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Review Article

NANOSPONGES: AN INNOVATIVE DRUG DELIVERY SYSTEM

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ABSTRACT

For prolonged time there is a delusion for efficacious targeted drug delivery system, but the chemistry hold complex form had made situations thorny, but the development of new colloidal carrier called nanosponges (NSs) likely circumvent these problems. NSs are the nanoporous particles that can entangle a huge range of material and then be engulfed into a suitable formulation depend on the route of administration. They prevent the drug-protein degradation, lengthen the drug release in a controlled manner, and release the medicament to the target site. They can travel around the body and attach on the surface and liberate the drug in a controlled and predictable manner at the specific target site. They are fine aqueous solubility which makes them a bearer for low water-soluble drugs. Drugs having low bioavailability are best suited for this type of carrier system. Both lipophilic and hydrophilic drugs can be included in NSs. Particle size can change from smaller to bigger by varying the amount of crosslinker to the polymer. Various applications of NSs such as recovering bioavailability of active ingredient molecule and delivery of active ingredient into oral, topical, parenteral, and nasal route make them a superior candidate for targeted delivery of drugs. It can be used as a shipper for biocatalysts in the transport and release of enzymes, proteins, vaccines, and antibodies. They can be prepared by different methods such as emulsion solvent diffusion method, melt method, ultrasound-assisted method, Quasi emulsion solvent diffusion method. This analysis is focusing on the advantages, formulation, evaluation, application, and patent report of the NSs.

Keywords: Nanosponges, Cyclodextrin, Cross-linking agents, Controlled release, Polymers.

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INTRODUCTION

For the treatment of diseases related to chemical and biological problems, pharmaceutical and health-care industry fabricated nano-scale materials [1]. So far nanotechnology resulted in variants of formulations such as nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, and nanoerythosomes, these all systems contribute to the targeted drug delivery system [2]. Targeted drug delivery system also is known as a smart drug delivery system which distributes the medicament to a patient in such a way that enhances the proportion of the drug at the targeted organ [3]. Nanosponges (NSs) are such type of targeted drug delivery system which delivers the drug at the target site in a controlled and predictable way. They are non-mutagenic, non-allergenic, non-irritant, and nontoxic [4]. NSs are spongy spheres have countless interconnected voids. These NSs have a high power of entrapping wide ranges of active ingredients, and they can bind poorly soluble drugs within its matrix and improve their bioavailability [5,6]. By reacting cyclodextrin with best-fitted crosslinkers, a NSs can be shaped [7]. They can cover many types of molecules by forming inclusion and non-inclusion complexes [8,9]. Due to their inner lipophilic cavities and outer hydrophilic branching, they can carry both hydrophilic and lipophilic drug molecules. By carrying a reaction of cyclodextrin with an acceptable crosslinker a novel nano-sized material consisting of hyper crosslinked cyclodextrin can be acquired, called as NSs [10-13]. They can be used to change liquid substances into solid and can be used to masquerade displeasing flavor. The crosslinkers used in the NSs enables them to combine to the target site. They are solid in character and can be found harmless for various routes [13]. Nanoparticles are obtainable in various forms such as polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, NSs, carbon nanotubes, micellar systems, and dendrimers [14]. Depending on the route of administration, they can be originated as oral, topical, parenteral, and inhalational formulations. For the oral route, the prepared NSs may be disseminated in a matrix of excipients, diluents, lubricants, and anticaking agents fitting for the fabrication of capsules or tablets [15]. For the parenteral route, the compound may be simply used in sterile water, saline, or other aqueous solutions. For the topical route, they can be successfully integrated into the topical hydrogel [16].

EDGES OF NSS [7,14-19]

1. Decrease the annoyance of the medicament without reducing the effectiveness.
2. Targeted site-specific drug release.
3. Lesser harmful side effects.
4. Biodegradable.
5. Predictable and controlled release.
6. Improving patient compliance.
7. Drug is protected from degradation.
8. Particle size can be adjusted by changing the amount of cross-linker to the polymer.
9. Provide therapeutic start of the action.
10. They are non-mutagenic, non-irritant.

COMPOSITION OF NSS [20-25]

Composition of NSS are shown in Table 1

Process of arrangement: Following methods are used for the preparation of NSs:

1. Melt method
2. Solvent diffusion methods
   - Emulsion solvent diffusion method
   - Quasi – emulsion solvent diffusion
3. Solvent Method
4. Ultrasound Assisted Method.

Melt technique

Melt technique In melt technique cyclodextrin is react with a suitable crosslinker such as dimethyl carbonate, diphenyl carbonate, isocyanates, diaryl carbonates, carbonyldiimidazole (C7H6N40), carboxylic acid anhydrides, and 2, 2-bis (acrylamide) acetic acid [8]. All ingredient are

delicately integrated and put in a 250 mL flask warmth at 100°C, and the reaction is conceded out for 5 h using magnetic stirrer [17]. the mixture is endorsed to cool and the prepared product is bust down and to eradicate unreacted excipients the product is washed with a proper solvent [Figure 1].

Solvent diffusion method

Emulsion solvent diffusion technique

In this technique, two diverse extents of organic and aqueous phases are used. In organic phase, drug and polymer are integrated, and in aqueous phase, polyvinyl alcohol (PVA) is used [26]. After dissolving drug and polymer to the right organic solvent, this phase is slowly mixed to the aqueous phase and agitates for 2 or more h at 1000 rpm using magnetic stirrer [27]. Then, the ready NSs are composed by filtration washed and then dried in air at room temp or in vacuum oven 40°C for 24 h [28] [Figure 2].

Quasi-emulsion solvent diffusion

In this process, the polymer is dispersed in an acceptable solvent, and this phase is called an inner phase [29]. In ultrasonication at 35°C, drug is mixed to this solution [30]. Then, the inner phase is poured into the outer phase, which contains a mixture of PVA in water [31]. Then, the suspension is agitated for 60 min using magnetic stirrer at 1000 rpm. Then, the produced NSs are filtered and dried in a hot air oven at 40°C for 2 h [32].

Solvent method

In this type, the polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide is added with a suitable polymer. Then, this blend is mixed to a huge amount of the crosslinker in the molar proportion of 4–16 [33]. The response is conceded out at a temperature ranging from 10°C to the reflux temperature of the solvent, for time vary from 1 to 48 h. Favored crosslinkers are carbonyl compounds dimethyl carbonate and carbonyldiimidazole (C7H6N4O) etc. [34]. After finishing of the reaction, the mixture is sanctioned to cool at room temperature, then the compound is mixed to an overload of distilled water and improved the compound by percolation under vacuum and instantly purified by long-lasting Soxhlet extraction with ethanol, and finally the product is dried out under vacuum. To obtain a fine powder, the dried product is grinded in a mechanical mill [35].

Ultrasound-assisted technique

In this method, the polymer is reacted with crosslinkers in the dearth of solvent and under sonication [36]. The formed NSs will be spherical, uniform in size and smaller than 5 μm [37]. In this technique, di-phenyl carbonate or pyromellitic anhydride is utilized as crosslinker. A sufficient quantity of anhydrous cyclodextrin is a place to act in melted di-phenyl carbonate at 90°C for time interval of 5 h [38]. Permit the combination to refrigerate and smash the formulation roughly. Then give washing to the product with water and Soxhlet extracted with ethanol to get rid of both unwanted and unreacted diphenyl carbonate [39]. Later than decontamination, NSs is stored at 25°C until extra use [40].

Estimation of NSs

Solubility studies

Higuchi and Connors explained the phase solubility method, is the most extensively worn approach to revise inclusion complexation, which evaluates the consequences of a formulation on the solubility of drug [32]. Degree of complexation was signified by the phase solubility figure [48].

Particle size evaluation

Using laser light diffractometry or Malvern zeta sizer and zeta potential the particle size of burdened and unburdened NSs were evaluated. Every sample was checked for 3 times and after which mean value was used for more measures [49,50].

Microscopy studies

To check the morphology, surface topography and microscopic aspects of the creation, (active pharmaceutical ingredients [API]/NSs complex), scanning electron microscopy, and transmission electron microscopy can be worn [51,52].

Entrapment efficiency

Weighed amount of drug loaded NSs are dispersed in methanol, centrifuged at 1000 rpm for half an hour, the supernatant withdrawn, suitably diluted with methanol and are subjected to ultraviolet (UV) spectroscopy for taking absorbance of the sample against blank methanol [53]. The percentage of drug entrapment is calculated by the following equation. The entrapment efficiency (%) of NSs can be resolute by [54,55]:

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Zeta potential

The surface charge or zeta potential of prepared NSs is determined by zeta sizer [56,57]. The NSs emulsion is diluted with water and placed in the electrophoretic cell [58].

Porosity

This study is used to confirm the series of nanochannels and nanocavities made up. Helium pycnometer is worn to make sure porosity of NSs, as helium gas is capable to perforate inter- and intra-particular channels of substances. Percent porosity is specified by equation [59,60]:

$$\%\text{Porosity} = \frac{\text{Bulk volume - True volume}}{\text{Bulk volume}} \times 100$$

Fourier transform infrared (FTIR) analysis

To check the interaction of chemical bonds between drug and polymer FTIR analysis is used. Powder was scanned in the range from 400 to 4000/cm and carbon black position [61,62].

Polydispersibility index (PDI)

PDI is an index of width within the particle size allotment. PDI form scattered sample is lower, whereas PDI is superior for wider particle size allocation [63,64].

Production yield (PY)

By measuring the starting weight of raw materials and final weight of NSs the PY can be resolute [65,66].

$$\text{PY}: \frac{\text{Practical mass of nanosponge}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

Dissolution studies

900 ml of phosphate buffer pH 6.8 was placed in vessel and the USP apparatus Type II (paddle method) is assembled. The medium was allowed to equilibrate to a temperature of 37°C±0.5°C. Prepared NSs powder was placed in the vessel and operated for 12 h at 75 rpm. At definite time intervals, 5 ml of the receptor fluid were withdrawn, filtered, diluted, and analyzed spectrophotometrically [67-69].

Drug content

Formulation is put in 100 ml volumetric flask having 50 ml methanol and shake for 30 min and allowed to stand for 2 h. The volume is made with methanol up to 100 ml. 1ml of the above solution is further diluted to 10 ml with 6.8 pH phosphate buffer. The drug content is determined by measuring the absorbance using UV-Visible spectrophotometer [70,71].

Drug release kinetics

The *in vitro* drug release mechanisms of NSs are further checked for their kinetic behavior to check their kinetic mechanism involved in the release of NSs [58]. Zero-order, First-order, Higuchi model, and Korsmeyer–Peppas models are used to check the mechanism of drug release from NSs. The mathematical appearance that describes the dissolution curve are summarized in Table 2 [72].

Swelling and water uptake

Swellable polymers such as polyamidomine NSs, water, and swelling uptake can be determined by the following formula [75]:

$$\text{Percentage of swelling} = \frac{\text{Marking of the cylinder at specified time point}}{\text{Initial marking before swelling}} \times 100$$

$$\text{Percentage of water uptake} = \frac{\text{Mass of hydrogel after 72 hour}}{\text{Initial mass of polymer}} \times 100$$

FUNCTIONS OF NSs

As an oral route

The oral route of drug delivery has been accredited for decades as the most extensively utilized route of administration and has the highest patient compliance [73]. However, for efficient oral delivery, it is extreme importance that the drug is devoid of dissolution rate-limited bioavailability issues. According to Torne et al., when compared to the commercially accessible product Taxol (control), paclitaxel-loaded cyclodextrin-based NSs showed a threefold rise in bioavailability following its administration in rats by oral gavage. Torne et al. have developed tamoxifen for oral drug delivery by encapsulating it in β-Cyclodextrin NSs crosslinked with carbonyldiimidazole. The pharmacokinetics of complexes of cyclodextrin-based NSs and tamoxifen have been originate to be enhanced than the plain drug. In addition, a higher cytotoxic activity of drug – cyclodextrin-based NSs complex was seen compared to the tamoxifen monotherapy when studied were carried out on MCF cell lines. Manyam *et al*. prepared a NSs loaded extended-release tablet of trimethoprim by emulsion solvent evaporation method. As trimethoprim is an antibiotic primarily used in the treatment of bladder infections and urinary tract infections due to its low aqueous solubility leads to poor oral bioavailability. Its low aqueous solubility leads to poor oral bioavailability. To enhance its solubility, they prepared trimethoprim NSs loaded extended-release tablets to delay the drug release at the urinary tract. From this study, it was concluded that NSs loaded extended-release tablets of trimethoprim showed extended drug release for about 10 h with enhanced solubility and dissolution [74,75].

Table 1: Composition of NSs

Composition of NSs	
Polymers	Hyper cross-linked polystyrene
	Cyclodextrin and its derivatives like β- Cyclodextrin
	Alkyloxycarbonyl Cyclodextrin
	2hydroxy propyl β- Cyclodextrin
Copolymers	Poly (valerolactone-allylvalerolactone) and Poly (Valero lactone
	Allyl valerolactone oxepanidione)
	Ethyl Cellulose
Crosslinkers	PVA
	Diphenyl Carbonate
	Diary carbonates
	Isocyanates
	Pyromellitic anhydride
	Carbonyldiimidazole
	Epichloridrine
	Glutaraldehyde
	Carboxylic acid anhydrides
	2,2-bis (acrylamido)
	Acetic acid and dichloromethane

NSs: Nanosponges, PVA: polyvinyl alcohol

Table 2: Represents mathematical appearance that describes the dissolution curve

Model	Equation
Zero-Order	$Q_t=Q_0+K_0t$
Higuchi model	$Q_t=Q_0+K_ht^{1/2}$
Korsmeyer–Peppas model	$Q_t=K_{kp}t^n$

For protein relief

Bovine serum albumin (BSA) protein in solution is not constant; therefore, it is stored in the lyophilized state. However, proteins can reversibly be denatured on lyophilization and adopts conformation patently different from the native structure. To preserve native structure during dispensation and long-term storage is the major drawback in protein formulation and development. In the NSs-based approach proteins like BSA are engulfed in swellable cyclodextrin-based poly(amid amine) NSs to raise the stability of proteins [76].

NSs in drug delivery

Due to nanoporous nature they are used as a bearer for water-insoluble drugs (biopharmaceutical classification system Class-II drugs). These complexes can be worn to increase the dissolution rate, solubility, and stability of drugs as well as to mask the unpleasant flavors. Beta-cyclodextrin based NSs are reported to carry the drug to the target site 3–5 times more successfully than direct injection [77].

NSs can be developed as oral, parental, topical, or inhalation dosage forms. For oral route, the complexes can be distributed in the matrix of excipients such as diluents, lubricants, and anti-caking agents suitable for the fabrication of capsules and tablets. For the parenteral administration, the complex may be merely carried in sterile water, saline, or other aqueous solution. For topical administration, they can be efficaciously integrated into the topical hydrogel. NSs used topically have the reward in decreasing skin itching while maintaining effectiveness. They can be fabricated as topical gels, lotions, creams, etc. [78]. List of drugs formulated as NSs are listed in Table 3.

In engulfment of gases

Three different gases can be put in a nutshell in the cyclodextrin-based NSs such as 1-methylcyclopropene, oxygen, and carbon dioxide. These formulations can be gifted to store oxygen and release it to the hypoxic tissues in controlled and predictable way. Later on, they could be one valuable instrument for the distribution of some crucial gases [87].

NSs that soaks up toxins

The bloodstream based on polymeric nanoparticles that can deactivate and separate a lane range of toxins from pore-forming toxins (PFTs),which strike cells by hammering cavities in their membranes and changing their permeability, are one of the most usual toxins formed by bacteria as well as harmful species of bees scorpions and snakes hindering PFTs can decrease the seriousness of *Staphylococcus aureus* infections and has healing potential for serving other common pathogen such as *Escherichia coli* [88,89].

Antiviral application

They are used in the nasal, pulmonary route of administration. They mostly deliver antiviral drug on RNA to lungs or nasal route all the way through nanocarriers for targeting virus which may originate contamination to RTI such as influenza virus and rhinovirus. Medicament such as zidovudine and saquinavir is used as nanocarrriers [90].

Solubility improvement

β-Cyclodextrin-based NSs of itraconazole, simvastatin, and rilpivirine have increase solubility of the badly soluble drug. The solubility enhanced by 50 folds contrast to ternary dispersion system, for example, copolyvidonum and simvastatin [91-93]

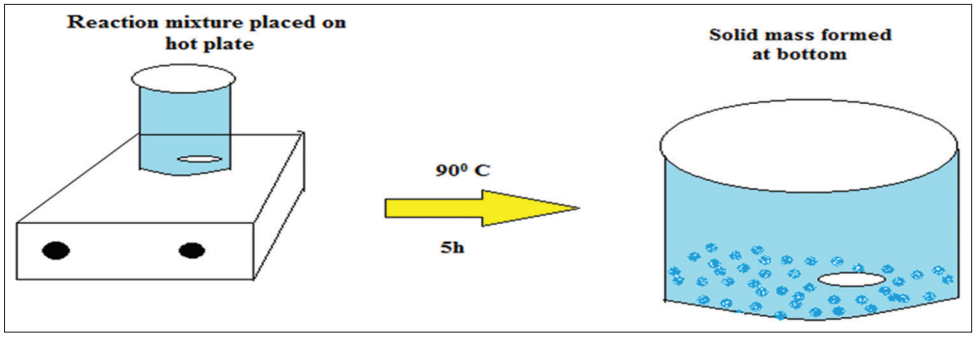

Fig. 1: Factorial representation of fabrication of nanosponges by melt technique

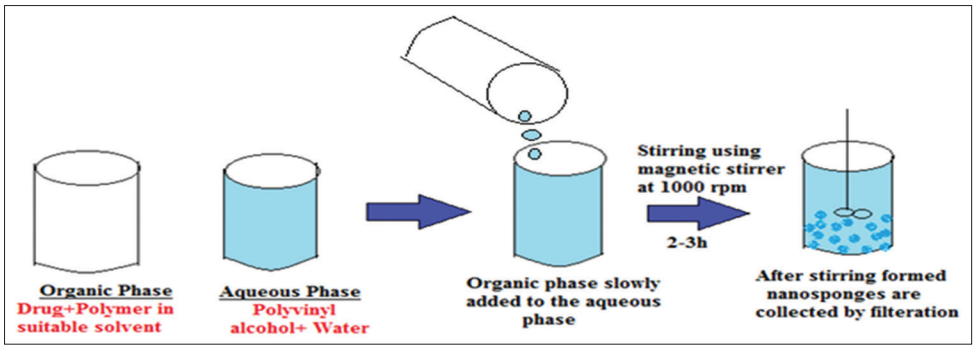

Fig. 2: Fabrication of nanosponges by emulsion solvent diffusion technique

Loading of drug into the NSS [Fig. 3] [37,38,40,41].

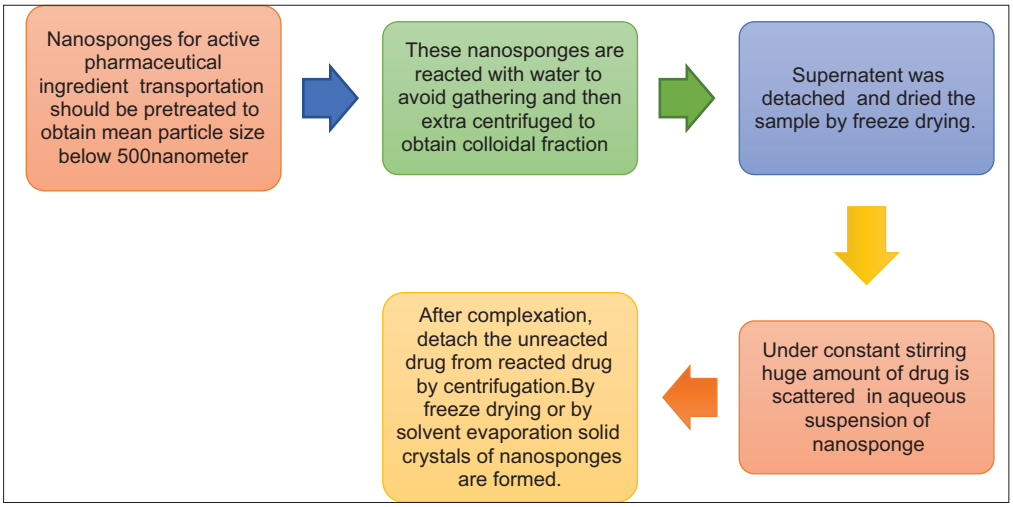

Fig. 3: Loading of drug into the nanosponges

Table 3: List of drugs fabricated as nanosponges

S. No.	Drug	Nanosponges Vehicle	Administration route	Reference
1.	Dexamethasone	βCD, diphenyl carbonate	Oral, parenteral	[79,80]
2.	Tamoxifen	βCD, carbonyldiimidazole	Oral	[81]
3.	Itraconazole	β-CD, copolyvidonum	Oral, topical	[82]
4.	Atorvastatin	β-Cyclodextrin	Oral	[83]
5.	Paclitaxel	β-Cyclodextrin	Parenteral	[84]
6.	Resveratrol	β-Cyclodextrin, carbonyldiimidazole	Oral	[85]
7.	Curcumin	Beta-Cyclodextrin, diphenyl carbonate	Parenteral	[86]

Safety from light or dilapidation

NSs can also be used as a bearer to guard engulfed molecules from light or from chemical- and enzyme instigate degradation. To estimate the possible preservation implementation, 5-fluorouracil was used as a heat-sensitive model drug. Beta-CD NSs were capable to engulf up to 30% of 5-(F-Uracil). The *in vitro* release of 5-fluorouracil, assessed by

Part disturbing the creation of nanosponges [Fig. 4] [42-47].

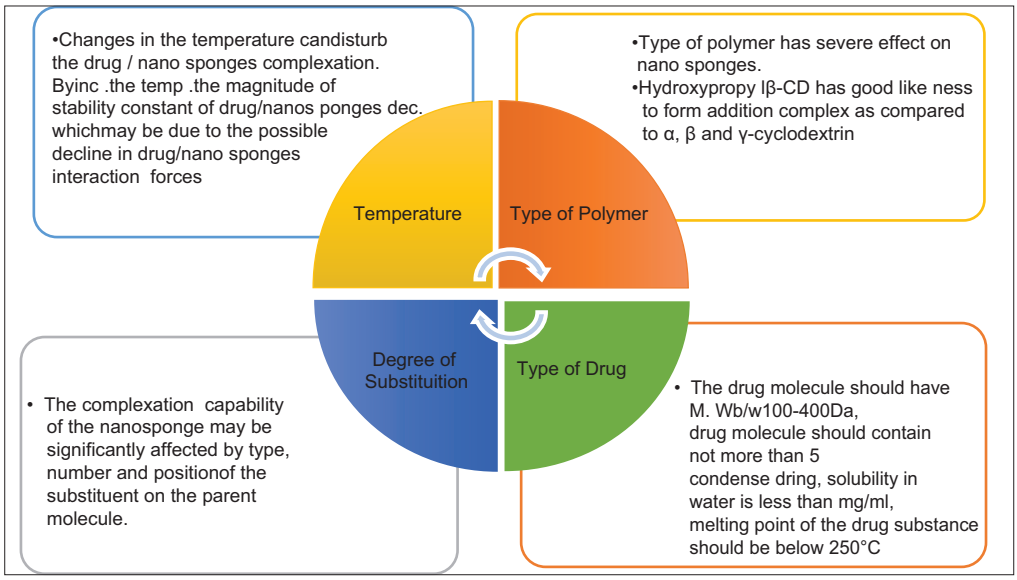

Fig. 4: Factors disturbing nanosponges preparation

Table 4: Patent reports on nanosponges

Patent/App. No.	Applicant	Tittle
WO2006002814A1	Francesco Trotta, Wander Tumiatti, Orfeo Zerbinati , Carlo Roggero , Roberto Vallero	Ultrasound-assisted synthesis of cyclodextrin-based nanosponges
W02009149883A1	Gianfranco Gilardi, Francesco Trotta, Roberta Cavalli, Paolo ferruti, Elisabetta Ranucci, Giovanna Di Nardo, Carlo Maria Roggero, Vander Tumiatti	Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies.
WO2006002814A1	Francesco Trotta, Roberta Cavalli Wander Tumiatti, Orfeo Zerbinati, Roberto Vallero	Ultrasound-assisted synthesis of Cyclodextrin-based nanosponges
W02012147069A1	Universita'DegliStudi Di Torino Sea Marconi, Technologies Di	Method of preparing dextrin nanosponges
CA2692493A1	Sea Marconi, Technologies Di VanderTumiatti, S.A.S, FrancesscoTrotta, Vander Tumiatti, RobertaCavalli, Carlo Maria Roggero, BarbarMognetti, Giovanni, Nicolao Berta	Cyclodextrin based nanosponges as a vehicle for antitumoral drugs

employing the dialysis-bag technique at pH 7.4, was about 60% of the envelope amount after 2 h staging an interaction linking the API and the NSs figure, in spite of the hydrophilicity of the drug. The enclosement of camptothecin in NSs was employed to boost the shelf life and release of the API. The NSs solubilized bulky amounts of the API and safeguard the lactone ring from opening due to its high inclusion potentiality, thereby enhancing stability [94-96].

In cancer therapy

With the help of NSs various anticancer drugs are targeted to specific site avoiding the obstacle created by the immune system. Different cancer cells had been treated by NSs such as breast cancer or fast acting glioma type with the help of a single dose of injections [97].

Topical agents

NSs technology is a different technology for the controlled release of various topical agents. Other dermatological and personal care products provide a short duration of action but in high concentration. Hence, to get rid of this problem, a wide variety of drugs can be encapsulated in NSs and can be formulated as a gel, lotion, cream, ointment, etc. [98]. Various drugs which are formulated as a topical drug delivery system incorporated in NSs are listed below

S. No.	Drug used	Method used	Reference
1.	Miconazole nitrate	Solvent evaporation technique	[99]
2.	Isoniazid	Emulsion solvent diffusion method	[100]
3.	Tazarotene	Emulsion solvent diffusion method	[55]
4.	Cephalexin	Emulsion Solvent diffusion method	[101]

Patent account on NSs [102-104]: Table 4

Future outlook

Due to NSs exclusive characteristics such as improved product performance and elegancy, extended release, enhanced API release profile, lower itching, ameliorate physical, chemical, and thermal stability, which makes it pliable to grow novel outcomes. The real provocation of NSs in upcoming days is the expansion of the delivery system for the oral peptide delivery by the differing ratio of polymers. Bioerodible and biodegradable polymers worn for the API delivery allow the secured delivery of the active material. Due to their smoothness, these carrier systems have also established their implementation in cosmetics. These novelties in methodology

also unlocked new ways for drug delivery. The cytotoxicity of the nanoparticles or their humiliation product remains a main provocation and enhancement in bioavailability is major responsibilities in upcoming investigations.

CONCLUSION

At last, it was concluded that the NSs are small mesh-like shape that may use in the dealing of various illnesses and this nanotechnology is 4–5 times more valuable at delivering drugs than the conventional method. Due to their tiny size, they can be incorporated into many formulations such as parenteral, aerosol, topical, tablets, and capsules. NSs are nano-sized colloidal bearer, so they easily pierce into the skin. They recommend engulfment of both lipophilic and hydrophilic drugs and discharge them in a controlled and predictable manner at the target site. This nanotechnology upgrades the solubility of poorly soluble drug specifically BCS Class II drugs.

AUTHORS' CONTRIBUTIONS

Ms. Simranjot Kaur has been compiled the data and summarized all the information. Dr. Sandeep Kumar has supervised the manuscript and revised it critically for important intellectual content.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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