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Review Article

Nanosponges: An Innovative Class of Drug Delivery System - Review

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Abstract

Productive targeted drug delivery systems are a massive construct from an extended time, however it's been stricken by the advanced chemistry that's concerned within the development of latest system. To overcome these problems, significant step have been taken in invention of nanosponges. Nanosponges are the tiny mesh like structure in which large variety of drugs can be filled. These have inclusion and non-inclusion behavior and have high solubility for poor soluble drugs. These little sponges will flow into round the body till they realize binding surface and begins to unleash the drug. They can load both hydrophobic and hydrophilic drugs. They are simple to produce and are biologically safe. They can load each hydrophobic and hydrophilic medicine. They will be ready by cross linking differing kinds of cyclodextrins with a cross linker. Nanosponge technology has been explored for numerous applications like sustained unharness drug delivery system and delivery of medicine into the oral, epithelial duct further as topical routes. Nanosponges also can be used for unharness of enzymes, vaccines, proteins, antibodies and as a carrier for biocatalysts.

Keywords: Nanosponges; Cross Linking Agent; Cyclodextrins

Introduction

Nanosponges square measure the little mesh like structure within which giant type of substances are often encapsulated [1,2]. They need a evidenced spherical nature, because of their inclusion and non-inclusion behavior, they reportable to possess terribly high solubilisation capability for poorly soluble medication [3]. Their need recently been developed and projected for drug delivery. Nanosponges will give prolonged unharness and solubilize poorly water soluble medication by rising medication bioavailability [4]. Because of individual flexibility of nanosponges they are able to load each deliquescent and hydrophobic drug molecules as a result of their inner hydrophobic cavities and external deliquescent branching [5]. Nanosponges square measure in three dimensional network or scaffold. It have long length backbone of polyester that is mixed in resolution with tiny molecules referred to as crosslinkers that act like little grapping hooks to lock completely different components of chemical compound along [6].

It has been rumored that, a completely unique nanostructured material consisting of hyper-cross-linked cyclodextrins may be obtained by reacting cyclodextrins (cyclic oligosaccharides) with appropriate cross-linking reagents [7-9]. They can be synthesized as neutral or acid and might be swellable consistent with the agent used as crosslinkers [10]. Net impact is to make spherical formed

particles stuffed with cavities wherever drug molecules may be kept [11].

To get a tailored unharness profile, the cross-linking-to-cyclodextrin magnitude relation may be varied throughout the preparation to boost the drug loading [12-14]. The cross-linking-to-cyclodextrin offers higher drug loading compared with the parent cyclodextrin molecules Figure 1 and that they orient themselves in nanosponge's inclusion yet as act in non-inclusion fashion because of their extremely porous nanomeric nature [12].

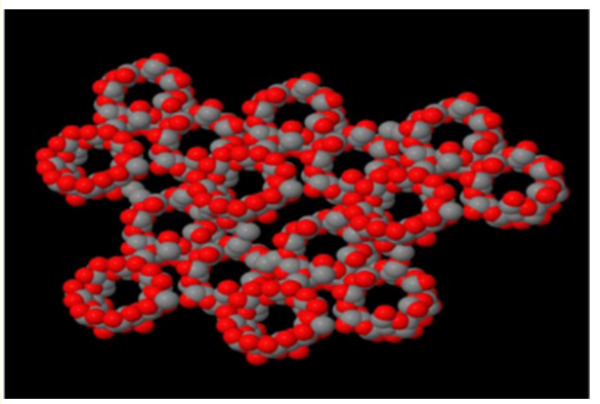

Figure 1: Molecular structure of cyclodextrin carbonates nanosponges.

The regeneration of nanosponge's can be done by different treatments, such as stripping with moderately inert hot gases, washing with eco-compatible solvents, changing pH or ionic strength or mild heating. So these are more advantageous than nanoparticles. All these characteristics of nanosponges made them more applicable in fields like pharmaceutical sector and cosmetics [15,16].

For the drug delivery they may function potential carrier and are found to be safe for oral and invasive route [14,15]. They are solid nature [17]. Nanosponges encapsulate the drug within its core and these are encapsulating type of nanoparticles [18]. The respiratory organ and blood vessel delivery of nanosponges is feasible because of little form of nanosponges [19]. For the preparation of tablets or capsules, the complexes could also be spread in a very matrix of lubricants, diluents, anti-caking agents and excipients are ready for oral administration. The advanced could also be merely carried in sterile water, saline or alternative binary compound solutions for the parentral preparation. They can also be effectively incorporated into topical hydrogel for topical administration [20,21].

Method of Preparation

Solvent method

In this method a suitable solvent is mixed with the polymer, particularly in a polar aprotic solvent such as dimethylsulfoxide, dimethylformamide. Above mixture is value-added to excess amount of crosslinker, ideally in crosslinker/polymer molar quantitative relation of four to sixteen. To hold out the reaction the temperature ought to be ranging from ten C to reflux temperature of the solvent, from time starting from one to forty eight h. Carbonyl compounds (dimethyl carbonate and carbonyl diimidazole) are the preferred cross linkers [19].

When the reaction is completed, it is allowed to cool down at room temperature, then this product is accessorial to giant far more than bidistilled water and recovered the merchandise was dried below vacuum. To obtain unvaried powder the merchandise was dried below vacuum and grinded in a very mechanical mill [22].

Ultrasound-assisted synthesis

By reacting polymers with crosslinkers beneath sonication and within the absence of solvent, nanosponges are obtained that are spherical and uniform in size [17]. In flask chemical compound was mixed with the crosslinker in particularly molar magnitude relation and place the flask in ultrasound bathtub crammed with water and heated it to 90 C. Then sonicate the mixture for 5 h. Then permit obtained mixture to chill and brook product roughly. To get rid of the non-reacted chemical compound, the merchandise is washed with water and later sublimate by prolonged soxhlet extraction with ethyl alcohol. The obtained product is dried beneath vacuum and kept at 25 C for further use [17,22].

Loading of drug into nanosponges

To obtain the nanosponges of particle size below 500 nm the drug should be pretreated. Then suspend the nanosponges in water and to avoid the presence of aggregates it is sonicated and to obtain the colloidal fraction centrifuge the suspension. Separate the supernatant and sample is dried by freeze drying. Prepare the

binary compound suspension of nanosponges and excess quantity of drug is distributed and constant stirring of suspension is maintained underneath specific time needed for complexation. By centrifugation action, the uncomplexed (undissolved) drug was separated from complexed drug once complexation is over. Then by solid evaporation or by freeze drying the solid crystals of nanosponges were obtained [19,22]. To form complexation with drug, the crystal structure of nanosponges plays a really vital role. When compared to crystalline nanosponges, paracrystalline nanosponges showed totally different loading capacities a study unconcealed. The drug loading is lesser in paracystalline one than crystalline nanosponges.

Characterization of nanosponges

A systematic changing and structural characterization of cyclodextrin nanosponges have some essential difficulties because of bound factors like i) presence of huge variety of reaction sites on every CD unit, ii) extended cross-linking of CD units leading in formation of insoluble chemical compound iii) type of amorphous systems that depends on the kind of synthesis method, and iv) the random nature of synthesis (cross-linking and polymerization) process of nanosponges.

Saturation state interaction

To find the saturated solution interaction study UV spectroscopy is used. To the increasing concentration of nanosponges solution, fixed amount of drug is added. Then keep the sample overnight. Drug loading is decide by analyzing the shift of absorbance maxima (lambda max) within the spectra compared to pure drug and by scanning of the formulation in ultraviolet light vary [12].

Porosity

Porosity offers the extent of nanocavities and nanochannels fashioned in the nanosponges. To study porosity helium pycnometer is used. Porosity due to helium gas to penetrate intra and inter particular channels of material. From the extend of helium displacement the true volume of material can be determined. By the following formula percent porosity is calculated [23,24].

$$\%\text{Porosity (E)} = \text{Bulk volume} - \text{True volume} \times 100/\text{Bulk volume}$$

Entrapment efficiency and drug loading

For drug loading, water dispersion of cyclodextrin nanosponges is incubated with additional drug mixture. At room temperature this dispersion is agitated for approximate time, filtered and also the nanosponge aliquot is freeze dried. To observe the quantity of drug available in system the outcome obtained when lyophilization is employed. For the denial potency experiment, the drug loaded nanosponges are distributed in solvent within which drug is soluble. For disruption of the network system the above distributed solution is subjected to sonication so that the drug loaded into the nanosponges dissolves within the solvent. With the aid of appropriate analytical techniques the quantity of drug available is checked by UV-violet spectrophotometer [25] and High Performance Liquid Chromatography (HPLC) techniques [23,26]. The entrapment efficiency can be calculated using following formula [27].

%Drug entrapment efficiency = Drug Encapsulated/ Drug Total × 100s

Part solubility studies

To check inclusion complexation described by Higuchi and Connors, it is pre-owned to notice the result of nanosponge on solubility of drug. With the aid of part solubility diagrams the degree of complexation of drug to nanosponges is studied [28]. To obtain saturated mixture, add excess drug into appropriate solvent by that part solubility constant is determined. In various increasing concentration blank nanosponges are treated with saturated drug solution. Owing to this a lot of medicines react with the nanosponges. Study is switched out till the equilibrium is obtained. As per the Higuchi and Connors classification, the plot is outlined as a graph is represented between NS concentration versus drug concentration [29,30]. The extent of interaction between nanosponges and drug is indicated by resulted stability constant worth. Dissolution rate and solubility of poorly water soluble drug will increase, as interaction of drug to naosponges will increases [12,23].

In vitro release studies

By *in vitro* liberate study, the discharge behavior of drug from nanosponges may be ended. Multi-compartment rotating cell that have 2 compartments separated with a hydrophilic qualitative analysis membrane. It have receptor compartment stuffed with phosphate buffer at applicable hydrogen ion concentration associate degreed donor compartment is stuffed with an liquid dispersion of nanosponges containing the drug used for this study. The receptor buffer is replaced with fresh buffer and old buffer is completely withdrawn at fixed time. The quantity of drug is set and

drug liberation is calculated by using appropriate analytical ways [23,31].

Water uptake and swelling index

For the swellable polymer-based NS, water uptake and swelling index is done. By direct soaking NS in water this could be performed. Following equations area unit accustomed to calculate water uptake and swelling index severally [23].

Percent swelling = St x 100/ S0

Where, St = cylinder marking at nominal time extra point after soaking and S0 = initial cylinder marking before soaking.

Percent water uptake = Mt X 100/ M0

Where, Mt = mass of colloidal gel once specific time and M0 = initial mass of dry compound.

Average diameter and polydispersity

To determine the typical diameter and polydispersity particle size analyzer is employed by applying the principle of dynamic light scattering (DLS) that is additionally called photon correlation spectroscopy (PCS) [32-36]. With auto-correlation perform PCS helps to correlate the variation in intensity of scattered light to particle size [37]. DLS/PCS measures the hydrodynamic diameter and hence it considers all the particles as spherical. By considering the effective consistence, index of refraction of the dispersion medium and temperature, DLS/PCS provides the particle size. Chemical analysis which might be perpetually most popular and may be done by examining those particles by transmission electron microscopy (TEM), scanning electron microscopy(SEM)or environmental scanning electron microscopy (ESEM) analysis. Morphology and particle size may be done by operating TEM, SEM or ESEM by dispersing sample in water or in alternate appropriate solvents [25,27].

Powder X-ray diffraction (PXRD)

PXRD helps in the determination of chemical decomposition and complexation is additionally distributed. Drug forms network with the cyclodextrin/NS and additionally there is a modification in crystalline nature of the drug because of variation in optical phenomenon. PXRD pattern of the sample is found as a perform of scattering angle [23,38]. Sharpening of peaks, appearance/disappearance of peaks furthermore as shifting of bound peaks is due advanced formation. With powder X-ray diffractometry it is doable to discover inclusion complexation within the solid state. No optical phenomenon pattern is seen in liquids, from uncomplexed nanosponges the optical phenomenon pattern of a new shaped substance conspicuously differs. By this optical phenomenon pattern advanced formation is showed. Comparison is completed between the diffractogram of the expected advanced mixture of the drug and compound molecules for solid drug sample. To see the elaborate inclusion structure single crystal X-ray analysis is also used. Precise Geometrical relationships are often established and host and guest molecule interaction are often recognized [39].

Fourier transform-infrared spectroscopy (FTIR)

For structural elucidation, FTIR is the most important technique particularly for functional group detection. During chemical change reaction monomers get connected to make chemical compound wherever purposeful bundle of peaks within the spectrum of FTIR are the characteristic indication of chemical change [12]. The vary of 4000-650cm-1 is employed to require FTIR spectra of chemical compound, drug, blank NS, drug-polymer physical mixture, drug loaded nanosponges and determined for any attainable interaction. It also shows sites on nanosponges like hydrophobic and hydrophilic. In case of hydrophobic drug disappearing of any useful cluster peak is owing to its inclusion in cyclodextrin/NS cavity [12].

Analysis of moisture

Retention of crystal structure throughout natural process and absorption of water content and non-hygroscopic nature of nanosponges is confirmed by dynamic vapour activity studies [40].

Circular dichroism

For example circular dichroic absorption, chirality and appropriate electron-optical absorption are needed. CDs do not absorb within the ultraviolet/visible (UV/Vis) even if CDs possess chirality. On different hand, guest molecules absorb luminescence. On addition of drug molecule into the nanosponge cavity, elicited circular dichroism spectra could also be made [40].

Molecular modeling studies

Molecular stimulation of dry and hydrous CD nanosponge models was studied to review their swelling behaviour by Raffaini., *et*

al. In stimulation methodology, the model nanosponges were generated by linking ring wise eight beta CD or five beta CD and six beta CD with a pendant tail of two beta CD through Pyromellitic dianhydride (PMA) moieties. Two stimulation approaches (a) in specific water (to study the immersion and swelling of the nanosponges and water potency strategy) and (b) in vacuo (to study the properties of a dry system) were adopted within the study. NS model showed a really compact structure in dry state throughout molecular dynamics stimulations. The molecular dynamics runs showed important nanosponge swelling, once the specific water solvent was introduced, restricted but by the topology of the model [40].

Raman spectroscopy

Raman peaks are quite responsive to molecular environment, intermolecular reactions and confirmation. Raman spectroscopic analysis is a particularly great tool in molecular study because the dimension, intensity and wavenumber of Raman peaks. Elucidation of CD-NS once moving into swollen kind from dry state is by Raman spectroscopic analysis. By analysis vibration modes of decoupled O-H and C-H cluster from bulk water background, dynamics of immersion are examined. This additionally provides info regarding illustration on state of water and dissolved matter within nanoporous NS architecture; with metriculous importance to diffusion from gelled condition [40].

Thermal analysis

Thermo analytical strategies like differential thermal analysis (DTA), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) are very necessary strategies to work out crystallization temperatures (Tc), melting temperature (Tm), degree of crystallinity (Xc), thermal and thermal-oxidative stability of drug and drug-NS advanced [40]. The DSC and DTA will be discovered for any shifting broadening and look of latest peaks or disappearance of few existing peaks. Molecular dispersion of drug in polymer is indicated by shallowness or disappearance of peak [39,40]. Another indication of inclusion complex formation is weight loss variation. For assessment of nature, interaction pattern and crystallinity of NS thermal analysis is extraordinarily necessary [40].

NMR spectroscopy

The C 13 NMR, 2D-NMR(ROESEY and COESEY), H1 NMR, high-resolution magic angle spinning (HR-MAS) PMR techniques have become a vital tool to check structure of cyclodextrin cross-linked polymers [40]. To evaluate the molecular mobilities of the cyclodextrin in nanosponge structure and examination of the interactions in advancement of drug-polymer is finished by exploitation PMR technique [40]. In PMR experiments, the exchange of nucleon between the reacting species, thereby orthodox the formation of nanosponges is indicated by modification in chemical shift values (δ). The spectra obtained exploitation of this new PMR technique will be accustomed characterize cross-linked materials having a restricted quality and it is additionally accustomed to determine the chemical compound structures that were planned by Crini., *et al*. A HRMAS spectrum of insoluble polymers of β-CD was first time used by Crini., *et al*.

Zeta potential

Any drug distribution within the body and interaction with biological membrane is greatly stricken by surface charge of any system or particle that eventually decides the fate of that system. Hence, surface charge is measured in terms of zeta potential which is prime importance. Electric potential of the system is calculated exploitation smoluchowski or strokes equation that later on reworked to zeta potential [40]. While calculating zeta potential the pH scale and electrolyte concentration are the parameters that also are though-about [40].

Stability studies

It is essential to hold out stability studies as per ICH pointers to determine stability information of the outcome as stability is that the key issue associated to drug product. Below accelerated stability study and exposure to UV illumination lamp nanosponges are studied for their stability. A stability chamber maintained at 25°C/65% RH within which accelerated stability study of nanosponges of calcium was administered by shende., *et al*. By using 1, 1' – carbonyldiimidazole and β-Cyclodextrin the nanosponges were prepared. Analysis was done regularly of three months for samples of stability for physical look; size and nature of drug were found stable. No important changes are determined in parameters i.e. physical appearance, size, nature of drug in formulation over a quantity of 3 months a study discovered [40]. Resveratrol loaded dimethyl formamide cross-linked nanosponges system was exposure degraded and studied by exposing nanosponges formulation hold at 10 cm from the UV illumination lamp for 1 h. The complex of nanosponges and drug was found more photostable than plain drug [25].

Merits and demerits of NSs

Merits of NSs

In order to boost the properties of existing materials many analysis studies are being conducted that comprise increased drug solubility, controlled drug particle size, increased drug loading capacity yet as controlled drug liberation properties. Nanosponges show attractive features because it has potential and which are summarized below.

- They act as a reservoir for varied pharmaceutical substances, because of the greater entrapment efficiency (EE) of NSs.
- Degradation of molecules is protected by nanosponges.
- Aqueous solubility of lipophilic drugs can be improved by nanosponges.
- For varied routes of administration within the physical body nanosponges facilitate to formulate totally different drug delivery systems.
- Nanosponges may be regenerated by totally different treatments basically, the way of preparation of NSs are easy, such as, removal with adequately inert hot gases, cleaning with eco-compatible solvents, slight heating or varied pH or ionic strength, that build it additional valuable as compared to micro- and nanoparticles.
- They will be accustomed convert liquid material into a solid type as a result of they will absorb liquids into their nonporous structure.
- Once ready within the existence of compound with magnetic properties nanosponges can also can be magnetized.
- In cancer targeting NSs based mostly drug delivery systems are with been successfully developed as a result of it releases the drug specifically at the tumor site, shows additional impact at a given dose. As a smaller quantity of the drug comes in contact in grips with healthy tissue thus this shows fewer aspect effects [41].

Demerits and challenges

NSs suffers from a fewer disadvantages, tiny drug molecules with mass but 500 Dalton(Da) will solely entrapped in NSs thus drugs with larger particle sizes cannot be delivered via NSs [41]. The NSs is either para-crystalline or crystalline. Degree of crystallization affects the loading of the drug inside NSs. Dose selling incidences square measure attainable sometimes. To beat such issues, to enhance the loading of high mass drug molecules chemical compound blends is used and by modifying the concentration of crosslinking agents. Besides this for the event of NSs 3D printing technology will well tried to be smart and wherever it is attainable to switch the NSs in line with our desires [41].

Impact of various factors on NSs properties

Polymers and crosslinkers

The use of polymer markedly affects the development and performance of NSs [41]. For delivery of active drug molecules NSs can be formulated for both hydrophilic and hydrophobic by using varying concentration of crosslinkers. Depending on the character of cross-linkers, soluble or insoluble NSs structure is obtained and additionally completely different cross-linking agents might dramatically modify very important characteristics, hydrophilicity/hydrophobicity and swelling ability of the chemical compound. Within the formulation of NSs, the molar quantitative relation of chemical compound and crosslinker additionally play a crucial role just in case of CD NSs [41]. Table one summarizes crosslinkers and polymers used for the formulation of NSs [41].

Type of drugs

Drug molecules should have certain traits to be encapsulated inside NSs, such as, i) within the structure of the drug molecule, it ought to have but five condensed rings, ii) the molecular weight of drug molecule should be between 100 and 400 Da, iii) the freezing point of the substances ought be underneath 250°C and iv) the water solubility should be less than 10 mg/ml [41]. Once loaded into NSs compounds with high melting points do not have high stability constant values [41].

Temperature

The complexation of medicine and NSs could also be plagued by variation in temperature. A decrease within the extent of apparent stability constant of the drug-NSs system are often discovered with the rise in temperature. This may happens because of depletion in drug/NSs interaction forces, like hydrophobic forces and van-der Waal forces with the rise in temperature [41].

Method of preparation

The drug loading in NSs gets plagued by drug/NSs complexation and depends upon the plan of action entrapping the drug

Composition of NS	Example	Ref
Polymer	β-CD 2-Hydroxypropyl-β-CD	[41]
	Randomly methylated β-CD	
	Branched β-CD	
	Hyper crosslinked polystyrene	
	Ethylcellulose	[41]
	PVA	[41]
Crosslinker	Poly(valerolactone-allylvalerolactoneoxepanedione)	[41]
	Carbonyldiimidazole	[41]
	Diphenyl carbonate	[41]
	Hexamethylene diisocyanate	[41]
	Hexamethylene diisocyanate	[41]
	Epichlorohydrin	[41]
	Diisocyanates	[41]
	Diaryl carbonates	[41]
	Glutaraldehyde	

Table 1: Polymers and crosslinkers used for the formulation of NSs.

into them. The productivity of a way is additionally laid low with the characteristics of the drug and compound. By drying up the potency of the complexation of the drug was found in most cases [41].

Degree of substitution

Position, number and type of the substituent on the parent molecule is greatly affects the complexation capacity with the drug [41].

Applications of NSs

Protein delivery

Because of extremely unstable nature of macromolecule, the formulation of the macromolecule drug delivery system is major challenge. For the delivery of proteins through totally different routes, swellable CD-based NSs were developed. By victimization totally different artificial routes, swellable CD-based NSs were developed for macromolecule delivery [42,43].

Ocular delivery systems

In ocular delivery dexamethasone exhibits poor corneal membrane porosity, henceforward ocular suspension of dexamethasone causes many worries on excessive installation. Dexamethasone NSs using β-CD and diphenyl carbonate that increased the therapeutic activity of dexamethasone with larger ocular permeation and retention was synthesized by Swaminathan., *et al*. (2013) [44].

Photothermal therapy

Nanosponges have recently fascinated attention, as they generate heat below lighting with radiation. Different therapies like conventional photothermal therapy (PTT) were not appropriate

because it was harming traditional cells in conjugation with cancer cells. Now a days, nanocarrier based mostly PTT has gained larger attention as a result of by this it is doable to regulate the light-activated heating nanocarrier at the neoplasm site. By this medical aid, the destruction of normal healthy tissues or cells decreases and it solely permits the warmth (thermal ablation) at the neoplasm site [45].

Gas delivery

Gas delivery is useful in pharmaceutical industries. Various gases are entrapped in NSs such as carbon dioxide (CO_2) and oxygen (O_2) which is found to be useful in cosmetic, pharmaceutical industries and biology. Encapsulation of those gases within the NSs structures, are verified by different researchers. O_2, CO_2 and 1-methyl cyclopropene are some of carrier gases which have been employed in CD NSs [46].

Absorbent in blood poison treatment

For the employment of nanocarriers for detoxification of blood, distinctive approaches of NSs have return to illustrious. NSs will sop up the toxins by injecting NSs in blood, as another antitoxin. By injecting NSs in blood, NSs can sop up the toxins as an alternative of antidote. These appearance similar to RBCs, this tricks toxins into offensive it, sop up them and their path turns faraway from cellular target [47].

Conclusion

Nanosponges are new type of drug delivery system which has been recognized as drug delivery system to encapsulate or accumulate for both lipophilic and hydrophilic drug by forming a complex. CD-Nanosponges are cross-linked compound possess explicit properties in terms of their biocompatibility, encapsulation ability and solubilisation capability with relevance totally different style of molecules. In a controlled manner drug is delivered at target site effectively. Topical preparation can be incorporated in Nanosponges such as cream, ointment and lotions etc. This technology offers targeting of drug to particular site by improving stability, formulation flexibility, and better patient compliance and reduces side effects, which is advantageous. It offers applications in biomedical, catalysis, bioremediation process, and cosmetics etc.

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Volume 5 Issue 11 November 2021