieties at controlled rate and targeted delivery have attracted the attention of research community and hence, pursued vigorously [1–4]. Further, effective and safe delivery of therapeutic drug molecules has always posed challenge for formulation scientists. For this purpose, numerous nanocarriers have been fabricated and explored. Nanoformulations are highly multifunctional delivery systems possessing a range of applications such as enhanced solubility, stability, specific targeting, on-demand release and degradation within suitable period of time [5].

Nanoformulations and nanoparticles have already been applied as carriers of active moieties with great success; and they have an even greater potential for many applications, like gene therapy, anti-tumor therapy, radiotherapy and AIDS therapy, in the delivery of virostatics, antibiotics, proteins and vaccines [6]. Among the various novel forms of drug delivery nanovehicle, colloidal systems like nanosponges have emerged as promising and potential carrier for promising drug delivery of tough molecules in the past few decades [5] because other novel carrier systems have their own drawbacks enlisted in **Table 1**.

Nanosponges are a new class of structures based on hyper reticulated polymers that have cavities in the nanorange [7, 8]. Nanosponge technology offers pay load of active moieties and thought to help in reducing side effects, increase elegance, improve formulation flexibility and stability. These are non-mutagenic, non-irritating, non-toxic and non-allergenic. In comparison with other nanostructures, NS are insoluble in organic solvents and water. NS are non-toxic, porous, biodegradable and highly stable (up to 300°C) [9]. These nanostructures are able to transport both hydrophilic and lipophilic moieties and improve the solubilization efficacy of drugs. Nanosponge based drug delivery system is used to improve the performance of drugs administered orally, parenterally, pulmonary and topically [10]. Many active moieties with different pharmacological activities, structures and solubility have been encapsulated in NSs, including camptothecin, paclitaxel, doxorubicin, dexamethasone, 5-fluorouracil, itraconazole, nelfinavir mesylate, progesterone, tamoxifen and resveratrol [11]. Further, we acknowledge some excellent reviews that have been published earlier on nanosponges [8, 12–15]. Some of the well-known nanosponges are titanium based NS, silicon NS and cyclodextrin NS [16]. Nanosponges possess various attractive features [17] like

- Can be employed to mask unpleasant flavors and to turn liquid substances to solids
- Targeted site specific drug delivery.
- Being suitable aqueous solubility, the hydrophobic drugs can be encapsulated in these, after mixing with cross-linker.
- Less harmful side effects (since small amount of the active moiety is in contact with healthy tissue).
- Particle size can be varied by using different proportion of cross-linker to polymer.
- Easy to scale-up.
- Simple method production
- The drug profile can be tailored from fast, medium to slow release as per need.
- Gives predictable release.

Despite of these advantages, nanosponges have some limitations also. Only small molecules can be entrapped which depend on loading capacities [18]. Cyclodextrin nanosponges can be categorized into four successive generations, on the basis their chemical configuration and features (**Table 2**).

S. No.	Novel drug carrier systems	Limitations	References
1	Microspheres	Premature release of active molecules, deficient entrapment of active molecules, Expediently taken up by reticular endothelial system (RES)	[19]
2	Liposphere	Weak loading capacity, limited chemical and physical stability during storage, rapid drug leakage,	[20]
3	Polymeric Nanoparticle	Challenging large-scale up, polymer toxicity,	[21, 22]
4	Solid lipid Nanoparticle	Insufficient stability and reproducibility, problematic sterilization, low payload	[23]
5	Nanolipid Carriers	Sterilization difficulties	[23, 24]
6	Micelle	Not good for hydrophilic drugs	[25]
7	Dendrimers	Polymer dependent biocompatibility	[26]
8	Liposome	Weak load capacity, poor chemical and physical stability on storage, rapid drug leakage,	[20, 27]
9	Niosome	Less skin penetration	[28]
10	Transferosome	Chemically unstable, very expensive	[29]
11	Sphingosome	Low entrapment efficacy, high cost of sphingolipids	[30]
12	Ethosome	Poor yield	[31]
13	Phytosomes	Low stability	[32]

Table 1.
Novel drug carrier systems with their limitations.

Generation	Category	Sub category	References
First	Plain nanosponges	Cyclodextrin-based urethane nanosponges ether nanosponges, cyclodextrin-based carbonate nanosponges, ester nanosponges	[33–36]
Second	Modified nanosponges	Fluorescent carbonate nanosponges, fluorescent carboxylated nanosponges, electrically charged CD-NSs, hydrophobic NSs	[37, 38]
Third	Stimuli nanosponges	pH responsive cross-linked CD based hydrogels, glutathione-responsive NSs, aminocyclodextrin nanosponges	[39–41]
Fourth	Molecularly imprinted nanosponges	Molecularly imprinted polymers based CD nanosponges	[42, 43]

Table 2.
Evolution of cyclodextrin based nanosponges.

2. Architecture of nanosponges

Typically, nanosponges have been constructed from cyclodextrin cross-linked with organic carbonates. Nanosponges mainly comprise of three components- polymer cross linking agent and drug moiety [44].

Nature and type of polymer used can impact the formulation and the performance of NS. The selection of polymer relies on the nature of drug and purpose for which drug is encapsulated. For drug targeting the polymer should possess

the capacity to bind with specific ligands. The capacity of the polymer to be cross-linked depends on its active and functional groups to be substituted [44]. Polymers used for architecting the NS are include polyvinyl alcohol (PVA), ethyl cellulose, polymethylmethacrylate, hyper connected polystyrenes, cyclodextrins and their derivatives like methyl beta cyclodextrins, alkyloxycarbonylcyclodextrins [45]. Among these, cyclodextrins (CDs) have been the most popularly employed for fabrication of nanosponges. These cone-shaped truncated cyclic oligosaccharides are comprised of glucopyranose units aligned around the hydrophobic cavity that may lodge guest moieties owing to inclusion complexes formation [46]. The basic physicochemical features of CD have been discovered in the early 1950s and since then they have been applied to improve the pharmaceutical and physicochemical properties, like stability, solubility and bioavailability of active moieties [47]. Conventionally, these nanosponges have been applied for decontamination of water [48]. However, nowadays they have been investigated and employed as nanocarriers for drug delivery in the field of pharmaceuticals.

Cyclodextrin complexes prepared with biocompatible hydrophilic polymers have been reported to enhance the solubility of encapsulated categories in aqueous media. Recently, it has been described that, by reacting cyclodextrins with cross-linkers, a new hyper-crosslinked nanostructured material can be obtained; these are termed as nanosponges [49].

Selection of crosslinker depends on the structure of polymer employed and active moiety to be incorporated [44]. Efficient crosslinkers help to transform molecular nanocavities into three-dimensional nanoporous products. By varying the degree of crosslinking, either hydrophobic or hydrophilic matrix can be formulated and possesses ability to entrap targeted moieties. By taking epichlorohydrin as a crosslinker, hydrophilic nanosponges can be developed, which can modify the amount of active moiety release, increase the absorption of active moiety through biological barriers and act as a potential system for immediate release formulations. Other cross-linking agents, like pyromellitic anhydride, diphenyl carbonate, diisocyanates, diarylcarbonates, glutaraldehyde, carbonyldiimidazoles, 2,2-bis(acrylamido) acetic acid and carboxylic acid dianhydrides result in hydrophobic nanosponges [16, 50].

3. Engineering of cyclodextrin based nanosponges

Nanosponges are synthesized depending on type of delivery system, polymer and nature of drug and solvents [14]. Various approaches used for formation of nanosponges are (Table 3).

3.1 Techniques for synthesis of cyclodextrin based nanosponges

Several techniques have been reported for synthesis of nanosponges, however melt method and solvent evaporation techniques have been widely reported in literature for preparation of these porous colloidal nanostructures (Figure 1).

An account of various methods that have been proposed is presented below:

3.1.1 Melt method

In brief way, the cross-linking agent is melted with CD and all components are homogenized and heated at 100°C with stirring magnetically for 5 hrs. Then, above matrix is allowed to cool. Frequent bathing is done to eliminate by-products and unreacted components [47].

Types of nanosponge	Crosslinkers	Example of crosslinkers	Method	Encapsulated drugs	References
Cyclodextrin carbonate nanosponges	Carbonyl cross-linkers	Diphenyl carbonate, Carbonyl diimidazole, Dimethyl carbonate	Solvent extraction, Thermal desorption	L-DOPA, erlotinib, quercetin, telmisartan, curcumin, resveratrol, tamoxifen, paclitaxel, Itraconazole, Camptothecin,	[43, 51–59]
Cyclodextrin carbamate nanosponges	Diisocyanate cross-linkers	Hexamethylene diisocyanate and Toluene diisocyanate	Solvent method	Dextromethorphan, Steroids, Dyes and Naringin	[60–63]
Cyclodextrin anhydride nanosponges	Anhydride cross-linkers	Pyromellitic dianhydride, Ethylenediaminetetraacetic acid dianhydride	Solvent method	Ibuprofen, doxorubicin, meloxicam, acetylsalicylic acid and strigolactones	[36, 39, 64–66]
Epichlorohydrin cyclodextrin nanosponges	Epichlorohydrin cross linkers	Epichlorohydrin	Solvent method	Creatinine, cilazapril captopril and enalapril	[67, 68]

Table 3.
 Engineering of cyclodextrin based nanosponges.

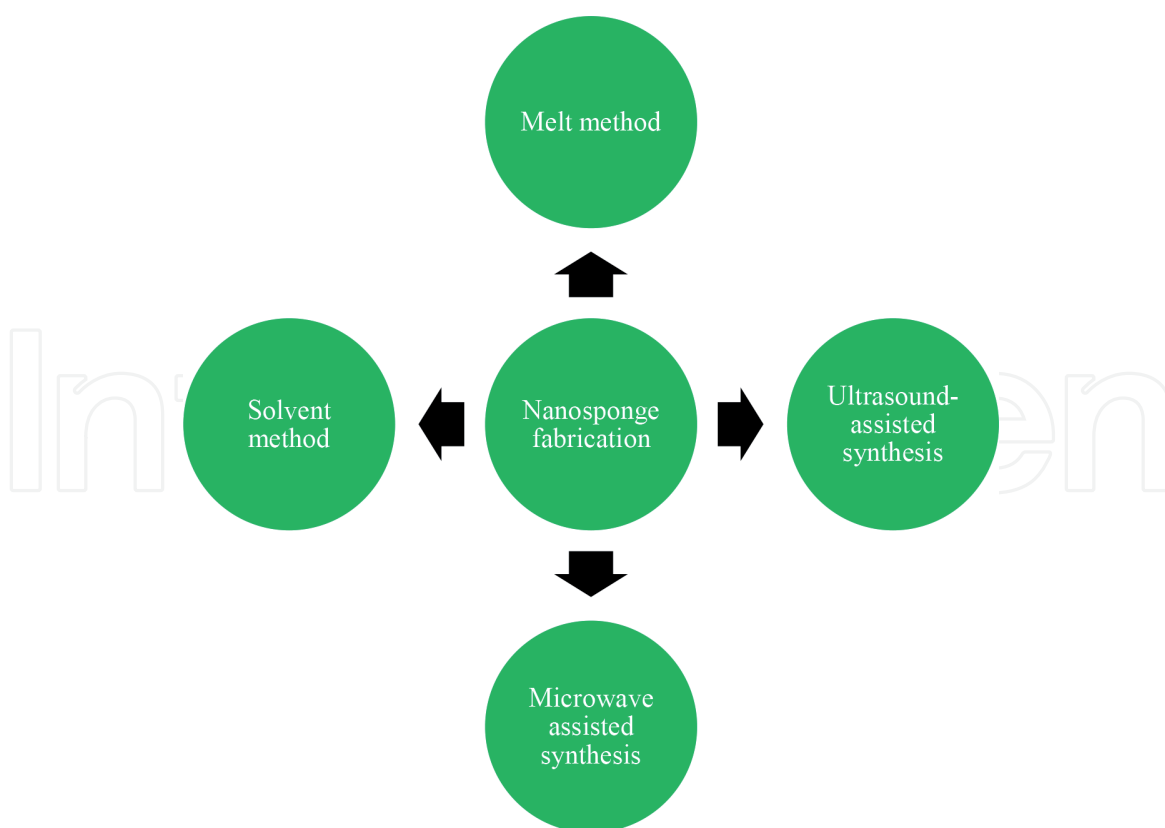


Figure 1.
Various techniques for fabrication of nanosponges.

3.1.2 Solvent evaporation technique

In solvent evaporation method, the fusion step is avoided and solvents like dimethylsulfoxide (DMSO) or dimethylformamide (DMF) are employed to solubilize the cross-linking agent. Polymer is mixed with solvent (polar aprotic) and the mixture obtained is put in solution of cross-linker and refluxed for 1–48 hrs. By adding cold solution to a large surplus of distilled water, the product is achieved. Finally, filtration is done to recover of the final product and is purified using Soxhlet extraction for prolonged periods. The product achieved is spherical and nanostructures with high water solubility either by non-inclusion or inclusion mechanism. The size of NS can be reduced by high pressure homogenization where water suspension of prepared nanosponges is homogenized at constant speed for 10 min [48, 49, 69].

3.1.3 Ultrasound-assisted synthesis

In ultrasound-assisted fabrication, in first, cyclodextrins are reacted with cross-linking agents under ultrasound without solvents. Anhydrous β -CD and DPC are taken in a vial and put in an ultrasound bath, pre-filled with water (at 90°C) and sonicated for 5 hrs. Furthermore, crystallization and purification steps are same as in solvent evaporation and melt technique [70].

3.1.4 Microwave assisted synthesis

It is the simplest method for synthesizing of CDNS using microwave irradiation, remarkably retards the reaction time. The resultant NS possess higher degree of crystallization. In comparison to common melt method, microwave assisted fabrication had exhibited four time reduction in reaction time. The process led to production of particle homogeneous distribution and crystallinity [52].

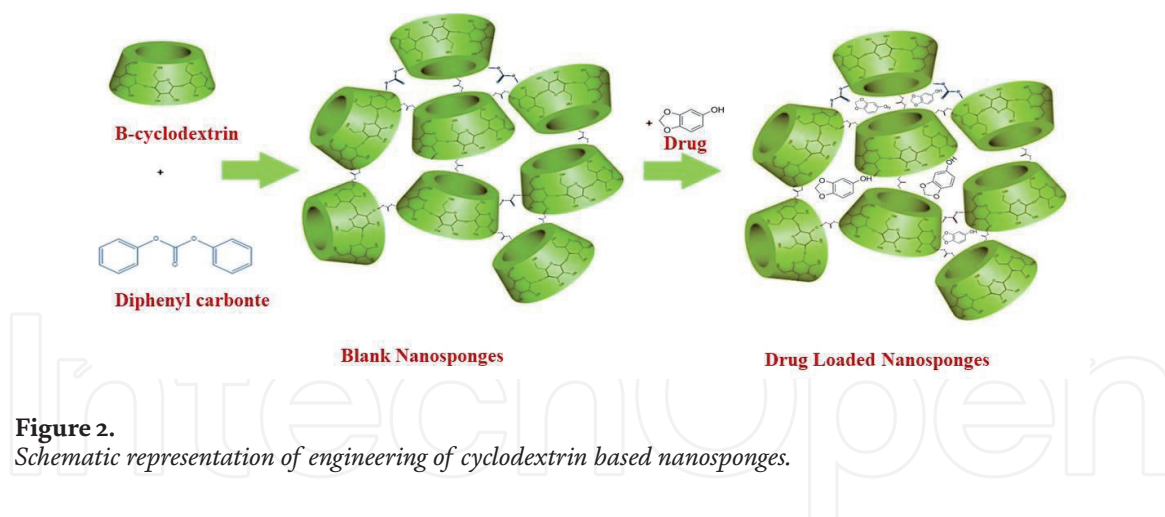


Figure 2.
Schematic representation of engineering of cyclodextrin based nanosponges.

3.2 Drug loading into blank NS

Crystal structure of the active moiety acts as one of the important criteria that determine its complex efficiency with CD and nanosponges. Paracrystalline and crystalline NS vary in the drug loading capacities. When compared, crystalline NS result in higher drug pay load the paracrystalline NS [47, 58, 71]. The porous cross-linked blank NS have numerous interactive sites for inclusion of drug moieties than parent CD. Further, these possess numerous mesh polarities owing to hydrophobic channels of CD which are enclosed by hydrophilic nanocavities of the polymeric matrix, allowing for large interactions with guests of variable lipophilicities and structures [72]. The resultant polymeric network of NS may be responsible for NS protection and solubilization compared to original CD as shown in **Figure 2** [58, 71]. The active moieties are entrapped into nanopores of blank nanosponges by dispersing them within drug dispersion and consequently freeze drying. The solvent evaporation is one another method reported for loading active moieties into NS using organic solvents suitable for dissolving the active moiety. Finally, NS are added to the prepared active moiety dispersion and triturated until the solvent evaporates [47, 73, 74].

4. Analytical techniques to characterize nanosponges

4.1 Spectroscopic techniques

Spectroscopic analytical tools represent a complementary tool to evaluate nanosponges. The variation in properties such as fluorescence intensity, wave number, absorbance and NMR shift of NS can be investigated by different spectroscopic analytical tools.

4.1.1 Ultraviolet: Visible spectrophotometry

To analyze NS in solution (liquid medium), UV-Visible spectrophotometry is a fast, simple, valuable and economic tool. The solubilization efficacy of various molecules such as telmisartan (296 nm) [53], acetyl salicylic acid (234 nm) [65], resveratrol (303 nm) [55], repaglinide (283 nm) [75], quercetin (372 nm) [76] and efavirenz (286 nm) [73] entrapped in NS have been analyzed using this tool.

Anandam and Selvamuthukumar checked payload, stability assay in simulated intestinal fluid, *in vitro* release, metal chelating and photostability investigation for quercetin NS via this spectrophotometric tool (λ_{max} 372 nm) [76].

4.1.2 Fourier-transform infrared spectroscopy

It is major employed technique for characterization of nanosponges. In general, measurements of FTIR absorption are carried out on dry samples, in the range 400–4000 cm^{-1} [77]. In case of nanosponges, during the reticulation (cross linking), the vibrational modes of cross-linkers, polymers and moieties are displayed from parent positions, broadening or disappearance of the prominent peaks of the molecule, polymer and cross-linkers [78, 79].

In FTIR spectra of the placebo NS, bands that varies from 1700 to 1750 cm^{-1} evidences the carbonate bond. Although, the parent polymer for NS fabrication, β -CD does not show peak at 1750 cm^{-1} in FTIR spectrum [76]. Cavalli and his colleagues explored the occurrence of carbonate bond (1700 cm^{-1}) in NS [80].

4.1.3 Raman spectroscopy (RS)

Nowadays, it is suggested as a useful analytical tool to study drug entrapment in NS [81]. Not only this, it can be employed together with FTIR to provide a better image to investigate interactions of active moiety and NS. Swaminathan and his colleagues performed RS to investigate dexamethasone and nanosponge interaction. On complexation with nanosponges, the prominent bands of the dexamethasone at 1620, 1480, 1440, 950 and 680 cm^{-1} in Raman spectra of the active moiety were substantially masked or displaced, advocating the inclusion phenomenon [82].

4.1.4 Nuclear magnetic resonance

It is based on the principle of radiofrequency radiation absorption by atomic nuclei having non zero spins in a high magnetic field [83]. Olteanu and co-workers performed the physicochemical characterization of NS using ^1H -NMR. High alteration in the chemical shift (0.47–0.24 ppm) of repaglinide A ring protons was observed. It was envisioned that inclusion in hydrophobic pores of CD and steric hinderance owing to CD substitution, have been considered responsible for interaction phenomenon [75].

4.2 Differential scanning calorimetry

It is a thermoanalytical technique to measure the change in physical or chemical properties of nanostructures and their fabricating materials owing to alteration in temperature. In general, thermal processes (both exothermic and endothermic) are evidenced by the peak direction [84]. This tool explored the exothermic and endothermic processes at the temperature range from -120 to 600°C [85–88]. The thermal behavior of the various drugs (dexamethasone, furbiprofen, doxorubicin [80], Itraconazole [59], camptothecin [58], resverarol [55], amino salicylic acid [65], gamma-oryzanol [89], telmisartan [53], curcumin [54], acyclovir [37], quercetin [76] and meloxicam [64]) entrapped in the NS was examined by DSC.

The complete disappearance of the therapeutic molecule fusion peak in graph of the NS complex is commonly considered as a confirmatory evidence of the encapsulation of therapeutic molecule within the NS cavity [90]. This may be due to conversion of the crystalline nature to amorphous ones [91]. Other evidence for confirming NS fabrication reported by research scientists include alterations in temperature peak and shape of cyclodextrins, alongwith disappearance of active moiety fusion peak and appearance of new peaks [92].

4.3 Thermogravimetric analysis

Thermogravimetric analysis (TGA) is crucial for supply of fundamental data for NS characterization. Due to its very simplicity, relative reliability and rapidity, TGA is widespread approach to solid-state characterization of nanosponges.

TGA chart of dexamethasone, quercetin, silibinin, apple polyphenols NS have been explored. In drug loaded NS thermograms, endotherms of the pure drug disappeared fully, evidencing the potential encapsulation of these molecules in nanostructures [82, 93, 94].

4.4 X-ray diffraction techniques

It gives detailed information on phases, texture, structures and other structural parameters (crystallinity, crystal defects and deformation) [95]. Unlike thermal techniques, sample does not suffer any physical or chemical changes during analysis. Furthermore, XRPD studies can support the results of thermal methods. The complete amorphization of the sample in DSC analysis, can be validated by this technique.

Crystalline and paracrystalline nature of NS and porosity can be revealed using this technique. A number of molecules (acetyl salicylic acid [65], camptothecin [58], telmisartan [53], resveratrol [55], acyclovir [37], quercetin [76], meloxicam [64], curcumin [54], and dexamethasone [82]) encapsulated in nanosponges have been evaluated using this technique.

4.5 Microscopic techniques

Microscopy can be used as an imaging analytical technique for qualitative analysis of NS with respect to their aggregation, size and shape. This section provides information on the microscopic methods like AFM, SEM, TEM, and CLSM that are properly used for NS characterization [96].

Scanning electron microscopy is used for observation of surface processes and is capable of obtaining images of bulky samples with a greater depth. It is also employed in solid state evaluation of nanosponges [97]. The topographic changes (related to the interactions of the polymer, active moiety and cross-linking agent) are provided [98]. Various pharmacological active molecules like resveratrol [55], telmisartan [53], dexamethasone [82], and meloxicam [64] have been explored microscopically using SEM.

A nanoscale imaging tool, TEM is used to visualize and characterize various types of nanoparticles [99, 100]. It is relatively expensive and slow technique. Surface morphology via TEM has also been performed for several NS such as ibuprofen [36], quercetin [76], acyclovir [37], paclitaxel [57], dexamethasone [82], camptothecin [58], resveratrol [55], acetyl salicylic acid [65].

Recently developed microscopic technique with high resolution, atomic force microscopy (AFM) is used for viewing atoms and molecules [101]. AFM has been applied to image the molecular nature of β -CDNS in the distilled water and to investigate their mechanical properties. The paracrystalline NS presented spherical colloidal structures (nearly 600 nm), whereas the crystalline NS presented the spectacular crystal planes (nearby 500 nm) [82].

Confocal laser scanning microscopy (CLSM) is recently emerging tool to improve the optical contrast and resolution of sample graph [102]. Lembo and his co-workers examined carboxylated NS loaded with acyclovir for cellular uptake of nanopreparation through CLSM. For this, fluorescent carboxylated NS were prepared [37].

4.6 Measurement of zeta potential

The zeta potential (ZP) is employed to measure the electrokinetic potential of nanomedicines. Simply, it is used for quantifying the charge [103]. To investigate the charge on the nanostructures, ZP must be carried out by suspending them in distilled water or suspension medium [104]. CDNS have been evaluated via the electrophoretic light scattering technique [53, 80, 105]. In practice, ZP predicts surface charge and colloidal stability of nanomaterials.

5. Nanosponges in drug delivery

Owing to their versatile, biocompatible and nanoporous nature, nanosponges have variety of applications in pharmaceuticals, cosmetics, agriculture, environment, food and polymer industry [55, 80, 106–108]. Among these, they have been predominantly studied for drug delivery. Numerous active molecules including lipophilic and hydrophilic actives and volatile oils can be conventionally entrapped in these multifaceted nanostructures for solubility and stability enhancement and for controlled delivery [7]. Hence, these novel carriers have attracted much interest of formulation scientists as they hold promise in addressing other challenges like poor bioavailability, permeation and therapeutic activity [69]. Cyclodextrin nanosponges have also been explored for drug delivery and drug targeting for cancer management [40, 109, 110]. In the following sections, information regarding their applications in pharmaceutical field has been summarized (**Table 4**).

Drug candidate	Category	Route of administration	Remarks	References
Dexamethasone	Anti-inflammatory	Oral, Parenteral	Improved aqueous solubility	[80, 82]
Flurbiprofen	Anti-inflammatory	Oral	Improved aqueous solubility	[80]
Doxorubicin	Antineoplastic	Parenteral	Enhanced aqueous solubility	[80]
Itraconazole	Antifungal	Oral, Topical	Improved solubilization efficiency	[59]
Tamoxifen	Antiestrogen	Oral	Enhanced pharmacokinetic activity of drug	[56]
Resveratrol	Antioxidant	Oral, Topical	Enhanced permeation, stability and cytotoxicity against HCPC-1 cells	[55]
Paclitaxel	Antineoplastic	Parenteral	<i>In vitro</i> enhancement of anticancer activity	[57, 111]
Camptothecin	Antineoplastic	Parenteral	Inhibits the adhesion and migration of tumor cells	[58]
Curcumin	Anti-cancer	Oral	Higher solubilization potential	[54, 112]
Acetylsalicylic acid	Analgesic	Oral	Controlled release	[65]
Acyclovir	Antiviral	Oral, topical, parenteral	Enhanced antiviral activity against HSV-1 (clinical isolates)	[37]

Drug candidate	Category	Route of administration	Remarks	References
Gamma-oryzanol	Antioxidant	Topical	Improved antioxidant potential and photostability	[89]
Repaglinide	Hypoglycemic agent	Oral	Solubility enhancement	[75]
Apple polyphenols (Rutin, phloridzin and chlorogenic acid)	Antioxidant antiaging and anti-inflammatroy	Topical	High degree of retention and protection	[93]
Telmisartan	Antihypertensive	Oral	Improved intrinsic solubility and bioavailability	[53]
Efavirenz	Anti HIV	Oral	Bioavailability enhancement	[73]
Lansoprazole	Antiulcer	Oral	Prolonged drug release	[113]
Tamoxifen and quercetin	Anti-cancer	—	Dual drug delivery	[114]
Lysozyme	Antihypcaalcemic	Oral	Inhibit depletion of calcium in antibiotic associated hypocalcemic condition	[105]
Meloxicam	Anti-inflammatory and analgesic	Oral	Controlled release	[64]
Quercetin	Antioxidant	—	Enhanced photostability and anti-oxidant activity; Improved dissolution profile	[76]
Tazarotene	Anti acne	topical	Improved bioavailability and skin retention of drug	[115]
Levodopa	Anti Parkinson's disease	Oral	Prolonged release of drug	[43]
N,N Diethyl-Meta-Toluamide	Insect Repellent	Topical	Prolong the persistence	[116]
Atorvastatin Calcium	Anti-hyperlipidemic	Oral	Bioavailability enhancement	[117]
Rosuvastatin	Anti-hyperlipidemic	Oral	Bioavailability enhancement	[118]
Strigolactones	Anti-cancer	—	Targeted delivery to prostate cancer cells	[66]
<i>Salvia officinalis</i> essential oil	Hypoglycemic activity	Oral	Enhancement of stability and hypoglycemic activity	[119]
Rilpivavir	Anti-retroviral	Oral	Increased in Bioavailability	[74]
Norfloxacin	fluoroquinolone antibiotic	Oral	Enhancement in intestinal permeation and antibacterial activity	[120]

Drug candidate	Category	Route of administration	Remarks	References
Ellagic acid	Antioxidant, Anticancer	Oral	Enhancement in oral bioavailability	[121]
Doxirubicin	Anti-cancer	Oral	Site specific drug delivery	[122]
Babchi oil	Anti-psoriatic	Topical	Enhanced photostability, solubility and anti psoriatic efficacy	[123, 124]
Imiquimod	Anti-cancer	Topical	Enhanced skin retention and permeation	[125]

Table 4.
Active molecules encapsulated in cyclodextrin based nanosponges.

5.1 Improved stability

Cyclodextrin nanosponges can prevent degradation of drug molecules which are susceptible to degradation when exposed to water, oxygen (air), heat or radiation. Such interactions are being widely studied in nanosponges. The nanosponges safeguard the drug molecules from oxidation, hydrolysis, racemization, polymerization and enzyme hydrolysis [126, 127]. A number of molecules including L-DOPA, resveratrol, camptothecin and γ -oryzanol and have been encapsulated in nanosponges are reported for stability enhancement and reported [43, 55, 58, 89]. Anandam and Selvamuthukumar found that photostability of anti-oxidant drug quercetin increased on incorporating into nanosponges. The main hindrance in its utility is its photodegradation. In addition, dissolution rate of the biomolecule was also remarkably enhanced in quercetin nanosponges.

5.2 Enhanced solubility

Poor solubility of BCS (Biopharmaceutical Classification System) class II drugs possesses a challenge in their formulation. However, these drugs can be successfully incorporated into cyclodextrin nanosponges with better efficacy. These nanocarriers improve their aqueous solubility *via* formation of inclusion complexes by enhancing their wetting and solubility in water. The drug dissolution enhancement consequently enhances their bioavailability. Curcumin is a upcoming herbal active drug having potential for treatment of various fatal diseases including cancer. Though, it has higher efficacy and safety profile, its poor solubility and low bioavailability limit its therapeutic application. Darandale and Vavia fabricated cyclodextrin based nanosponges of curcumin to increase solubility and control its release. These nanosponges were obtained using dimethyl carbonate as linking agent. The prepared nanoformulation showed enhanced solubility, prolonged drug release and reduced cytotoxicity against MCF-7 cells. Besides this, other drug moieties which have been successfully encapsulated in cyclodextrin nanosponges for improved dissolution include doxorubicin [80], itraconazole [59], flurbiprofen, dexamethasone [80], telmisartan [53], tamoxifen [56], repaglinide [75] and paclitaxel [111].

5.3 Reduction in volatility of essential oil and material handling benefits

Nanosponges have been reported to protect volatile oils against lost by evaporation. These nanosponges can have resulted in long lasting effect due to slow release

of chief volatile components of oils [72]. Further, volatile oil liquids (at room temperature) can be difficult to handle and hence needed to be formulated into stable solid formulations. Nanosponges may help to convert these substances into amorphous or microcrystalline powders which are convenient to handle [49].

5.4 Modulated drug release

Judicious loading of therapeutic actives into nanosponges ensures a tailored drug release. Developing controlled drug delivery systems is the topic of interest for research community while maintaining therapeutic effectiveness of drug. Employing these nanocarriers ensures optimal drug use with improved patient compliance owing to reduced frequency of administration. Nanosponges showed strong potential for providing sustained drug release in a controlled fashion. Shende et al., prepared meloxicam loaded cyclodextrin nanosponges to enhance solubility and stability and to prolong its release. *In vitro* and *in vivo* results demonstrated controlled release of meloxicam from the nanocarrier for 24 hrs. It was discussed that slow release of drug might have been due to large degree of cross linking that permitted the entrapment of drug as inclusion complex in the nanosponges. Decrease in crystallinity and enhancement in solubility also led to improve *in vitro* release behavior [64].

5.5 Drug targeting

Besides enhancing effectiveness of drug, drug targeting also helps in reducing its adverse effects on healthy cells. By using nanosponges for drug delivery, drug is released at the specific site preventing its circulation throughout the body. A limited number of research papers were found on drug targeting using nanosponges. Harth and Diaz have widely explored nanosponges for targeted drug delivery. Polyester nanosponges were fabricated using special chemical “linkers” for delivery of anti-cancer drugs. These linkers ensure that nanosponge bound selectively to tumor cells, on injection. These nanosponges stick to the surface of tumor cells and release the drug in a controlled fashion [128].

5.6 Oral drug delivery

Oral drug delivery has been well-established route of administration having high patient compliance. However, delivery of molecules *via* this route poses challenges owing to poor solubility, presystemic activation and inefficient intestinal permeability. Cyclodextrin based nanosponges have emerged as potential carriers for oral delivery without any compromise on safety issues. An excellent mini review on cyclodextrin nanosystems for oral delivery of drugs have been recently published by Adeoye and Cabral-Marques [129].

Zidan et al., have developed atorvastatin calcium for oral drug delivery by encapsulating it in β - cyclodextrin nanosponges cross linked with carbonyldiimidazole. The prepared nanosponges were found to increase bioavailability of drug up to 2.13-folds in comparison to its suspension. In addition, pharmacokinetic studies revealed remarkable decrease in total cholesterol, LDL-C (Low Density Lipoprotein Cholesterol) and triglyceride and improved level of HDL-C (High Density Lipoprotein Cholesterol) leading to improvement of liver steatosis [117].

5.7 Topical drug delivery

Nanosponges can also be incorporated in cream and gels for topical delivery of drugs. Although least explored, nanosponges may prove very promising

for treatment of skin disorders *via* this route. Besides drug targeting nanosponges also improved drug delivery from topical gel, if entrapped successfully. Nanosponges for topical delivery of drugs have been mentioned for resveratrol, γ -oryzanol, diclofenac sodium and babchi oil in literature [55, 89, 106, 124]. In addition, this nanoformulation also helps to alleviate local irritation problem associated with topical drugs. Conte et al., developed cyclodextrin nanosponges with pyromellitic dianhydride as cross linker and loaded them in semi-solid formulations for skin delivery. Skin permeation studies in diclofenac sodium loaded nanosponge gel and cream gels significantly retarded the drug permeation through skin while enhancing its concentration in viable epidermis and stratum corneum, confirming the localization of highly penetrating drugs in external layers of skin [11].

5.8 Pulmonary drug delivery

The pulmonary route is an alternative option to parenteral drug delivery, however, for delivery *via* this route, the drug must be in the form of aerosol. The nanosponges possess the advantage of reduced interparticle attraction forces and better flow characteristics. Further, they possess low bulk density and small narrow dynamic diameter resulting in their greater deposition in lower pulmonary area. For pulmonary delivery, nanosponges of sodium cromoglicate, budesinide, bendroflumethazide using sugar excipients like trehalose and raffinose have been reported [130–133].

Additionally, nanosponges have also been used for protein encapsulation, enzyme immobilization and stabilization. The enzymes like isomerase, hydrolyase, oxidoreductase, ligase, and transferase has been studied. Bovine serum albumin when encapsulated as nanosponges resulted in prolonged release [13]. NS can also be employed as carrier of gases like carbondioxide and oxygen. Oxygen loaded NS can be used to supply oxygen to hypoxic tissues in different disorders [134].

6. Conclusion

Cyclodextrin nanosponges are colloidal nanoparticles made from inexpensive, biodegradable materials and can be used for internal or external administration. As such, these offer a versatile platform to address challenges like solubility, stability and toxicity for therapeutically effective drugs. Cyclodextrin nanosponges are developing rapidly in the field of nanotechnology possessing several applications in drug targeting, delivery and research, as well as in other fields. Due to their unique porous nature and size-dependent properties, they present the possibility to develop new therapeutic options. Their ability to entrap drugs and controlled release features offer a new mode in drug delivery resulting in higher levels of drug targeting. Therefore, cyclodextrin nanosponges are a great promise to achieve the goal of site specific and controlled delivery aspects and can open new perspectives in the management of complex diseases, in coming future.

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Conflict of interest

The authors have no conflict of interest to declare and are responsible for the content and writing of the manuscript.

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