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Review Article Nanosponges: A FuturisticNanoversionasan Innovative Approach for the Enhancementof Bioavailability and Solubility ofPoorly Soluble Drugs

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Abstract: During the manufacturing of various drugs and formulations, the "solubility and bioavailability" are pivotal aspects because approx. 40% of novel drugs have low aqueous solubility which cause a greater challenge in the pharmaceutical applications. In the conventional drug delivery system, an oral route is a most acceptable route for administration of various drugs however, this route also acts as a barrier to achieve a desired pharmacological action of many drugs. When a drug is administered into the body, it crosses numerous barriers (that are present in our body) and after that drug will then be reached at the target site where it could not be able to reveals its complete pharmacological action since most of its activity has lost via several barriers such as (Saliva, Liver and GIT, etc.). That's why the solubility and bioavailability have been getting affected in a large extent so to overcome these issues, the scientists have been developed an "Innovative approach" that's called the "Nanosponges". Nanosponges are the innovative nano-sized material containing hyper crosslinked cyclodextrin that can be manufactured through interaction of cyclodextrin with an appropriate cross linker. β-cyclodextrin is a characteristic polymer that boosts an entrapment efficiency of nanosponges and microparticles, etc., and also responsible for enhancing the solubility and bioavailability of poorly aqueous soluble drugs. Nanosponges have three-dimensional framework or scaffold structure that hold both hydrophilic and lipophilic drugs since their inner core contain lipophilic properties while outer part have hydrophilic branching. One of greater benefits of the nanosponges are improve patient compliance and to achieve targeted and controlled release of drugs in an extensive manner. They are crystalline or paracrystalline in nature. An entrapment efficiency of therapeutic agents can be decided via paracrystalline nanosponges. They are non-toxic, biodegradable and do not produce any discomfort. Nanosponges contain size below<1um, their size is small however, their functions have a greater impact not only in the pharmaceutical sectors but also play a significant role in various fields including "Biomedical engineering, Purification of water, Gene therapy, as a Chemical Sensor, Biocatalysts" and much more. In this review article, authors have highlighted the basic Introduction of Nanosponges, Characteristic features, Classification, Composition, Mechanism and loading of Drug intoNanosponges, Methods of Preparation, their Evaluation, Marketed formulations of Nanosponges, Illustrations of Nanosponges with their several Applications.

Keywords: Nanosponges, Encapsulating Nanoparticles,Application of Nanosponges Benefits of Nanosponges Categorized Classes of Nanosponges Mechanism and loading of Drug intoNanosponges, Methods of Preparation, their Evaluation, Marketed formulations of Nanosponges, β-cyclodextrin

I.INTRODUCTION

Nanospongesare a newer category in the novel drug delivery system that composed of small spherical nanoparticles contains broad cavities of a few micrometers where, it is possible to envelop a wide range of materials can be used[1].They are microscopic mesh-like 3D framework with their spongy structure andhave small size below <1um. The novel class of these three-dimensional framework have the capacity to contain both hydrophilic and lipophilic drugs in an extensive manner because their core consist lipophilic properties and a hydrophilic branching, thus enhance solubility, bioavailability of poorly water-soluble compounds and minimizing side effects[1,2,7].

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The delivery of Nanoparticulate drugs have shown greater benefits in terms of increasing bioavailability, localized therapies and have potential to upgrade the management of various ailments. The recent studies and clinical trials predicting that this approach has five times highly potent to administered medicines in the patient of breast cancer in the contrast of traditional approaches[3,4].

The Nanosponges have a 'backbone' (Scaffold structure) of biodegradable polyester with an around the size of a virus. The strands of polyester consist extended length that are dissolved in solution along with tiny materials are known as "cross-linkers" which have a special preference for definite parts of the polyester. These "cross-linked" polyester strands create a spherical structure with various cavities in which active ingredient can be loaded easily[1].The biodegradable nature of polyester has been proved that an active ingredient could be released at a predetermined time, once it degrades into the body[1,4].Nanosponges are anencapsulated nanoparticles that encapsulates the pharmaceutical ingredient inside their core[4].

The structure of nanoporous substances is significantly categorized into "Nanoporous membrane", "Nanoporous hydrogels" and "Nanoporous particles". The porosity and size both are the distinguish feature that separates nanoparticles from nanosponges where an average size of nanoparticles is measured in 'nanometers', whilst the nanosponges containing pores are measured in 'nanometers' meanwhile, an actual size of NS might range below <5um (micrometers). Nanoporous particles/ microparticles have been identified as Nanosponges (NS)[5].

Nanosponges have several structural domains in their composition because they contain both hydrophobic and hydrophilic groups[6]. An innovative nano-sized material containing hyper cross-linked cyclodextrin can be manufactured through interaction of cyclodextrin with an appropriate cross-linker known as Nanosponges (NS)[7].

On the basis of associating with drug, the nanoparticles may be categorized into three classes: -

1-Encapsulating Nanoparticles-Nanosponges and Nanocapsules are representatives of this class. *Alginate Nanosponges* are sponge-like nanoparticles comprising several pores which hold an active ingredient. Nanocapsules such as *Poly (isobutyl cyanoacrylate) (IBCA)* also falls under the class of encapsulating nanoparticles. They are able to enveloped the drug particles in their hydrophilic core[4,5].

2-Complexing Nanoparticles-In the class of complexing nanoparticles, the drug substances are attracted via electrostatic charges[1,4].

3-Conjugating Nanoparticles- This class of nanoparticles represent the conjugation of nanoparticles with a therapeutic agent via covalent bond[5].

II.A DISTINCTIVE ATTRIBUTES OF NANOSPONGES[1,5,8,13,10]

1) Nanosponges have a wide variety of diameters (250nm – 1um) and polarity of the cavities that can be adjusted.
2) They have a capacity to encapsulate, distribute and selective release of a wide range of drugs.
3) The certain dimension of nanosponges can be formed by altering the crosslinker to polymer ratio.
4) They are biodegradable, tiny particles and impervious in many organic solvents and can also withstand the temperature up to 300° C.
5) They can resist a pH range of 1 to 11.
6) To produce transparent and opaque suspension in water.
7) Nanosponges are crystalline or paracrystalline in nature. The crystalline structure of nanosponges play a significant role during drug complexation.
8) Loading of drug capabilities are determined by the degree of crystallization.
9) An entrapment efficiency of therapeutic compounds could be established through paracrystalline nanosponges.
10) Due to their ability to interact with multiple functional groups, nanosponges can be placed at various target sites.
11) The chemical linkers provide preferential target location to nanosponges for entrapment.
12) Nanosponges have porous structure with a high-watersolubility used primarily to entrap pharmaceuticals that are poorly soluble in aqueous medium.
13) They have a capacity to hold both hydrophilic and lipophilic drugs.
14) Nanosponges synthesize the inclusion and non-inclusion complexes via multiple drugs formed complex with them.
15) They provide the protection of pharmaceutical agent against physiochemical decomposition.
16) They can purify water by removing organic contaminants.

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17) If Magnetic particles are added to the reaction mixture, nanosponges could also be given magnetic characteristics.

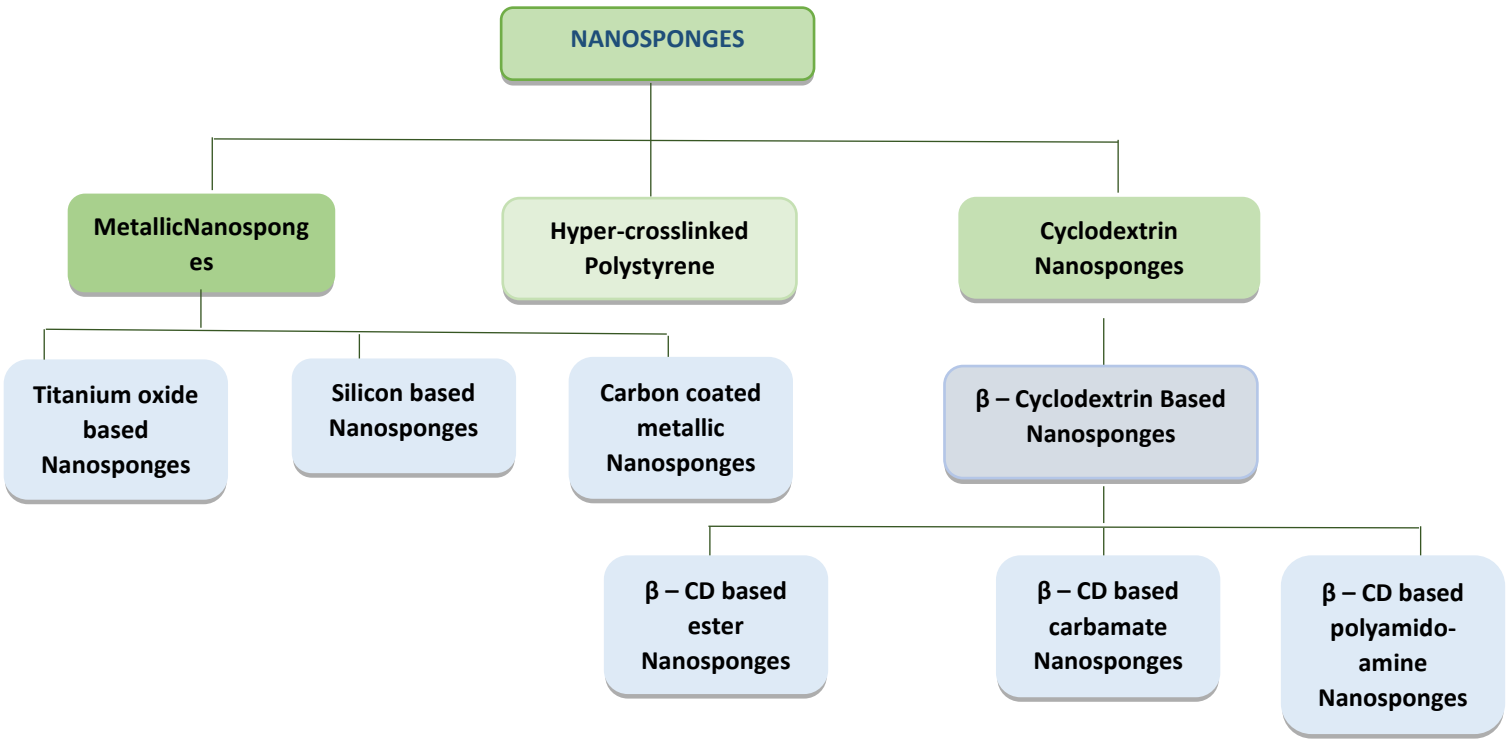
III. BENEFITS OF NANOSPONGES [7,11,12,13,14]

1) Nanosponges are non-toxic, non-allergic, biodegradable and do not produce any discomfort.
2) They are highly stable at pH 1 to 11.
3) To enhance the hydrophilicity of poorly water-soluble drugs.
4) They have self-sterilizing property due to non-penetrability of bacteria (average pore size is 0.25um).
5) Most of the additives, components and vehicles are suitable with composition of nanosponges.
6) Nanosponges aid in the removal of toxins and poisons from the body.
7) This innovative approach can be used to entrap active components with minimize toxic effects, boost stability, enhance efficiency as well as elegancy and maintain the flexibility of formulations.
8) They are miscible in aqueous medium since, encapsulation can be achieved inside via incorporating ancillary agents.
9) They required less dose frequency and quantity.
10) Improve the compliance of patients.
11) Drug release is constant and free flowing.
12) They have an extended-release mechanism that allows for continuous action for up to 12 hours.
13) They are used to hide undesirable taste of drugs and turn liquids into solids.
14) The ratio of cross-linker to polymer can be modified to make particles smaller or larger.
15) These formulations are economically effective.

IV. LIMITATIONS OF NANOSPONGES [12,13,14,13]

1) The main limitation of nanosponges may occur i.e., Dose dumping.
2) Nanosponges have an ability to entrap only smaller molecules of molecular weight less than <500 Daltons, they do not contain larger size molecules (>500 Daltons).
3) The degree of crystallization is main factor to decide the loading capability of Nanosponges that's why crystalline form is also a drawback of nanosponges.

V. CLASSIFICATION OF NANOSPONGES



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A. Cyclodextrin Nanosponges

The word Cyclodextrin Nanosponges (CDNS) was coined by *"DeQuan Li and Min Ma"* in 1998 to described a crosslinked β-cyclodextrin with organic diisocyanates resulting in the development of an insoluble network that shows greater inclusion complex with many organic contaminants[5].To boost the entrapment efficiency of liposomes, microparticles and nanoparticles, cyclodextrin and its analogues have been employed as solubilizers[17].

Cyclodextrin can be divided into three parts:-

a). β-Cyclodextrin b). γ-Cyclodextrin c). δ- Cyclodextrin. All three natural CDs varies from their solubility and size of the ring.

Unlike-Cyclodextrin, the natural β-Cyclodextrin and δ-Cyclodextrin are not degraded by human salivary enzymes or pancreatic amylases; however, all three are metabolized by an intestinal microflora. Hydrophilic CDs are harmless at moderate oral dosages. In oral and topical formulations, naturally occurring CD as well as its derivatives are employed. However, only δ-Cyclodextrin and hydrophilic derivatives of β and γ-Cyclodextrin could be used in injectable preparations. In aqueous medium, cyclodextrin produces visual clumps making it unsuitable for parenteral applications[5].Cyclodextrin based nanosponges is made via treating cyclodextrin with many cross-linking agents such as activated carbonyl compounds including carbonyl diimidazole, pyromellitic dianhydride and carboxylic acids[18]. The proportion of CD - crosslinker can be modified throughout the fabrication, to enhance entrapment efficiency of drug and an achieve customized release profile[21].Amphiphilic β-Cyclodextrins or γ- Cyclodextrins altered on the primary face containing hydrocarbon chains of different lengths (C_6 and C_{14}) were examined as new excipients for nanomaterial preparations that can contain numerous medications without inducing harmful effects in cell cultures[19].

B. Cyclodextrin-Based Carbamate Nanosponges

CDs are treated under the existence of DMF solution at 70° C over 16 to 24 hours in a nitrogen environment with an appropriate diisocyanates such as hexamethylene diisocyanate and toluene-2,4-diisocyante. By gently washing with acetone, any remaining DMF is removed and powder of the cross-linked polymer is produced. CD-based carbamate nanosponges can bind to organic compounds and are employed in the filtration of water. Organic compounds have the loading capability of 20 to 40 mg per cm^3[5,16].

C. Cyclodextrin Based Ester Nanosponges

For the manufacturing of these nanosponges, an appropriate dianhydride, including pyromellitic anhydride, is utilized as a cross-linking agent. A reaction of exothermic cross-linking is a quick and occurs at room temperature that involves the combining of CD with dianhydride in DMSO in the presence of an organic bases like pyridine or trimethylamine (to carried out reaction towards the forward direction). Due to the presence of a polar free carboxylic acid group, this variety of nanosponge can hold both non-polar organic compounds and cations at the same time[5,16].

D.Polyamidoamine Nanosponges

The reaction for this kind of nanosponge is carried out in water. After a long time, polymerization of CD with acetic acid 2,20-bis (acrylamide) occurred at room temperature for 74 hours. They possess both acidic and basic overage and expand in aqueous medium (shows pH dependent action)[5].

E. Hyper Cross-Linked Polystyrene Nanosponges

Hyper cross-linked polystyrene is a light weight contains porous structure and transparent materials with a strong absorption efficiency and an internal surface area of about 1000 m^2/g. They are also employed to remove trace elements from solids. This sort of NS has a very unique fabrication. An extensive length of polymeric chain, firstly expands by an initial solution and keeps firmly solvated throughout the network design phase. These nanosponges are used in targeted drug delivery system, implant material and also for diagnostic purpose. Anti-cancerous drugs such as Paclitaxel and Temozolomide can be administered via help of polystyrene nanosponges[12].

VI.COMPOSITION USED IN THE MANUFACTURING OF NANOSPONGES[3,5,7,20]

A. Polymer

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Selection of polymer may have a greater impact on the development and functioning of nanosponges. The cavity size of a nanosponges must be enough to hold an active ingredient of a specific size for binding. The cross linking of the polymer is depending on the substitution of functional groups and active moieties. The choice of polymer is governed by the desired release of drug and the drug to be encapsulated.

B.Cross-Linkers

The cross linkers are decided based on the design of polymer and the medication to be manufactured.

C. Active Ingredient

Active ingredients that will be used to make nanosponges must have specific traits:

a). Molecular weight of a drug molecule should be of 100 to 400 Daltons.

b). A drug molecule is made up of less than five combined rings.

c). Aqueous solubility should be < 10mg/ml.

d). The melting point of the compound should be less than 250° C.

POLYMERS	Hyper cross-linked polystyrene, Cyclodextrin and its derivatives like β-Cyclodextrin, Alkyloxy Carbonyl Cyclodextrin, 2-Hydoxy Propyl β-Cyclodextrin, Methyl β-Cyclodextrin.
CO-POLYMERS	Poly(valerolactone-allylvalerolactone) and Poly(valerolactone-allylvalerolactone oxepanedione), Ethyl cellulose, Polyvinyl alcohol.
CROSS-LINKERS	Carbonyl diimidazoles, Carboxylic acid dianhydrides, Diphenyl carbonate, Diaryl carbonates, Disocyanates, Pyromellitic anhydride, Epichloridine, Glutaraldehyde, 2,2-bis(acrylamido), Acetic acid and Dichloromethane.
VEHICLES	Dimethyl Sulfoxide (DMSO), Dimethyl formamide (DMF).

TABLE I CHEMICALS EMPLOYED IN SYNTHESIS OF NS

VII. ENCAPSULATION OF DRUG INTO NANOSPONGES

The pretreatment of nanosponges for delivering of drugs must result in a particle size of less than 500nm. Nanosponges are suspended in water and then sonicated to eliminate any clumps. The separation of suspension is done to get the colloidal fraction. The supernatant is withdrawn and the sample will be freeze dried. Aqueous suspension of nanopsonges is formed and disseminated in an abundance of the medication and for the formation of complexation, the suspension is required to be kept under steady stirring for a definite period of time and the centrifugation is done for an extraction of uncomplexed drug from complexed drug. Therefore, the solid crystals of nanosponges are prepared through an evaporation of the solvent or freeze drying. The crystalline pattern of nanosponge is an essential for complexation of drug. When crystalline nanosponges were compared to paracrystalline nanosponges, there was found that paracrystalline nanosponges possessed variable loading limits. In contrast to paracrystalline nanosponges, crystalline nanosponges have a higher capacity for loading of drugs. The encapsulation of drug in the weakly crystalline nanosponges willform mechanicalmixture instead of an inclusion complex[13,14,25].

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VIII.DRUG RELEASE MECHANISM FROM NANOSPONGES

The sponge atoms have a porous structure, allowing an active moiety to travel freely into and out of particles and into the vehicle until equilibrium is attained. During the topical application, when the finished product is administered onto the skin, an active component which is earlier present in the vehicle would be released at the target tissue. As a result of reducing the vehicle, it will be causing unsaturation thus an equilibrium will be disrupted. The active component will proceed from the sponge particles into the vehicle and subsequently to the skin until the vehicle has either been absorbed or dried. After the sponge particles are deposited on the surface of stratum corneum, it will provide the drug to release for extended period of time[5,13].

IX.SOME CONSIDERATIONS THAT AFFECTING THE FABRICATION OF NANOSPONGES

There are few considerations that affect during the synthesis of nanosponges:-

A. Character of Polymer and Cross-Linkers

The character of polymer employed in nanosponges may have an impact on their formulation and functioning. The nanosponges cavity or pore size ought to be capable of containing an appropriate therapeutic molecule. Molecular nanocavities are transformed into a three-dimensional nanoporous form by an effective cross-linker[4,5].

B.Drugs

The complexation of therapeutic agent with nanosponges must have the number of characterizations, they are shown below as:-

a). Molecular mass in the lies between 100-400 Daltons.
b). A therapeutic moiety must possess less than five fused rings.
c). The solubility of water should be less than 10mg/ml.
d). The melting point of material must be lower than 250^{o} C[1,13].

C. Degree of Substitution

The position, number and type of substitution of the drug substance have all influenced the nanosponges complexation. Depending on the location of the substituents, β-CD derivatives are accessible in the numerous forms like, β-CD, CD-Carbamate, CD-Carbonate Nanosponges[12].

D. Temperature

Variations in the temperature, may have an influence on the drug complexation. When the temperature is raised, then decreases an apparent stability of the drug/nanospomge complex, potentially due to drop in the forces that act between the drug and nanosponge complexation including Vander Waal's forces and Hydrophobic forces[16].

E. Method of Preparation

The loading of drug into nanosponge has an impact on complexation of drug/nanosponge. The nature of the therapeutic agent and the polymer plays a significant role in the efficiency of method; in several instances, the most efficient approach for complexation of drug is freeze drying[13,16].

X.METHODOLOGIES USED IN THE SYNTHESIS OF NANOSPONGES

By using different methodologies, we can synthesize the nanosponges. Thesemethodologies are:

A. Solvent method
B. Hyper cross-linked β-cyclodextrin
C. Emulsion solvent diffusion method
D. Ultrasound-assisted synthesis
E. Quasi-emulsion solvent diffusion
F. Polymerization

A. Solvent Method

Thepolymeris dissolved in an appropriate solvent (preferably in a polar aprotic solvent) i.e., dimethyl sulfoxide, dimethyl formamide. Then, this combination is incorporated into excess amount of the cross-linker, typically in 4 to 16

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molar ratio of cross-linker to polymer. The most commonly cross-linkers are carbonyl compounds including diphenyl carbonated and carbonyl diimidazole). The reaction is carried out for 1 to 48 hours at a temperature range from 10^0 C to the solvent's reflux temperature. After the ending of reaction, an additional quantity of distilled water is added and allowed to cool at room temperature. The recovery of product is accomplished via vacuum filtration and purification is done by Soxhlet extraction with solvent ethanol is used. After the extraction and purification, the product is dried using vacuum, and a mechanical mill is used to grind it into a homogenous powder[5,13].

B. Hyper Cross-Linked β-Cyclodextrin

Nanosponges is a 3-dimensional network made up of hyper cross-linked cyclodextrin polymers that are nanostructured to produce a strongly spherical structure around the size of a protein with channels and inside the pores. To obtain this porous structure, the reaction is occurred between cyclodextrin and cross-linking agents like as diisocyanate, diaryl carbonates, dimethyl carbonate, diphenyl carbonate and carbonyl diimidazoles, carboxylic acid dianhydrides and 2,2-bis (acrylamido) acetic acid. The dimension of sponges is determined by their porosity and surface charge density for joining of multiple molecules. The rapid release of drug is achieved by nanosponge with low cross-linking[14,20].

C. Emulsion Solvent Diffusion Method

In this method, two different amounts of organic and aqueous phases are used. Drug and polymer are combined in the organic phase, whereas Polyvinyl Alcohol (PVA) is employed in the aqueous phase. After combining the drug with polymer in an appropriate organic solvent, this phase is gently combined into the aqueous phase and agitated at 1000 rpm with the help of magnetic stirrer for 2 or more hours. The filtration is used to obtain the nanosponges which are then dried for 24 hours at 40° C and after that stored in a container[7,20].

D. Ultrasound-Assisted Synthesis

In this technique, ultrasound is used in the laboratory for several applications and has the wide range of physical and chemicals effects. Ultrasonic is produced by using an ultrasound probe or a sonicator bath. Sonication is often employed in nano-technology to disperse the nanoparticles uniformly in a liquid environment. Since the cross-linker are not soluble or sonicated in this approach, while the polymers react. The direct ultrasonication of β-Cyclodextrin and its derivatives are used to synthesize naosponge. As cross-linkers, organic carbonates are utilized. In this technique, there is no need of solvent. The reaction is usually carried at 90° C for 4-5 hours. The mixture is then allowed to cool before being broken up into rough tiny pieces. After that, the product will be rinsed with excess water to eliminate any unreacted solvent, and ethanol is used for Soxhlet extraction and thus finally, the product will be dried under vacuum and collect them. This process yields spherical nanosponges with homogenous size of particles[3,16].

E. Quasi-Emulsion Solvent Diffusion

The nanosponges could also be synthesized via Quasi-emulsion solvent diffusion technique with different concentrations of polymers. Eudragit RS 100 is dissolved in an appropriate solvent to obtained the inner phase. After that, during ultrasonication at 35° C, an active ingredient will be added and mixed into the solution. The inner phase will be put into the water-based PVA solution (outer phase). The slurry will filter after 60 minutes of stirring to isolate the nanosponges. Finally, the nanosponges are dried for 12 hours at 400° C inside a hot air oven[5,8,20].

F. Polymerization

The process of polymerization results in the production of a reservoir type structure with pores that opens at the surface, where in an aqueous phase, generally comprising surfactant and dispersant to aid suspension is introduced. When a suspension with distinct droplets of the required size has been formed, polymerization is achieved through activation of the monomers either via catalyst or through raising the temperature[5,8].

XI.ESTIMATION OF NANOSPONGES

A. Particle Size and Polydispersity Index

The dynamic light scattering with a 90 plus particle size combined with MAS OPTION particle sizing software, laser light diffractometry or Malvern Zeta Sizer can be used to estimate the size of particles. The mean diameter and polydispersity index can also be calculated. If particle size is greater than 30m may reveal gritty sense whereas particle size lies between 10-25m is favored for application of topical medications[1,5,8].

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TABLE II POLYDISPERSITY INDEX

Polydispersity Index	Dispersion Type
0-0.05	Monodispersed Standard
0.05-0.08	Nearly Monodisperse
0.08-0.7	Midrange Polydispersity
>0.7	Very Polydisperse

B. Resiliency (Viscoelasticity)

Resiliency of nanosponges can be altered to form softer or tougher beads, based on the demands of finished formulation. Augmentation of cross linking can decrease the rate of release. As a result, the viscoelasticity of nanosponges will be investigated and enhanced according to the needs, taking into consideration that release serve as a consequence of cross-linking with time[20].

C. Microscopic Studies

The microscopic characteristics of an active ingredient, nanosponges and the products (drug/nanosponge complex) are estimated by Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Inclusion complexes are formed as a result of the variation in crystalline state. SEM estimates the surface structure of nanosponges[4,8].

D. Thermoanalytical Methods

Thermoanalytical techniques are used to estimate the alteration of active compound before the thermal decomposition of the nanosponge. There can be some variations that occur in the active component such as melting, evaporation, degradation, oxidation and polymorphic transition. The generation of complex is associated with an alternative of active component. The thermogram produced via DTA and DSC would be examined for broadening, shifting and the emergence of new peaks as well as the extinction of some existing peaks. There are variations in the weight reduction might potentially give indication to inclusion complex formation[1,25].

E. Fourier Transformer Infrared Spectroscopy (FT-IR)

The cross-linking in CD molecules could be estimated by Fourier transformer infrared spectroscopy (FT-IR) technique, which is a foremost interpretation for the structural assessment of nanosponges. Because of the existence of primary alcoholic groups, the FT-IR spectra of β-CD exhibit a characteristic peak of non-hydrogen bonded O-H stretching at 3450cm^{-1}. The lack of this peak in nanosponges indicate the cross-linking mechanism utilized all free primary alcoholic groups of β-CD. In the preparation of CD-NS , the diphenyl carbonate used as the cross-linking agent. The characteristic peak is formed through the carbonate group in Diphenyl Carbonate (DPC) is 1775cm^{-1} moves to 1750cm^{-1} as well as further CD-NS characteristic peaks can also be found between the spectrum of 1400-1600cm^{-1} and 1270-1290cm^{-1} respectively. Each and every spectrum was taken at a 4cm^{-1} resolution and an average of 100 repeating scans, leading to a high signal-to-noise ratio and good reliability[6,22].

F.Thin-Layer Chromatography

In thin-layer chromatography, the RF values of the therapeutic compound drop substantially which aids in the estimation of the drug-nanospongecomplexation[4].

G. Drug-Release Kinetics

This method is used to estimate the mode of drug release from the nanosponge and the release of drug data is determined by Zero Order Kinetics, First order kinetics, Hixon Crowell, Kopcha, Makoid-Banakar, Higuchi and Korsemeyer-Peppas Models[5].

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H. Entrapment Efficiency & Production Yield

An entrapment efficiency refers to the efficiency of a medicine entrapped into the nanoponges i.e., measured by the UV-spectrophotometer and HPLC techniques[11].

The loading efficiency (%) of the nanosponges is estimated by subsequent equation:-

$$\text{Loading Efficiency} = \frac{\text{Actual drug content in NS} \times 100}{\text{Theoretical drug content}}$$

Production Yield

By getting the relevant initial mass of raw materials and the final mass of the nanosponge produced, the following formula could be used to estimate production yield of the nanosponges[5].

$$\text{Production Yield} = \frac{\text{Practical mass of NS} \times 100}{\text{Theoretical mass (polymer+ drug)}}$$

I. Solubility Studies

The phase solubility method was proposed via "*Higuchi and Corners*" who investigated the influence of nanosponge on a drug solubility, is the most extensively used method for estimating an inclusion complex between the drug and nanosponge[8,11].

J. Stability Studies

The effect of the temperature variation on physical properties, loading efficiency and the drug contents are observed under the stability studies of modified nanosponges. The nanosponges are stored in an airtight container for 45 days at 40 ± 2^0C temperature and 75±5% relative humidity. After 15,30 and 45 days, the samples will be examined for given characteristics. According to ICH QIA (R_2) recommendations, the samples are collected after 15 days, 30 days and 45 days and evaluated for any alternation in their physical form and contents of the drug[9].

K. Dissolution Studies

The dissolution rate of nanosponges can be examined using a modified USP XXIII dissolution apparatus with 5m stainless steel mesh basket rotating at 150 rpm. To achieve sink conditions, the dissolution media is chosen when monitoring the solubility of the drug component. Analytical techniques may be used to estimate the samples from dissolution medium[5].

XII.APPLICATIONS OF NANOSPONGES

Nanosponges have a wide range of uses in the pharmaceutical sector since their biocompatibility and adaptability. Nanosponges can also be employed as excipients in the manufacturing of tablets, capsules, pellets, granules, suspensions, solid dispersion and topical formulations.

A. CLINICAL APPLICATIONS:

1). Nanosponges used as An Enhancement of Solubility

The low water solubility of several medications is one of the greatest challenges in their manufacturing. Approximately 40% of novel active agents are hydrophobic in nature thus, creating a challenge for their clinical use. Nanosponges used

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as an innovative carrier for enhancement or improvement the wettability and solubility of poorly soluble drugs. The active agents can be distributed molecularly inside the structure of nanosponge and then delivered as molecules by passing the dissolution stage. As a result , the apparent solubility of an active moiety may enhance. Due to the solubility enhancement and dissolving rate of a drug may alleviate a lot formulation and bioavailability issues, and nanosponges can help immensely to enhance the solubility of drugs[5,12].

2). Nanosponges used as Delivery of Drugs

The nanosponges are rigid type of structure that can be used in the variety of dosage forms including, oral, parenteral, topical and inhalational. β-CD nanosponges have been shown to delivered the drugs three to five times more efficiently as compared to intravenous administration. The complexes can be disseminated in a matrix of excipients, diluents, lubricants and anti-cancer agents facilitating the oral delivery. The complex can readily be placed in sterile water, saline or other aqueous solutions for the parenteral delivery. They may be successfully integrated in topical hydrogels to provide the topical delivery[5,15].

3). Nanosponges in Cancer Chemotherapy

Nanopsonges enable many anticancer agents to be targeted at specific sites with evading the barrier formed via the immune system. Nanopsonges have been used to treat numerous types of cancer cells, including breast cancer and fast-acting glioma through a single dose of injection[7].

Paclitaxel-loaded NS are made via employing β-CD based nanosponge utilizing the process of generation of an inclusion complex to enhanced bioavailability and cytotoxicity. It is a powerful anti-mitotic medication that employed as a chemotherapy although its bioavailability is only 6.5%. Introducing paclitaxel into NS complex improves absorption in Spargue Drawly Rats as well as cytotoxic effectiveness in MCF-7 cell lines[3].

4). Nanosponges employed as Antiviral Drug Delivery

Nasal and pulmonary delivery of drugs may possible by nanosponges (act as a carrier). It offers selectivity for administrating antiviral drugs over RNA to the lungs or nasal pathway using nanocarriers to target virus that can cause Respiratory tract infections, including Influenza virus and Rhinovirus. Antiviral drugs employed as nanocarriers such as Zidovudine and Saquinavir[11].

5). Nanosponges facilitates the Delivery of Topical Agents

Nanosponges act as a novel approach to achieve the controlled release of topical medications. Several dermatological and personal care goods have shorter period of action however, they release at higher amount. To overcome this issue, a broad range of medications may be incorporated into nanosponges as well as developed in the various formulations such as gel, lotion, cream, ointment, etc.[7].

Some topical drugs that are prepared for the topical delivery of drugs for encapsulation of nanosponges.

TABLE III

S.No.	Therapeutic Agent	Technique Employed	Ref.
1.	Miconazole Nitrate	Solvent evaporation	7
2.	Isoniazid	Emulsion solvent	7
3.	Tazarotem	Emulsion solvent	7
4.	Cephalexin	Emulsion solvent	7

6). Oxygen Delivery System

The gases hold a crucial position in the medical field, both diagnostically and therapeutically. In medical practice, it might have been challenging to provide oxygen in the sufficient quantity and dose. Hypoxia, or an absence of sufficient oxygen flow is associated with numerous types of diseases including from inflammation to cancer. As a result, it would be required to develop the oxygen delivery system[23].

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Cyclodextrin Nanosponges act as a nanocarrier for the delivery of oxygen. The three forms of nanosponges comprise of α, β and γ-cyclodextrin are suspended in water, saturated with oxygen and described as an in-vitro release to achieve this goal. Nanosponges can hold and release oxygen in a controlled manner. Nanosponges containing oxygen may provide oxygen to hypoxic tissues found in many pathological conditions[25].

7). Nanosponges act as a carrier for biocatalyst, providing the delivery and release of enzymes, proteins, vaccines and antibodies

Nanoparticles, microparticles, liposomes and hydrogels all these are the carriers that have been designed to transport enzymes and proteins. Transport in a specific system may shield proteins against degradation, alter their pharmacokinetics and optimize their in-vivo stability. Cyclodextrin-based nanosponges have now been discovered to be extremely effective as carriers for adsorbing proteins, enzymes, antibodies and macromolecules. It is feasible to sustain enzyme activity, efficacy and functioning, as well as enhance the pH and temperature range of activity and operate continuous flow activities, while enzymes are being employed. Furthermore, adsorption or encapsulation of proteins and other macromolecules in cyclodextrin nanosponges may also be used to transport them[5,25].

8). Nanosponges as an absorbent in removing poison from systemic circulation

By eliminating the poison, nanosponges are employed to extricate toxic substances that are harmful to the systemic circulation. When delivered via injection, nanosponges assimilate toxins faster as compared to antidotes. Nanosponges imitate as Red Blood Cells (RBCs) in the circulation, inducing toxins to target and digest them. Toxin compounds could be destroyed by nanosponges, based on the toxin[15].

9). Nanosponges used as a diagnostic agent

β-cyclodextrin is commonly employed in the production of varieties of diagnostic products. CD-NSs are ideal to be choose as a diagnostic tool because of their good biocompatibility, extended circulation time and homogenous size distribution facilitating permeability and greater accessibility to the target[15].

10). Nanosponges arrest the infection of SARS-COV2

The two forms of cellular nanosponges that are synthesized via plasma membrane of human lungs epithelial type II cells or human macrophages have been discovered. SARS-COV2 requires certain protein receptors, both recognized and unrecognized that are allowing cellular invasion, as shown through these nanosponges. Following that, nanoponges are incubated in SARS-COV2, that will be neutralized and unable to infect cells. Virus mutations are inhibited by the nanosponge. The detected host cell will retain information on the target of virus and the nanosponge would be capable to neutralize it[24].

B. NON-CLINICAL APPLICATIONS:

1). Water Purification

β-cyclodextrin nanosponges are entirely water insoluble and have the ability to encapsulate organic contaminants in water[20]. The traditional way to purify water via using activated carbon and zeolites has been shown to be insufficient at very trace amount of pollutants in water. β-CDNS may firmly bind to organic contaminants in water, this polymer is 10,000 much efficient as compared to conventional systems for eliminating organic contaminants from water[3].

Implantation of ceramic porous filter with these nanosponges create organic/inorganic hybrid filtration modules. These hybrid filter modules have been proven to efficiently clean the water and remove a wide range of contaminants[12]. This minimizes an expense of cleaning. Cyclodextrin nanosponges are being employed to extend the container life for *"Dianthus caryophylluscut flowers"*[3].

2). Biomedical Engineering

For proteomic purposes, polyionic nanosponges is used to fractionate peptides through MALDI-MS analysis. During cancer research, they are potentially employed as biomarkers. Gases including oxygen and carbon dioxide are transported by hyper cross-linked NS. Oxygen carried by nanosponges are used to deliver oxygen to hypoxic tissues involved with pathological conditions such as COPD (Chronic Obstructive Pulmonary Disease)[3].

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XIII.TOXICOLOGICAL REFLECTIONS OF NANOSPONGES

According to all investigations on toxicity, the cyclodextrin inclusion complexes given orally in rats were practically non-toxic, a feature linked to a lack of absorption by the gastrointestinal tract (GIT). CD-NS were found to be non-haemolytic up to 20mg/ml during haemolytic activity testing on healthy red blood cells. The cytotoxicity of NS on HT-29 cells revealed that contact time for 24 and 48 hours did not result in the decline in cell viability, however exposure for 72 hours resulting in the modest drop in cell viability[6].

TABLE IV BIOPHARMACEUTICALCLASSIFICATIONSYSTEM:CLASS-II DRUGS[1,8,20]

DRUG CATEGORY	DRUGS
Antianxiety agents	Lorazepam
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
Antiarrhythmic agents	Amiodarone hydrochloride
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
Anticoagulant	Warfarin
Antiepileptic agents	Phenytoin
Antidiabetic agents	Glibenclamide, Glipizide, Troglitazone
Antihyperlipidemic drugs	Atorvastatin, Lovastatin, Fenofibrate
Antifungal drugs	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Voriconazole
Antihypertensive agents	Felodipine, Nicardipine, Nifedipine
Anti-histamines	Terfenadine
Antioxidant	Resveratrol
Antineoplastic drugs	Camptothecin, Docetaxel, Paclitaxel, Etoposide, Flutamide, Irinotecan
Antipsychotic agents	Chlorpromazine hydrochloride
Antiulcer drugs	Lansoprazole, Omeprazole
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
Antihelmintics	Albendazole, Mebendazole, Praziquantel
Diuretics	Chlorothiazide, Spironolactone
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Immunosuppressants	Cyclosporine, Sirolimus, Tacrolimus
NSAIDs	Dapsone, Diclofenac, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Nimesulide, Piroxicam
Gastroprokinetic agent	Cisapride
Steroids	Danazol, Dexamethasone
Miscellaneous	Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone

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TABLE V MARKETED FORMULATIONS OF NANOSPONGES[12,24]

DRUG	CATEGORY	ROUTE	DOSAGE FORM	TRADE NAME
Piroxicam	Anti-inflammatory	Oral	Capsule	Brexin
Iodine	Antiseptic	Topical	Solution	Mena-gargle
Dexamethasone	Anticancer	Dermal	Ointment	Glymesason
Alprostadil	Erectile dysfunction	Intravenous	Injection	Prostavasin

TABLE VII SOME ILLUSTRATIONS OF NANOSPONGES[3,5,12,20]

DRUG	CLINICAL USE	NANOSPONGE VEHICLE	CROSS-LINKER	STUDY
Paclitaxel	Cancer	β-Cyclodextrin	Cabonyldiimidazole	Bioavailability Cytotoxicity
Camptothecin	Cancer	β-Cyclodextrin	Diphenyl Carbonate	Haemolytic activity Cytotoxicity
Tamoxifen	Breast Cancer	β-Cyclodextrin	Dichloromethane	Cytotoxicity
Econazole nitrate	Antifungal	Ethyl Cellulose Polyvinyl Alcohol	Epichlorohydrin	Irritation Study
Dexamethasone	Brain Tumor	β-Cyclodextrin	Diphenhydramine	Drug Release
Itraconazole	Antifungal	β-Cyclodextrin Copolyvidonum	Cabonyldiimidazole	Saturation Solubility
Resveratrol	Antioxidant	β-Cyclodextrin	Cabonyldiimidazole	Cytotoxicity Stability Permeation
Anti-sense Oligonucleotides	Cancer Viral Infections	Sodium Alginate Poly L-lysine	Poly L-lysine	Pharmacokinetic Studies

XIV.CONCLUSION

The final conclusion of above study on the "Nanosponges'' are clarify that they reveal promising effect to improve and enhance the bioavailability and solubilities of poorly water-soluble drugs because of an ability to contain both hydrophilic and lipophilic drugs. They can be targeted at different sites in the body since their ability to interact with multiple functional groups. The chemical linkers provide a preferential target location to nanosponges for binding. This innovative agent has immense applications not just only in the pharmaceutical sectors, however also in the various fields that have already been discussed above in this article. We hope that this futuristic nanotechnology will play a prominence role in the future also.

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