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Nanosponges a Novel Approach for Targeted Drug Delivery System: A Review

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Abstract

Nanotechnology is a dynamic and multi-disciplinary field, embracing vast, generically diverse spheres such as nanoelectronics, information technology, biotechnology, and cellular and molecular biology. It also has had a profound impact on life sciences, including drug delivery, diagnostics, nutraceuticals, and the production of biomaterials. Nanosponges (NS) are one such carrier systems that are being explored for their role in drug delivery. NS are in nanosize with a sponge-like morphology and also can solubilize poorly water-soluble drugs and provide prolonged release as well as improving drug bioavailability. Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. The invention of nanosponges has become a significant step toward overcoming these problems. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility. The goal of this paper is to explain the general introduction, characteristics, method of preparation, characterization and applications of nanosponges.

Keywords: Nanosponges, polymers, targeted drug delivery, controlled drug delivery, colloidal carrier.

Introduction

His drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets. Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administrationwith improvements in therapeutic efficacy, reduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preidentified (preselected) target in therapeutic concentration, while restricting its access to non-target normal cellular linings and thus minimizing toxic effects and maximizing therapeutic index of the drug.[1]

Nanosponge is a novel approach which offers controlled drug delivery for topical use. Nanosponge is an emerging technology for topical drug delivery. Nanosponge drug delivery system is employed for the improvement of performance of topically

applied drugs. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. [2] Nanosponges have emerged as one of the most promising fields of life science because of their application in controlled drug delivery. [3] Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility.3 Nanosponges are non-irritating, non-mutagenic, non- allergenic and non-toxic. [4]

Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and this technology is five times more effective at delivering drugs for breast cancer than conventional methods.5 Nanosponges are made up of microscopic particles with

Nanosponges are a novel class of materials made up of small particles having a few nanometer-wide holes that may encapsulate a wide range of compounds. These particles are capable of transporting both lipophilic and hydrophilic molecules, as well as enhancing the solubility of molecules that are weakly water soluble.

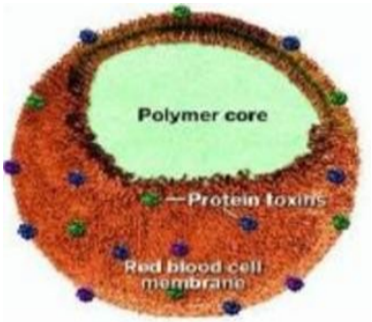

Figure 1: Structure of Nanosponges showing Loading of drugs

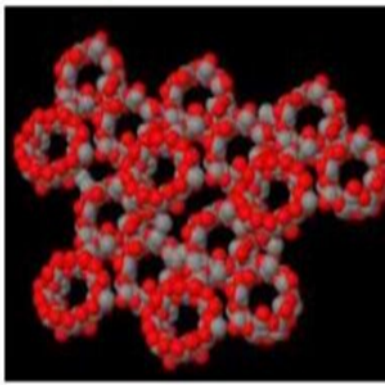

Figure 2: Molecular structure of cyclodextrin cavity for carbonates Nanosponges.

These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage. Another important feature of these nanosponges is their aqueous solubility which allows the use of these systems effectively for drugs with poor solubility.

The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules. [5] For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration,

they can be effectively incorporated into topical hydrogel.

The researchers at Vanderbilt University and Emory University recently reported on a controlled - release nanoparticle drug delivery system, which may be an improved delivery method for delivering anticancer therapies, including direct injection into tumour site. These nanoparticle circulate in the body until they encounter the surface of a tumour cell, where they adhere to the surface and start releasing the drug in a controlled and predictable manner.

Targeted drug delivery systems of this type have several basic advantages. As the drug is released at the tumor site instead of circulating widely through the body, it should be more effective for a given dosage. They also should have fewer harmful adverse effects because smaller amounts of the drug come into contact with healthy tissue. Another advantage is that the Nanosponge particles are soluble in water. Encapsulating the anticancer drug in Nanosponge allows the use of hydrophobic drugs that do not dissolve readily in water. Recently, these drugs must be mixed with adjuvant reagents, which potentially can reduce the efficacy of the drug or cause adverse effects. [6]

Polymers Used in Nanosponge Preparation2

There are various polymers and cross linkers are used in the preparation of nanosponges, listed in table.

Drugs Formulated as Nanosponges Some drugs formulated as nanosponges are given in Table .

Table: Different polymers for nanosponge formulation

Polymers	Copolymers	Cross linkers
Hyper cross linked Polystyrenes,	Poly (valerolactone	Carbonyl diimidazoles, Carboxylic acid
Cyclodextrines and its derivatives like	allylvalerolactone), Poly	dianhydrides, Diarylcarbonates,
Alkyloxycarbonyl Cyclodextrins,	(valerolactone-allylvalerolactone	Dichloromethane, Diisocyanates, Diphenyl
Methyl β-Cyclodextrin, Hydroxy Propyl	oxepanedione), Ethyl Cellulose,	Carbonate, Epichloridine, Gluteraldehyde,
β-Cyclodextrins.	Poly vinyl alcohol.	Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid.

Advantages of Nanosponges[6,7]

- Nanosponges allow components to be entrapped and thus reduce adverse effects.
- Remains stable at pH levels ranging from 1 to 11.
- They can withstand temperatures of up to 1300°C.
- They act like self-sterilizer, because of their tiny pore size (0.25m) which does not allow bacteria to penetrate.
- They are of low-cost and free-flowing.
- They improve the solubility of drugs that aren't easily soluble.
- They increase the bioavailability of drug.
- They have improved formulation flexibility, improved stability, and increased elegance.

Characteristics of Nanosponges [8]

There are several characteristics of nanosponges which make it different from other nanoparticles. Such characteristics are being discussed below:

- Nanosponges are insoluble in organic solvents & water, porous, nontoxic, and thermostable up to 3000C, unlike other nanoparticles.
- Their size distribution is limited, with a mean diameter of less than 1 m.

- Carbonate nanosponges have a zeta potential of about 25 mV, which results with stable water suspensions that do not aggregate over time due to a higher zeta potential.
- Nanosponges protect the medication from physiological breakdown and are non-irritating, non- mutagenic, non-allergic, and non-toxic.
- By generating inclusion and non-inclusion complexes, nanosponges can encapsulate a variety of pharmacological compounds.
- Nanosponges are porous particles that are primarily utilized to encapsulate medications that are poorly soluble.

Demerits and Challenges [9]

- Nanosponges are only capable of encapsulating small molecules, making them unfit for bigger molecules.

Dosing dumping may occur.

Types of Nanosponges

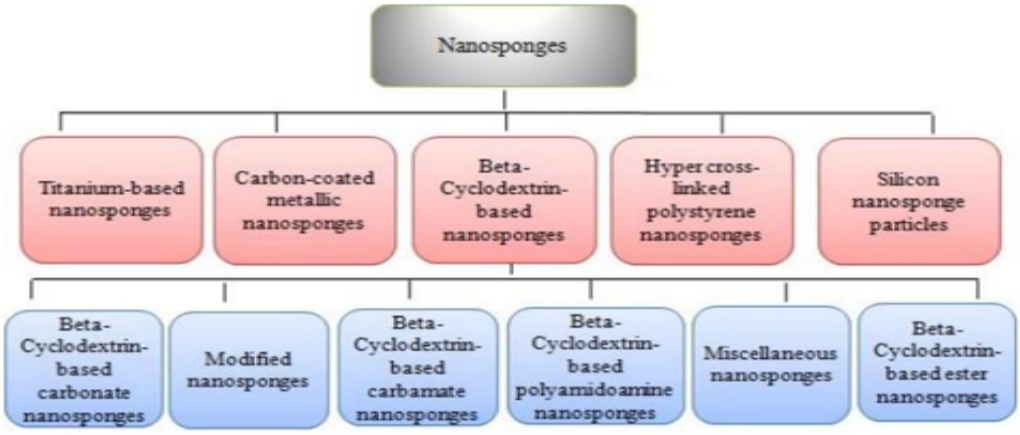

Figure 3: Types of Nanosponges

Composition of Nanosponges[10]

1. Polymer and copolymers

The choice of polymer can have an impact on the development and performance of nanosponges. The cavity size must be appropriate for incorporating the specific medication molecule. The polymer chosen is determined by the needed release and the medicine to be encapsulated. The chosen polymer should have the ability to bind to specified ligands. [11]

Eg. Cyclodextrins and their derivatives such as Methyl- cyclodextrin (-CD), alkyloxy carbonyl cyclodextrins, 2- hydroxy propyl-CDs, and copolymers such as poly (Valero lactoneallylvalero lactone) and poly (Valero lactone-allyl Valero lactone oxepanedione), Hyper cross-linked polystyrenes, ethyl cellulose and PVA are among the polymers used to make nanosponges. [12]

2. Cross linking agents

The cross-linking agent can be selected based on the structure of the polymer and the medicine that will be synthesized. Depending on the type of cross linkers used, water soluble or insoluble nanosponge structures are created.

Examples: Diphenyl Carbonate, Diarylcarbonates, Di- Isocyanates, Pyromellitic anhydride, Carbonyl-di- Imidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane. [13]

Factors Affecting Formulation Of Nanosponges [15,16,17]

1. Type of Drug
2. Type of Polymer used
3. Temperature
4. Method of preparation nanosponge
5. Degree of substitution

1. Type of Drug

The therapeutic molecules that will be used in incision and non-incision nanosponge complexes should have the following characteristics:

- The drug molecule's structure should not include more than five condensed rings.
- The drug's melting point should be less than 250°C.
- In water, drug solubility should be less than 10 mg/ml.
- The molecular weight of drug should be between 100 and 400 gm/mole.

2. Type of Polymers Used

The type of polymer employed in nanosponge formulation can have an impact on the nanosponge formation and performance. The polymer utilised in the formulation determines the size of the nanosponge cavity and drug complexation.

3. Temperature

The drug/nanosponge complexation can be affected by temperature changes. Reduces the perceived stability's magnitude by a factor of two. The constant increase in temperature of the Drug/Nanosponge complex could be related to the likely lowering of drug/Nanosponge contact forces as temperature rises.

4. Method of Preparation Nanosponges

The loading of a drug into a nanosponge has the potential to change the nanosponge/drug complexation. In any instance, the success of a method is determined by the nature of the drug and polymer. Freeze drying has proven to be the most effective way for drug complexation in many cases.

5. Degree of Substitution

The type, amount, and placement of the substituent on the parent molecule can all affect the ability of nanosponge to complex.

Method Preparation of Nanosponges[18]

There are several methods of preparation of Nanosponges:

1. Solvent method
2. Ultrasound-assisted synthesis
3. Emulsion solvent diffusion method
4. From Hyper crosslinked β-Cyclodextrin.

Solvent method

The polymer is combined with a suitable solvent, preferably a polar aprotic solvent such as dimethylformamide or dimethyl sulfoxide. This mixture is applied to an excess of crosslinker, preferably in a 4 to 16 molar ratio of crosslinker to polymer. The reaction is carried out at temperatures ranging from 10 °C to the solvent's reflux temperature for 1 to 48 hours. Carbonyl compounds are preferred cross linkers (dimethyl carbonate and carbonyl diimidazole).

Following the completion of the reaction, the solution is allowed to cool to room temperature before being added to a substantial amount of distilled water, filtered under vacuum, and purified using a long Soxhlet extraction with ethanol. The product is vacuum dried and pulverised in a mechanical mill to produce a homogenous powder.

Ultrasound-assisted synthesis

Nanosponges can be made using this process, which involves reacting polymers with cross-linkers in the absence of a solvent and sonication. The nanosponges produced will be spherical, homogenous in size, and less than 5 microns in diameter. The cross-linker in this approach is di-phenyl carbonate (or) pyromelitic anhydride. Place the flask in a water-filled ultrasonic bath and heat it to 90°C. For 5 hours, sonicate the mixture.

Emulsion solvent diffusion method

Different concentrations of ethyl cellulose and polyvinyl alcohol can be used to make nanosponges. To optimise drug loading and achieve a customised release, several drug-to-polymer ratios are used. The dispersed phase with drug and polymer dissolved in 20 mL dichloromethane, is slowly added to a specific amount of polyvinyl alcohol in 100 mL of aqueous external phase using a magnetic or mechanical stirrer at 1000-1500 rpm for 3-5 hours. The generated nanosponges are filtered and dried in an oven at 40°C for 24 hours before being placed in a container.

Hypercrosslinked β-Cyclodextrin

Cross connecting different types of cyclodextrins (CD's) with a carbonyl or dicarboxylate chemical as a cross linker can produce nanosponges. To optimise drug loading and obtain a customised release profile, the ratio of CD's can be changed during preparation. β -cyclodextrin nanosponges are generated by placing 100 ml of Dimethyl Formamide (DMF) in a round bottomed flask and adding 17.42g of

anhydrous β -CD to accomplish complete dissolution. The solution is then added to 9.96 g of carbonyl di-imidazole (61.42 mmol) and allowed to react for 4 hours at 100oC. The transparent block of hyper cross linked cyclodextrin is roughly crushed once condensation polymerization is done, and an excess of deionized water is added to remove DMF. Finally, by using Soxhlet extraction with ethanol, any leftover byproducts or unreacted chemicals are totally eliminated. The resulting white powder is dried in a 60°C oven overnight before being ground in a mortar. Water is used to disperse the fine powder that had been obtained. The colloidal part of the solution that remained suspended in water is extracted and lyophilized. The resulting nanosponges are sub-micron in size and spherical in shape.

Estimation of NSs[19]

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. [20]

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 [21]

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. [22]

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.

Production yield (PY)

By measuring the starting weight of raw materials and final weight of NSs the PY can be resolute. [23,24,25]

PY: Practicalmassof nanosponge×100 Theoreticalmass(polymer+ drug)

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. [26,27]

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. [228,29]

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. [30]

Thermo-analytical methods

Thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes.

Microscopy studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can

be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes.

X-ray diffractiometry and single crystal X-ray structure analysis

Powder X-ray diffractiometry can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the drug and polymer molecules.

A diffraction pattern of a physical mixture is often the sum of those of each component, while the diffraction pattern of complexes are apparently different from each constituent and lead to a "new" solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation.

The complex formation of drug with nanosponges alters the diffraction patterns and also changes the crystalline nature of the drug. The complex formation leads to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks.

Single crystal X-ray structure analysis may be used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established.

Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nanosponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation.

Infra-Red spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state.

Nanosponge bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges. The technique is not generally suitable to detect the inclusion complexes and is less clarifying than other methods.

The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infra- red spectral studies give information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band.

Thin Layer Chromatography

In Thin Layer Chromatography, the Rf values of a drug molecule diminishes to considerable extent and this helps in identifying the complex formation between the drug and nanosponge.

Loading efficiency

The loading efficiency of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer & HPLC methods.

Particle size and polydispersity

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software. From this the mean diameter and polydispersity index can be determine.

Zeta potential

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment.

Applications of Nanosponges[32,33,34]

1. Nanosponges for drug delivery

Because of their nonporous structure, nanosponges can advantageously carry water insoluble drugs (Biopharmaceutical Classification System class-II drugs). These complexes can be used to increase the dissolution rate, solubility and stability of drugs, to mask unpleasant flavors and to convert liquid substances to solids28.

2. Nanosponges as chemical sensors[35]

Nanosponges which are the type of "metal oxides" act as a chemical sensors which is used in highly sensitive detection of hydrogen using nanosponge titania. Nanosponge structure intially have no point of contact so there is less hinderance to electron transport and it results in higher 3D interconnect nanosponges titania which is sensitive to H2 gas.

3. Nanpsponge for oral delivery[36,37]

In oral application it forms the nanosponge system consist of pores which increase the rate of solubilization of poorly water soluble drugs which get entrapped the drug in pores. The surface area is increased due to nanosize form and increase rate of solubilization.

4. Solubility enhancement[38]

β-cyclodextrin based nanosponges of itraconazole have enhance solubility of poorly soluble drug. The solubility increased by 50 folds compared to ternary dispersion system e.g. - copolyvidonum.

5. Nanosponges as a carrier for biocatalysts and release of enzymes, proteins, vaccines and Antibodies[39,40]

It includes the process applied in industry which correlates with operational condition. Reactions which are not specific give rise to low yields and require high temperatures and pressures which consume large amount of energy and cooling water in down-stream process. This are the drawbacks can be removed by using enzymes as biocatalysts as this operate under high reaction speed, mild condition.

6. Antiviral application[41,42]

Nanosponges used in nasal, pulmonary route of administration. It provide specificity to deliver antiviral drug on RNA to lungs or nasal route through nanocarriers for targeting virus which may cause infection to RTI such as influenza virus, rhinovirus. Drugs used as nanocarrriers are- Zidovudine, Saquinavir.

7. Cancer

Targeting drug to specific site avoiding the obstacle created by immune system. Different cancer cells had been treated by nanosponges like breast cancer or fast acting glioma type with help of single dose of injections.

8. Oxygen Delivery System

Characterized by using α, β and ϒ cyclodextrins and this are suspended in water and get saturated with water. A silicone form of membrane can also be used for oxygen permeation with the help of nanosponge/ hydrogel system.

Conclusion

Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and this technology is five times more effective at delivering drugs for cancer than conventional methods. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules. Nanosponge are nano sized colloidal carrier so they easily penetrate through skin. The nanosponges have the ability to include either lipophilic or hydrophilic drugs and release them in a controlled and predictable manner at the target site. The nanosponges have the ability to incorporate many drugs and release them in a controlled and predictable manner at the target site. Topical nanosponge can be more patient compliant and provide sufficient patient benefits by reducing repeated doses and side effects. Nanosponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin. Hence present study concludes that nanosponges may play an important role for the treatment of different diseases.

Modulating Drug Release:

Modulated drug release dosage forms offer several advantages over the conventional

release formulation of a drug. The design of a modified-release product is generally intended to optimize the treatment regimen by providing slow, continuous delivery of the drug over the entire dosing interval. This makes it possible to decrease the dose administered, change the pharmacokinetic profile, and decrease side effects. In immediate-release preparations, hydrophilic CDNS are used to modify the release rate of drugs to enhance the absorption of drugs across biological barriers [56].

Hydrophobic CDNS such as an ethylated and acylated CD with low water solubility can be used as a sustained release carrier for water-soluble drugs. In an in-vitro test, doxorubicin showed very slow release at pH 1.2 (about 1% after 120 min), when incorporated into hydrophobic CD NS similarly the release was approximately 29% at pH 7.4. This behavior shows that the NS formula can protect drugs in the stomach environment and allow drug release in the intestine [57]-[58].

Solubility Enhancement:

One of the biggest limits to the development of various pharmaceuticals is the low water solubility of many drugs. About 40% of new drugs are poorly soluble in water, making it difficult for its clinical application [60]. NS can improve the wetting and solubility of molecules with very little solubility in water. Drugs are often molecularly dispersed within the NS structure and are then released as molecules, avoiding the dissolution step.

Consequently, the apparent solubility of the drug is often increased. Many formulation and bioavailability issues can be solved by improving the solubility and dissolution rate of a substance and NS can greatly improve the solubility of the drug [61].

The water solubility of the drug at physiological pH is about 1 ng/mL. The encapsulation of β-CD NS increases the solubility of drugs by more than 27 times [62]. When polyvinyl pyrrolidone(PVP k-30) is added as an auxiliary component by a solid dispersion system of the β-CD NS formula, the ratio rises to 55 times. Also, the drug dissolution profiles of the two preparations are faster than the commercial preparations. NS formula can therefore increase the bioavailability of itraconazole[58]-[63].

Another formulation reported in literature includes tamoxifen loaded NS by Narender Raja et al [64] they formulated tamoxifen loaded NS using emulsions solvent diffusion method. They observed greater in vitro percent release of tamoxifen loaded NS of 46.39% when compared to that of pure tamoxifen at 2.66%.

Figure 4: Applications of NSs.

Antiviral application:

NS deliver antiviral drugs to the lung and nasal epithelium where they inactivate or kill viruses that cause respiratory infections, such as influenza virus, respiratory syncytial virus, and rhinovirus [65]. β -CD NS have been used to enhance the solubility and bioavailability of acyclovir which has low bioavailability. Acyclovir competitively inhibits viral DNA polymerase and is used to treat Herpes Simplex Virus (HSV) infection. Incorporation of acyclovir in carboxylated β-CD NS, which contain dissociable carboxyl groups in its structure, can be specifically used for

encapsulating acyclovir. The basic principle of this synthesis as reported by D. Lembo et al was to obtain electrostatic interactions between the carboxyl groups in the NS structure and the amino groups of acyclovir thus increasing the drug loading capacity [66]. The carbonylated β-CD NS loaded with acyclovir showed high drug loading, which is suitable for improving solubility and prolonging in vitro release kinetics, and 20% of the drug was released after a period of 3 h [67].

Anti-Cancer Therapy:

NSs are three times more effective in reducing tumor cell growth. The complex of NS is loaded with a drug, which is then exposed to a targeting peptide induced by radiation to bind to tumor receptors. The NS that binds to the tumor receptor begins to release drug molecules. At the same dose, this provides an enhanced therapeutic effect while minimizing adverse effects [68]. 5-Fluorouracil (5-FU) is the drug of choice for the treatment of colorectal cancer, gastric malignant tumors, and cervical malignant growth. When taken orally, the absorption is poor due to low solubility. When administered parenterally, its half-life is very short (8-20 minutes). The side effects of intravenous administration are highly photosensitive. Therefore, to improve the properties of this drug, NS based on γ-CD was used. The direct compression method was used to prepare a 5-FU NS tablet which was reported by Raj et al. The excipients were mixed uniformly and then compressed into tablets of about 8 mm. The drug release in vitro increased to 96.66% with improved solubility [69]-[70]. Camptothecin (CPT) is a five-ring alkaloid, an inhibitor of DNA topoisomerase-I, and has extensive anticancer activity. The use of CPT is hampered by poor water solubility and a high degradation rate. However, evidence reported in literature suggests that CPTencapsulated in β-CD NS (CN-CPT) can overcomes these drawbacks and improves the inhibitory effect of CPT on the DU145 prostate tumor cell line and the growth of PC-3 in vitro[71].

Gas delivery systems:

CD NS have also been developed as an oxygen delivery system. NS can store and release oxygen slowly over time. NS filled with oxygen can provide oxygen to hypoxic tissues that exist in various diseases [72]. The β-CD NS/hydrogel combination system was used to obtain oxygen permeable to the silicon membrane [73]. It is also reported in the literature that CD-NS prepared with Carbodiimidazole cross linker can be used for the encapsulation of 1-methyl cyclopropane, oxygen, and carbon dioxide [74].

Purification of water:

CD NS can be used to remove organic pollutants from water. β-CD NS is completely insoluble in water and has the characteristic of encapsulating organic pollutants from water. Ceramic porous filters can be impregnated with these NS to form organic/inorganic hybrid filters module. These hybrid filter modules have been tested to effectively purify water and use a variety of water pollutants [75]. It has been determined that polycyclic aromatic hydrocarbons (PA-H) can be removed very easily. Effective removal of trihalomethanes (THMs) pollutant group (>95%), single aromatic Hydrocarbons (BTX), and pesticides (simazine) (> 80%) can also be achieved [76]. Torasso N et.al developed superhydrophobic carbonaceous NS using plasma polymerization of acetylene for oil sorption. The developed NS resulted in high oil sorbency of (33% ± 2w/w) and displayed potential utility in oil spills disasters in purifying water bodies [84].

Enzyme immobilization:

Enzymes immobilization on NS has shown to improve catalytic activity and enzyme stability. Boscolo et al [77] reported high-catalytic performance of Pseudomonas fluorescenslipase which was adsorbed on CD-based carbonate NS. Structural and functional stabilization was achieved for adsorbed enzymes even at temperatures above 40˚C, at pH 5 after incubation for 24h in 70%v/v methanol [77]. Catechol 1,2-dioxygenases obtained from Acinetobacterradio resistance S13 was immobilized on NS formed by β-CD linked by carbonate groups. The resulting immobilized enzyme showed improved activity and stability at different pH and temperature profiles. Improved thermostability of immobilized enzyme with 60% residual activity after 90min at 40˚C compared to 20% activity of the free enzyme was reported by Nardo et al [78].

Targeted delivery and diagnosis:

NS have recently been explored for ―Theranostics‖ (Therapeutic + Diagnostic) applications. Wang et al [79] have reported collagen-targeted theranostic NS delivery for matrix metalloproteinase 14 inhibitor napthofluorescein. The reported delivery is proposed to be beneficial in the treatment of cardiovascular disease. Degraded collagen is highly susceptible to rupture and is a hallmark of unstable atherosclerotic plaques. Caused by the action of matrix metalloproteinases (MMP), the developed NS delivery aids in the image the targeting and cell uptake and deliver the MMP14 inhibitor Naphthofluorescein. Another study reported by Gholibegloo et al describes the use of folic acid decorated magnetic NS for targeted delivery of Curcumin and Magnetic Resonance Imaging (MRI). They fabricated CD NS which were anchored to magnetic nanoparticles and decorated with folic acid. Curcumin was loaded in a CD NS cavity. Higher cell-toxicity in cytotoxicity assays and increased negative signal in a cell in in-vitro MRI was reported, proving therapeutic and diagnostic abilities of the developed nanocarrier [80].

Biomedical Engineering:

Use of NS substrates was recently explored for micropatterning of mammalian cells. Chung-Yao Yang, et.al reported method for micropatterning mammalian cells such as Chinese hamster ovary (CHO) cells, HIG-82 fibroblasts, and Madin–Darby canine kidney (MDCK) epithelial cells on oxidized silicon NS [81]. Another reported work of Chung- Yao Yang, et.al involved development of Chitosan NS using Silicon NS as mold. The developed Chitosan NS membrane were used as substrate to adhere Human breast cancer cells MDA-MB-231 and study different cellular behaviors and molecular-level structural responses of these adhered cells with modified NS [82]. 3D protein nanopatterning on silicon NS was reported by Stefano Borini, et.al. They demonstrated selective binding of proteins on activated site of silicon NS substrate. They also demonstrated development of possible glucose biosensor using the developed 3D nanopattern protein writing technology [83].

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