Chapter

Cyclodextrin Nanosponges: A Promising Approach for Modulating Drug Delivery

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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 nanostructres, 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, Expeditiously 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]
Thirrd	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, glutarldehyde, 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, reservertol, tamoxifen, paclitaxel, Itraconazole, Camptothecin,	[43, 51–59]
Cyclodextrin carbomate 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.

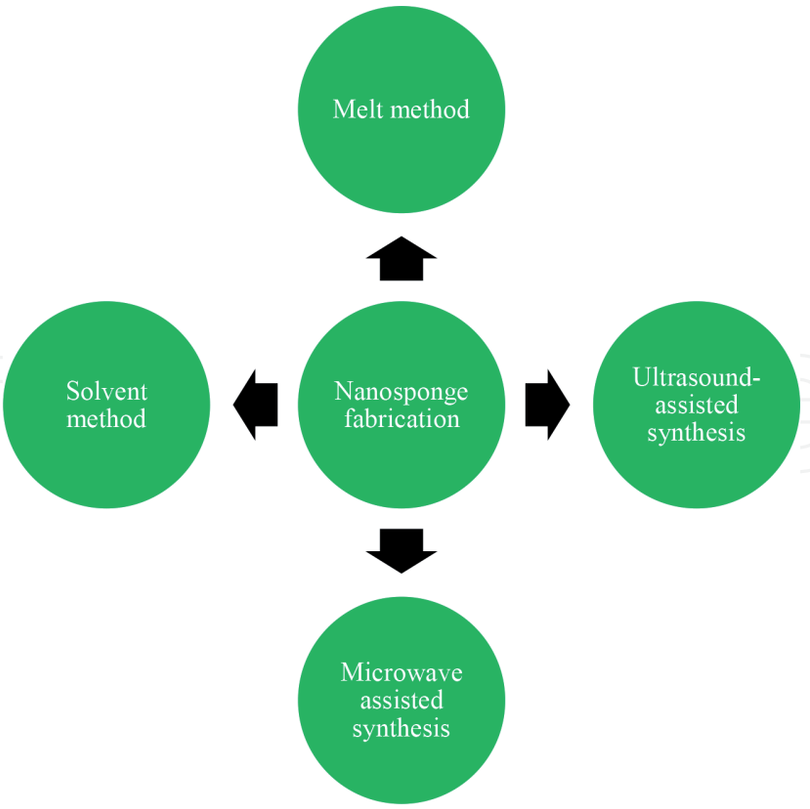

Figure 1.
Various techniques for fabrication of nanosponges.

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 solid 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].

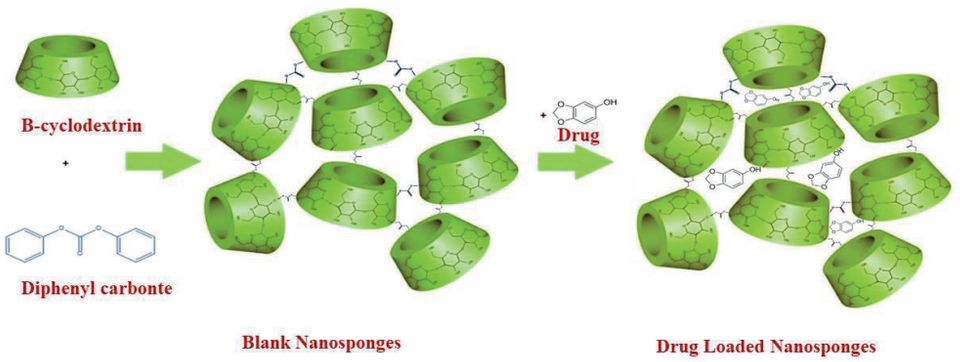

Figure 2.
Schematic representation of engineering of cyclodextrin based nanosponges.

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 salicyclic 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 spectrophotometeric 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]. Unlikely 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	*In vitro* 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]
Salvia officinalis essential oil	Hypoglycemic activity	Oral	Enhancement of stability and hypoglycemic activity	[119]
Rilpinavir	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	Toipcal	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 phototability 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 formulate 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, hydrolase, 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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References

[1] Panchagnula R. Transdermal delivery of drugs. Indian Journal of Pharmacology. 1997;**29**(3):140-156

[2] Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: Influence of plasticizers. Pharmaceutica Acta Helvetiae. 1997;**72**(1):47-51

[3] Rao PR, Diwan PV. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. Drug Development and Industrial Pharmacy. 1998;**24**(4):327-336

[4] Prasad M, Lambe UP, Brar B, Shah I, Manimegalai J, Ranjan K, et al. Nanotherapeutics: An insight into healthcare and multi-dimensional applications in medical sector of the modern world. Biomedicine and Pharmacotherapy. 2018;**97**:1521-1537

[5] Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: An updated review. International Journal of Pharmaceutical Investigation. 2012;**2**(1):2

[6] Singh R, Vyas SP. Topical liposomal system for localized and controlled drug delivery. Journal of Dermatological Science. 1996;**13**(2):107-111

[7] Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: A critical review. Carbohydrate Polymers. 2017;**173**:37-49

[8] Pawar S, Shende P, Trotta F. Diversity of β-cyclodextrin-based nanosponges for transformation of actives. International Journal of Pharmaceutics. 2019;**565**:333-350

[9] Salunkhe A, Kadam S, Magar S, Dangare K. Nanosponges: A modern formulation approach in drug delivery system. World Journal of Pharmacy and Pharmaceutical Sciences. 2018;**7**(2):575-592

[10] Patil TS, Nalawade NA, Kakade VK, Kale SN. Nanosponges: A novel targeted drug delivery for cancer treatment. International Journal for Advance Research and Development. 2017;**2**(4):55-62

[11] Conte C, Caldera F, Catanzano O, D'Angelo I, Ungaro F, Miro A, et al. β-Cyclodextrin nanosponges as multifunctional ingredient in water-containing semisolid formulations for skin delivery. Journal of Pharmaceutical Sciences. 2014;**103**(12):3941-3949

[12] Selvamuthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. Journal of Pharmacy and Pharmaceutical Sciences. 2012;**15**(1):103-111

[13] Jilsha G, Viswanad V. Nanosponges: A novel approach of drug delivery system. International Journal of Pharmaceutical Sciences Review and Research. 2013;**19**(2):119-123

[14] Pushpalatha R, Selvamuthukumar S, Kilimozhi D. Hierarchy analysis of different cross-linkers used for the preparation of cross-linked cyclodextrin as drug nanocarriers. Chemical Engineering Communications. 2018;**205**(6):759-771

[15] Kumar S, Rao R. Analytical tools for cyclodextrin nanosponges in pharmaceutical field: A review. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2019;**94**(1-2):11-30

[16] Panda S, Vijayalakshmi S, Pattnaik S, Swain RP. Nanosponges: A novel carrier for targeted drug delivery. International Journal of ChemTech Research. 2015;**8**(7):213-224

[17] Yadav GV, Panchory HP. Nanosponges–A boon to the targeted drug delivery system. Journal of Drug Delivery and Therapeutics. 2013;**3**(4):151-155

[18] Vishwakarma A, Nikam P, Mogal R, Talele S. Review on nanosponges: A benefication for novel drug delivery. International Journal PharmTech, Research. 2014;**6**:11-20

[19] Varde NK, Pack DW. Microspheres for controlled release drug delivery. Expert Opinion on Biological Therapy. 2004;**4**(1):35-51

[20] Touitou E, Junginger HE, Weiner ND, Nagai T, Mezei M. Liposomes as carriers for topical and transdermal delivery. Journal of Pharmaceutical Sciences. 1994;**83**(9):1189-1203

[21] Lherm C, Müller RH, Puisieux F, Couvreur P. Alkylcyanoacrylate drug carriers: II. Cytotoxicity of cyanoacrylate nanoparticles with different alkyl chain length. International Journal of Pharmaceutics. 1992;**84**(1):13-22

[22] Cortesi R, Esposito E, Luca G, Nastruzzi C. Production of lipospheres as carriers for bioactive compounds. Biomaterials. 2002;**23**(11):2283-2294

[23] Souto EB, Müller RH. Cosmetic features and applications of lipid nanoparticles (SLN®, NLC®). International Journal of Cosmetic Science. 2008;**30**(3):157-165

[24] Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. International Journal of Pharmaceutics. 2009;**366**(1-2):170-184

[25] Dhembre GN, Moon RS, Kshirsagar RV. A review on polymeric micellar nanocarriers. International Journal of Pharma and Bio Sciences. 2011;**2**(2):109-116

[26] Barbara K, Maria B. Review dendrimers: Properties and applications. Acta Biochimica Polonica. 2001;**48**(1):199-208

[27] Goyal P, Goyal K, Kumar SV, Singh AJ, Katare OP, Mishra DN. Liposomal drug delivery systems–clinical applications. Acta Pharmaceutica. 2005;**55**(1):1-25

[28] Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosomes: A novel drug delivery system. International Journal of Novel Trends in Pharmaceutical Sciences. 2012;**2**(1):25-31

[29] Prajapati ST, Patel CG, Patel CN. Transfersomes: A vesicular carrier system for transdermal drug delivery. Asian Journal of Biochemical and Pharmaceutical Research. 2011;**1**(2):507-524

[30] Saraf S, Gupta D, Kaur CD, Saraf S. Sphingosomes a novel approach to vesicular drug delivery. International Journal of Current Research. 2011;**1**(2):63-68

[31] Wahid AA, Ravouru N, Lakshman SR. Ethosomes: A tool for transdermal drug delivery. Circulation. 2011;**3**:14

[32] Suryawanshi JS. Phytosome: An emerging trend in herbal drug treatment. Journal of Medical Genetics and Genomics. 2011;**3**(6):109-114

[33] Li D, Ma M. Nanosponges: From inclusion chemistry to water purifying technology. ChemTech. 1999;**29**(5):31-37

[34] Machín R, Isasi JR, Vélaz I. β-Cyclodextrin hydrogels as potential drug delivery systems. Carbohydrate Polymers. 2012;**87**(3):2024-2030

[35] Rossi B, Caponi S, Castiglione F, Corezzi S, Fontana A, Giarola M, et al. Networking properties of cyclodextrin-based cross-linked polymers probed by inelastic light-scattering experiments.

The Journal of Physical Chemistry B. 2012;**116**(17):5323-5327

[36] Ferro M, Castiglione F, Punta C, Melone L, Panzeri W, Rossi B, et al. Anomalous diffusion of ibuprofen in cyclodextrin nanosponge hydrogels: An HRMAS NMR study. Beilstein Journal of Organic Chemistry. 2014;**10**:2715

[37] Lembo D, Swaminathan S, Donalisio M, Civra A, Pastero L, Aquilano D, et al. Encapsulation of acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. International Journal of Pharmaceutics. 2013;**443**(1-2):262-272

[38] Favier IM, Baudelet D, Fourmentin S. VOC trapping by new crosslinked cyclodextrin polymers. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2011;**69**(3-4):433-437

[39] Trotta F, Caldera F, Dianzani C, Argenziano M, Barrera G, Cavalli R. Cover picture: Glutathione bioresponsive cyclodextrin nanosponges (ChemPlusChem 5/2016). ChemPlusChem. 2016;**81**(5):433

[40] Daga M, Ullio C, Argenziano M, Dianzani C, Cavalli R, Trotta F, et al. GSH-targeted nanosponges increase doxorubicin-induced toxicity "in vitro" and "in vivo" in cancer cells with high antioxidant defenses. Free Radical Biology and Medicine. 2016;**97**:24-37

[41] Russo M, Saladino ML, Martino DC, Meo PL, Noto R. Polyaminocyclodextrin nanosponges: Synthesis, characterization and pH-responsive sequestration abilities. RSC Advances. 2016;**6**(55):49941-49953

[42] Deshmukh K, Tanwar YS, Shende P, Cavalli R. Biomimetic estimation of glucose using non-molecular and molecular imprinted polymer nanosponges. International Journal of Pharmaceutics. 2015;**494**(1):244-248

[43] Trotta F, Caldera F, Cavalli R, Soster M, Riedo C, Biasizzo M, et al. 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

[44] Eldose A, Parmar T, Shah H, Patel J, Zala T, Jain H. Nanosponge: A novel nano drug carrier. Journal of Advance Research in Pharmacy and Biological Science. 2015;**1**(7):1-7

[45] Ajinkya K, Prakash K, Vishal P. Scaffold based drug delivery system: A special emphasis on nanosponges. International Journal of Pharmaceuticas and Drug Analysis. 2015;**3**(4):98-104

[46] Caldera F, Tannous M, Cavalli R, Zanetti M, Trotta F. Evolution of cyclodextrin nanosponges. International Journal of Pharmaceutics. 2017;**531**(2):470-479

[47] Tejashri G, Amrita B, Darshana J. Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta Pharmaceutica. 2013;**63**(3):335-358

[48] Trotta F, Tumiatti W, inventors; Sea Marconi Technologies Di W Tumiatti Sas, assignee. Cross-linked polymers based on cyclodextrins for removing polluting agents. United States patent application US 10/510,792; 2005

[49] Trotta F, Cavalli R. Characterization and applications of new hyper-cross-linked cyclodextrins. Composite Interfaces. 2009;**16**(1):39-48

[50] Kaur G, Aggarwal G, Harikumar SL. Nanosponge: New colloidal drug delivery system for topical delivery. Indo Global Journal of Pharmaceutical Sciences. 2015;**5**(1):53-57

[51] Dora CP, Trotta F, Kushwah V, Devasari N, Singh C, Suresh S, et al. Potential of erlotinib cyclodextrin nanosponge complex to enhance solubility, dissolution rate, in vitro cytotoxicity and oral bioavailability. Carbohydrate Polymers. 2016;**137**:339-349

[52] Singireddy A, Subramanian S. Cyclodextrin nanosponges to enhance the dissolution profile of quercetin by inclusion complex formation. Particulate Science and Technology. 2016;**34**(3):341-346

[53] Rao M, Bajaj A, Khole I, Munjapara G, Trotta F. In vitro and in vivo evaluation of β-cyclodextrin-based nanosponges of telmisartan. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;**77**(1-4):135-145

[54] Darandale SS, Vavia PR. Cyclodextrin-based nanosponges of curcumin: Formulation and physicochemical characterization. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;**75**(3-4):315-322

[55] Ansari KA, Vavia PR, Trotta F, Cavalli R. Cyclodextrin-based nanosponges for delivery of resveratrol: In vitro characterisation, stability, cytotoxicity and permeation study. AAPS PharmSciTech. 2011;**12**(1):279-286

[56] Torne S, Darandale S, Vavia P, Trotta F, Cavalli R. Cyclodextrin-based nanosponges: Effective nanocarrier for Tamoxifen delivery. Pharmaceutical Development and Technology. 2013;**18**(3):619-625

[57] Torne SJ, Ansari KA, Vavia PR, Trotta F, Cavalli R. Enhanced oral paclitaxel bioavailability after administration of paclitaxel-loaded nanosponges. Drug Delivery. 2010;**17**(6):419-425

[58] Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D, et al. Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. European Journal of Pharmaceutics and Biopharmaceutics. 2010;**74**(2):193-201

[59] Swaminathan S, Vavia PR, Trotta F, Torne S. Formulation of betacyclodextrin based nanosponges of itraconazole. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2007;**57**(1-4):89-94

[60] Hishiya T, Shibata M, Kakazu M, Asanuma H, Komiyama M. Molecularly imprinted cyclodextrins as selective receptors for steroids. Macromolecules. 1999;**32**(7):2265-2269

[61] Roche PJ, Ng SM, Narayanaswamy R, Goddard N, Page KM. Multiple surface plasmon resonance quantification of dextromethorphan using a molecularly imprinted β-cyclodextrin polymer: A potential probe for drug–drug interactions. Sensors and Actuators, B: Chemical. 2009;**139**(1):22-29

[62] Ma X, Chen Z, Chen R, Zheng X, Chen X, Lan R. Imprinted β-cyclodextrin polymers using naringin as template. Polymer International. 2011;**60**(10):1455-1460

[63] Kyzas GZ, Lazaridis NK, Bikiaris DN. Optimization of chitosan and β-cyclodextrin molecularly imprinted polymer synthesis for dye adsorption. Carbohydrate Polymers. 2013;**91**(1):198-208

[64] Shende PK, Gaud RS, Bakal R, Patil D. Effect of inclusion complexation of meloxicam with β-cyclodextrin-and β-cyclodextrin-based nanosponges on solubility, in vitro release and stability studies. Colloids and Surfaces B: Biointerfaces. 2015;**136**:105-110

[65] Shende PK, Trotta F, Gaud RS, Deshmukh K, Cavalli R, Biasizzo M. Influence of different techniques on formulation and comparative characterization of inclusion complexes of ASA with β-cyclodextrin and inclusion complexes of ASA with PMDA cross-linked β-cyclodextrin nanosponges. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2012;**74**(1-4):447-454

[66] Argenziano M, Lombardi C, Ferrara B, Trotta F, Caldera F, Blangetti M, et al. Glutathione/pH-responsive nanosponges enhance strigolactone delivery to prostate cancer cells. Oncotarget. 2018;**9**(88):35813-35829

[67] Tsai HA, Syu MJ. Synthesis of creatinine-imprinted poly (β-cyclodextrin) for the specific binding of creatinine. Biomaterials. 2005;**26**(15):2759-2766

[68] Olteanu AA, Arama CC, Bleotu C, Lupuleasa D, Monciu CM. Investigation of cyclodextrin based nanosponges complexes with angiotensin I converting enzyme inhibitors (Enalapril, captopril, cilazapril). Farmácia. 2015;**63**:492-503

[69] ChilajwarSV, PednekarPP, JadhavKR, Gupta GJ, Kadam VJ. Cyclodextrin-based nanosponges: A propitious platform for enhancing drug delivery. Expert Opinion on Drug Delivery. 2014;**11**(1):111-120

[70] Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Roggero C, Vallero R, inventors; Sea Marconi Technologies Di W Tumiatti Sas, assignee. Ultrasound-assisted synthesis of cyclodextrin-based nanosponges. United States patent application US 11/630,403; 2008

[71] Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosponge formulations as oxygen delivery systems. International Journal of Pharmaceutics. 2010;**402**(1-2):254-257

[72] Trotta F, Zanetti M, Cavalli R. Cyclodextrin-based nanosponges as drug carriers. Beilstein Journal of Organic Chemistry. 2012;**8**:2091

[73] Rao MR, Shirsath C. Enhancement of bioavailability of non-nucleoside reverse transciptase inhibitor using nanosponges. AAPS PharmSciTech. 2017;**18**(5):1728-1738

[74] Rao MR, Chaudhari J, Trotta F, Caldera F. Investigation of cyclodextrin-based nanosponges for solubility and bioavailability enhancement of rilpivirine. AAPS PharmSciTech. 2018;**19**(5):2358-2369

[75] Olteanu AA, Aramă CC, Radu C, Mihăescu C, Monciu CM. Effect of β-cyclodextrins based nanosponges on the solubility of lipophilic pharmacological active substances (repaglinide). Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2014;**80**(1-2):17-24

[76] Anandam S, Selvamuthukumar S. Fabrication of cyclodextrin nanosponges for quercetin delivery: Physicochemical characterization, photostability, and antioxidant effects. Journal of Materials Science. 2014;**49**(23):8140-8153

[77] Ahmed RZ, Patil G, Zaheer Z. Nanosponges–A completely new nano-horizon: Pharmaceutical applications and recent advances. Drug Development and Industrial Pharmacy. 2013;**39**(9):1263-1272

[78] Bragagni M, Maestrelli F, Mura P. Physical chemical characterization of binary systems of prilocaine hydrochloride with triacetyl-β-cyclodextrin. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2010;**68**(3-4):437-445

[79] Menezes PP, Serafini MR, Santana BV, Nunes RS, Quintans LJ Jr, Silva GF, et al. Solid-state β-cyclodextrin

complexes containing geraniol. Thermochimica Acta. 2012;**548**:45-50

[80] Cavalli R, Trotta F, Tumiatti W. Cyclodextrin-based nanosponges for drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2006;**56**(1-2):209-213

[81] Crupi V, Fontana A, Majolino D, Mele A, Melone L, Punta C, et al. Hydrogen-bond dynamics of water confined in cyclodextrin nanosponges hydrogel. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2014;**80**(1-2):69-75

[82] Swaminathan S, Vavia PR, Trotta F, Cavalli R, Tumbiolo S, Bertinetti L, et al. Structural evidence of differential forms of nanosponges of beta-cyclodextrin and its effect on solubilization of a model drug. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;**76**(1-2):201-211

[83] Ibañez E, Cifuentes A. New analytical techniques in food science. Critical Reviews in Food Science and Nutrition. 2001;**41**(6):413-450

[84] Biliaderis CG. Differential scanning calorimetry in food research—A review. Food Chemistry. 1983;**10**(4):239-265

[85] Chartoff RP. Thermoplastic Polymers in Thermal Characterization of Polymeric Materials. Academic Press: New York; 1997. p. 513

[86] Bair HE. Thermal analysis of additives in polymers. In: Turi A, editor. Thermal Characterization of Polymeric Materials. 1st ed. Cambridge, Massachusetts, USA: Academic Press, Elsevier; 1981. pp. 845-906

[87] Gallagher PK. Thermal Characterization of Polymeric Materials. San Diego: Academic Press; 1997

[88] Wunderlich B. Basics of thermal analysis. In: Wunderlich B, editor. Thermal Analysis of Polymeric Materials. Berlin, Heidelberg: Springer; 2005. pp. 71-188

[89] Sapino S, Carlotti ME, Cavalli R, Ugazio E, Berlier G, Gastaldi L, et al. Photochemical and antioxidant properties of gamma-oryzanol in beta-cyclodextrin-based nanosponges. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;**75**(1-2):69-76

[90] Chen W, Yang LJ, Ma SX, Yang XD, Fan BM, Lin J. Crassicauline A/β-cyclodextrin host–guest system: Preparation, characterization, inclusion mode, solubilization and stability. Carbohydrate Polymers. 2011;**84**(4):1321-1328

[91] Bettinetti G, Mura P, Faucci MT, Sorrenti M, Setti M. Interaction of naproxen with noncrystalline acetyl β-and acetyl γ-cyclodextrins in the solid and liquid state. European Journal of Pharmaceutical Sciences. 2002;**15**(1):21-29

[92] Wang DW, Ouyang CB, Liu Q, Yuan HL, Liu XH. Inclusion of quinestrol and 2, 6-di-O-methyl-β-cyclodextrin: Preparation, characterization, and inclusion mode. Carbohydrate Polymers. 2013;**93**(2):753-760

[93] Ramírez-Ambrosi M, Caldera F, Trotta F, Berrueta LÁ, Gallo B. Encapsulation of apple polyphenols in β-CD nanosponges. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2014;**80**(1-2):85-92

[94] Massaro M, Cinà V, Labbozzetta M, Lazzara G, Meo PL, Poma P, et al. Chemical and pharmaceutical evaluation of the relationship between triazole linkers and pore size on cyclodextrin–calixarene nanosponges used as carriers for natural drugs. RSC Advances. 2016;**6**(56):50858-50866

[95] Bunaciu AA, UdriŞTioiu EG, Aboul-Enein HY. X-ray diffraction: Instrumentation and applications. Critical Reviews in Analytical Chemistry. 2015;**45**(4):289-299

[96] Luykx DM, Peters RJ, van Ruth SM, Bouwmeester H. A review of analytical methods for the identification and characterization of nano delivery systems in food. Journal of Agricultural and Food Chemistry. 2008;**56**(18):8231-8247

[97] Fraunhofer W, Winter G. The use of asymmetrical flow field-flow fractionation in pharmaceutics and biopharmaceutics. European Journal of Pharmaceutics and Biopharmaceutics. 2004;**58**(2):369-383

[98] Maestrelli F, Cecchi M, Cirri M, Capasso G, Mennini N, Mura P. Comparative study of oxaprozin complexation with natural and chemically-modified cyclodextrins in solution and in the solid state. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2009;**63**(1-2):17-25

[99] Williams DB, Carter CB. The transmission electron microscope. In: Transmission Electron Microscopy. Boston, MA: Springer; 1996. pp. 3-17

[100] Wang ZL. Transmission electron microscopy of shape-controlled nanocrystals and their assemblies. The Journal of Physical Chemistry B. 2000;**104**:1153-1175

[101] Ruozi B, Tosi G, Forni F, Fresta M, Vandelli MA. Atomic force microscopy and photon correlation spectroscopy: Two techniques for rapid characterization of liposomes. European Journal of Pharmaceutical Sciences. 2005;**25**(1):81-89

[102] Jonkman J, Brown CM. Any way you slice it—A comparison of confocal microscopy techniques. Journal of Biomolecular Techniques: JBT. 2015;**26**(2):54

[103] Kutscher HL, Chao P, Deshmukh M, Rajan SS, Singh Y, Hu P, et al. Enhanced passive pulmonary targeting and retention of PEGylated rigid microparticles in rats. International Journal of Pharmaceutics. 2010;**402**(1-2):64-71

[104] Radomska-Soukharev A. Stability of lipid excipients in solid lipid nanoparticles. Advanced Drug Delivery Reviews. 2007;**59**(6):411-418

[105] Deshmukh K, Tanwar YS, Sharma S, Shende P, Cavalli R. Functionalized nanosponges for controlled antibacterial and antihypocalcemic actions. Biomedicine and Pharmacotherapy. 2016;**84**:485-494

[106] Montazer M, Mehr EB. Na-diclofenac β-cyclodextrin inclusion complex on cotton wound dressing. The Journal of The Textile Institute. 2010;**101**(5):373-379

[107] Seglie L, Martina K, Devecchi M, Roggero C, Trotta F, Scariot V. The effects of 1-MCP in cyclodextrin-based nanosponges to improve the vase life of Dianthus caryophyllus cut flowers. Postharvest Biology and Technology. 2011;**59**(2):200-205

[108] Seglie L, Spadaro D, Trotta F, Devecchi M, Gullino ML, Scariot V. Use of 1-methylcylopropene in cyclodextrin-based nanosponges to control grey mould caused by Botrytis cinerea on Dianthus caryophyllus cut flowers. Postharvest Biology and Technology. 2012;**64**(1):55-57

[109] Minelli R, Cavalli R, Ellis L, Pettazzoni P, Trotta F, Ciamporcero E, et al. Nanosponge-encapsulated camptothecin exerts anti-tumor activity in human prostate cancer cells. European Journal of Pharmaceutical Sciences. 2012;**47**(4):686-694

[110] Swaminathan S, Cavalli R, Trotta F. Cyclodextrin-based nanosponges:

A versatile platform for cancer nanotherapeutics development. Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology. 2016;**8**(4):579-601

[111] Mognetti B, Barberis A, Marino S, Berta G, De Francia S, Trotta F, et al. In vitro enhancement of anticancer activity of paclitaxel by a Cremophor free cyclodextrin-based nanosponge formulation. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2012;**74**(1-4):201-210

[112] 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

[113] Penjuri SC, Ravouru N, Damineni S, Bns S, Formulation PSR. Evaluation of lansoprazole loaded nanosponges. Turkish Journal of Pharmaceutical Sciences. 2016;**13**(3):304-310

[114] Lockhart JN, Stevens DM, Beezer DB, Kravitz A, Harth E. Dual drug delivery of tamoxifen and quercetin: Regulated metabolism for anticancer treatment with nanosponges. Journal of Controlled Release. 2015;**220**:751-757

[115] Aggarwal G, Nagpal M, Kaur G. Development and comparison of nanosponge and niosome based gel for the topical delivery of tazarotene. Pharmaceutical nanotechnology. 2016;**4**(3):213-228

[116] Peila R, Scordino P, Shanko DB, Caldera F, Trotta F, Ferri A. Synthesis and characterization of β-cyclodextrin nanosponges for N, N-diethyl-meta-toluamide complexation and their application on polyester fabrics. Reactive and Functional Polymers. 2017;**119**:87-94

[117] Zidan MF, Ibrahim HM, Afouna MI, Ibrahim EA. In vitro and in vivo evaluation of cyclodextrin-based nanosponges for enhancing oral bioavailability of atorvastatin calcium. Drug Development and Industrial Pharmacy. 2018;**44**(8):1243-1253

[118] Gabr MM, Mortada SM, Sallam MA. Carboxylate cross-linked cyclodextrin: A nanoporous scaffold for enhancement of rosuvastatin oral bioavailability. European Journal of Pharmaceutical Sciences. 2018;**111**:1-12

[119] Nait Bachir Y, Nait Bachir R, Hadj-Ziane-Zafour A. Nanodispersions stabilized by β-cyclodextrin nanosponges: Application for simultaneous enhancement of bioactivity and stability of sage essential oil. Drug Development and Industrial Pharmacy. 2019;**45**(2):333-347

[120] Mendes C, Meirelles GC, Barp CG, Assreuy J, Silva MA, Ponchel G. Cyclodextrin based nanosponge of norfloxacin: Intestinal permeation enhancement and improved antibacterial activity. Carbohydrate Polymers. 2018;**195**:586-592

[121] Mady FM, Ibrahim M, Ragab S. Cyclodextrin-based nanosponge for improvement of solubility and oral bioavailability of ellagic acid. Pakistan Journal of Pharmaceutical Sciences. 2018;**31**(5):2069-2076

[122] Singh P, Ren X, Guo T, Wu L, Shakya S, He Y, et al. Biofunctionalization of β-cyclodextrin nanosponges using cholesterol. Carbohydrate Polymers. 2018;**190**:23-30

[123] Kumar S, Trotta F, Rao R. Encapsulation of Babchi oil in cyclodextrin-based nanosponges: Physicochemical characterization, photodegradation, and in vitro cytotoxicity studies. Pharmaceutics. 2018;**10**(4):169. DOI: 10.3390/pharmaceutics10040169

[124] Kumar S, Singh KK, Rao R. Enhanced anti-psoriatic efficacy and regulation of oxidative stress of a novel topical babchi oil (*Psoralea corylifolia*) cyclodextrin-based nanogel in a mouse tail model. Journal of Microencapsulation. 2019;**36**(2):140-155. DOI: 10.1080/02652048.2019.1612475

[125] Argenziano M, Haimhoffer A, Bastiancich C, Jicsinszky L, Caldera F, Trotta F, et al. In vitro enhanced skin permeation and retention of imiquimod loaded in β-cyclodextrin nanosponge hydrogel. Pharmaceutics. 2019;**11**(3):138. DOI: 10.3390/pharmaceutics11030138

[126] Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. Journal of Pharmaceutical Sciences. 1996;**85**(10):1017-1025

[127] Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: An updated review. AAPS PharmSciTech. 2005;**6**(2):E329-E357

[128] Harth E, Diaz R. Nanosponge Drug Delivery System More Effective Than Direct Injection. Nanotechnology Now [Internet]. 2010. Available from: https://news.vanderbilt.edu/2010/06/01/nanosponge-drug-delivery-system-more-effective-than-direct-injection-116839/ [Accessed: May 11, 2019]

[129] Adeoye O, Cabral-Marques H. Cyclodextrin nanosystems in oral drug delivery: A mini review. International Journal of Pharmaceutics. 2017;**531**(2):521-531

[130] Healy AM, McDonald BF, Tajber L, Corrigan OI. Characterisation of excipient-free nanoporous microparticles (NPMPs) of bendroflumethiazide. European Journal of Pharmaceutics and Biopharmaceutics. 2008;**69**(3):1182-1186

[131] Nolan LM, Li J, Tajber L, Corrigan OI, Healy AM. Particle engineering of materials for oral inhalation by dry powder inhalers. II—Sodium cromoglicate. International Journal of Pharmaceutics. 2011;**405**(1-2):36-46

[132] Nolan LM, Tajber L, McDonald BF, Barham AS, Corrigan OI, Healy AM. Excipient-free nanoporous microparticles of budesonide for pulmonary delivery. European Journal of Pharmaceutical Sciences. 2009;**37**(5):593-602

[133] Ógáin ON, Li J, Tajber L, Corrigan OI, Healy AM. Particle engineering of materials for oral inhalation by dry powder inhalers. I—Particles of sugar excipients (trehalose and raffinose) for protein delivery. International Journal of Pharmaceutics. 2011;**405**(1-2):23-35

[134] Indira B, Bolisetti SS, Samrat C, Reddy SM, Reddy NS. Nanosponges: A new era in drug delivery. Journal of Pharmacy Research. 2012;**5**(12):5293-5296