IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

"NANOSPONGE: A NOVEL TREND OF DRUG DELIVERY SYSTEM"

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ABSTRACT
To developing effective and targeted drug delivery system has been dream for the reasearchers since couple of years. Nanotechnology shows the promising apporoach towards the developing the agent which has more and better advantages over the conventional drug delivery system. Nanotechnology has also shows the greatest impact in the field of life sciences, neutraceutical and manufacturing of biomaterials and others. The research on the nanosponge become a convinient step to deal with a a certain problems like as poor bioavailability, trug toxicity, targeted drug delivery and release of the drug in control and predictable manner. Nanosponge are the new class of the material and made up of microscopic particles with few nanometer wide cavities in which large variety of active drug substance (containing both hydrophilic and lipophilic) are encapsulated which release the drug in control manner. Nanosponge increases the solubility of the poorly water soluble drugs , increase drug bioavailability and release drug at specific site. In this review generally discussed about the nanosponge, their advantages and disadvantage, characteristics and properties, method of preparation, mechanism, factors affecting nanosponge, their evaluation parameters as well as their application.

Keywords: Nanospoge, Cyclodextrin, Drug delivery, Bioavailability.

1. Introduction
In recent years, taking the significant step in the investigation and research of new drugs had made health-care system more expensive as compared to conventional drug delivery systems and techniques for the optimization of therapy and cost-effective treatment, many researches are carried out on drug delivery systems [2]. The method from which a drug is delivered imparts significant effect on drug efficacy. Some drugs in optimum concentration range within which they shows maximum benefit , and concentrations above or below this range become a toxic or shows no therapeutic benefit . On the other side, the slow progress in the efficacy of the treatment of severe diseases, has suggested a more need of a multidisciplinary approach to the delivery of drug in targeted tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics parameters of the drug, The non-specific toxicity of drug, immunogenicity, biorecognition, and efficacy of drugs were created. These new ideas and strategies called Novel drug delivery systems (NDDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology [11].

The development in a field of nanotechnology has been started to change the basis of disease diagnosis, their treatment and prevention. Various types of nano-devices show significant effects on medical technology, greatly improves the efficacy of many drugs and construct the brand-new treatment methods [9]. Nanotechnology created variety of the formulations like nanoparticles, Nano capsules, Nano spheres, Nano suspensions, nanocrystals, nano-erythosomes etc. Nanotechnology is defined as creation and manipulation of materials at nanoscale level to make a product and formulation that have novel properties. In recent years, nanomaterials are getting a more attention. In 1959 Richard P. Feynman, a physicist, at Cal Tech, forecasted about nonmaterial. He said that, "There is plenty of room at the bottom," and suggested that scaling down to nano level and starting from the bottom was the key to future advancement in nanotechnology. Nanomaterials are defined as materials that are having at least one dimension in the 1-100 nm range. Depending on the method, the nanoparticles are classified into three types[18].

1. Encapsulating Nanoparticles: This type is generally represented by nanosponges and nanocapsules. Nanosponges like as alginate nanosponge, which have sponge like nanoparticles containing many holes which carry the drug molecules. Nanocapsules such as poly (isobutyl cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They entrap drug molecules in their aqueous core.

2. Complexing Nanoparticles: This category involves complexing nanoparticles, which attracts the molecules by electrostatic charges.

3. Conjugating Nanoparticles: These conjugating nanoparticles link to drugs by covalent bonding [18].

Nanosponges are the new class of structures based on hyper reticulated polymers which have cavities in the nanorange [1] .Nanosponges are tiny mesh-like structures that may shows significsnt effect in the treatment of many diseases , Nanosponges are made from the microscopic particles which has few nanometers wide cavities, in which a large variety of substances are encapsulated. These particles have ability to carry both lipophilic and hydrophilic substances and increase the solubility of poorly water soluble molecules. Nanosponges are insoluble in water and organic solvents and stable at high temperatures ranges upto the 300oC [10]. Nanosponge technology reduces the side effects, increase effectiveness of the drug, increases stability of formulation ,flexibility and bioavailability . Nanosponge has properties like they are non-mutagenic, non-irritating, non-toxic and non-allergenic[1]. Nanosponge is a virus sized, naturally degradable scaffold like structure[9]. They are solid in nature. They are found safe for oral administeration and invasive routes; so they act as an inherent carrier for drug delivery. For oral administeration, the complex are dispersed in the matrix of excipients (diluents, lubricants and anti-caking agents). For parenteral administeration , the complex carried in the sterile water, saline or other aqueous solutions. For topical delivery nanospong are effectively incorporated into topical hydrogel. Nanosponges are the encapsulating type of nanoparticles which encapsulates the active therapeutics within thrie core. A nanosponge are circulated in the body until they reach the specific target site, attach on the surface and release the drug in a predictable manner[12]

FORMATION

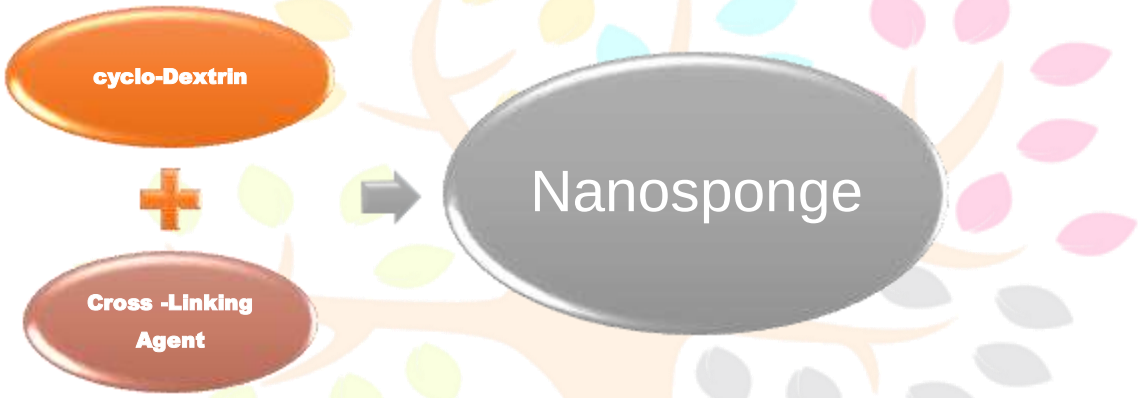

Figure 1 Formation of nanosponge

The polyesters (cyclodextrins) are reacted with the appropriate cross linking agents, a novel nanostructure material is obtained, generally called as nanosponges [12].The nanosponges shall formulated of a specific size and to release the drugs over time by vary in proportion of cross linker to polymer[17]..Nanosponges shall formulate as neutral or acids and shall swellable according to the agent used as the crosslinker. The total effect is to form spherically shaped particles filled with cavities within drug molecules are stored. The cross-linking-to-cyclodextrin ratio shall changing during manufacting to improves the drug loading and to obtain a tailored release profile. Their highly porous nanomeric nature makes drug molecules to orient themselves in nanosponge's inclusion as well as interact in the non-inclusion fashion, which gives higher drug loading compared to the parent cyclodextrin molecules [14].

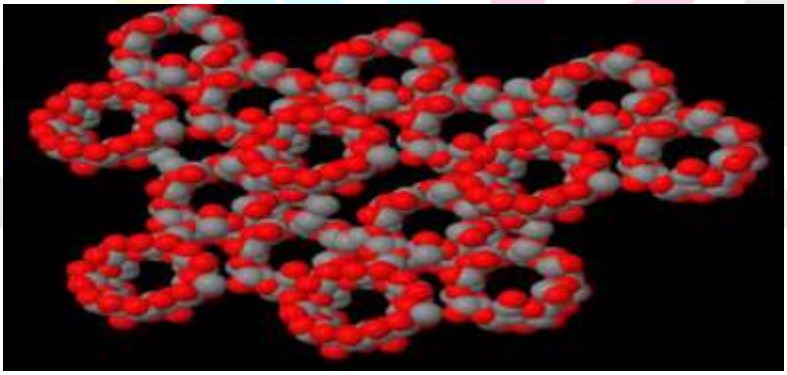

Figure 2Molecular structure of cyclodextrin carbonates nanosponges.

TYPES OF NANOSPONGE:

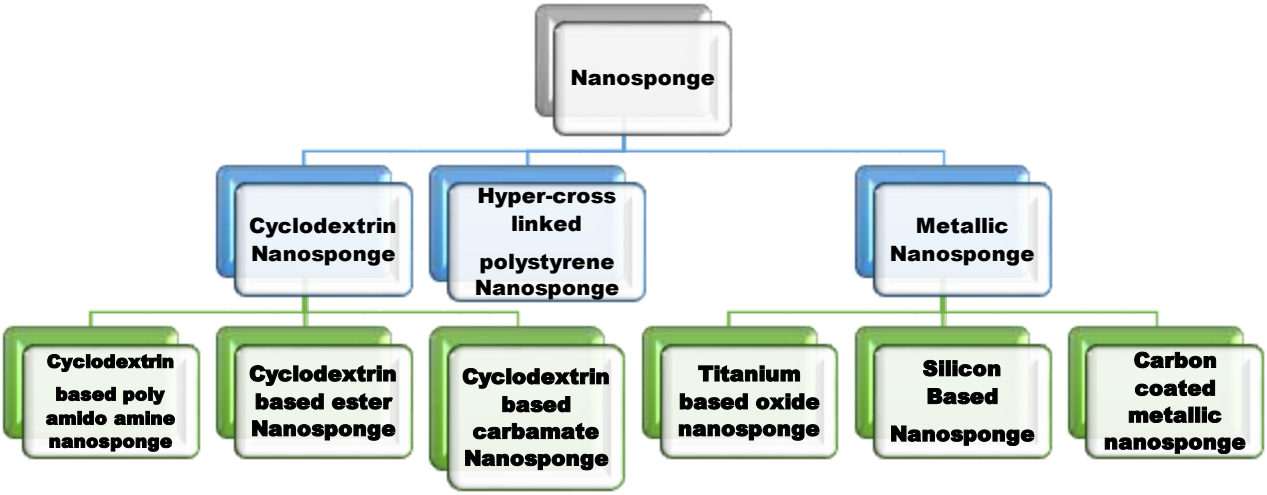

Figure 3 Types of nanosponge

1. Titanium Dioxide (Tio2) NS

Titanium dioxide (TiO2) nanosponge are explained as a porous metal oxide nanoparticle . Porous metal oxide NS are more popular because of their bulk analogs (nonporous) so they shows pronounced physical and chemical properties . Their high porosity resulted in more surface area, high mass transfer, and electron mobility. Varieties of methods are reported for manufacturing TiO2 NS. A method to formulate TiO2 NS has been reported by Guo et al. This method generally involves the synthesis of functional polystyrene nano dispersion which is used as a template for coating TiO2 by hydrolysis of tetra-n-butyl titanate. Metal oxide NS of TiO2 either alone or in combination with other metals have been created for various applications. Some applications involve photo catalytic properties, high-performance supercapacitors, Hydrogen chemical sensors, recyclable oil absorbents [5].

2. Silicon Ns (Si NS)

Porous Silicon particles are the derivatives of elemental Silicon (Si), they are sponge-like structures formed by chemical or electrochemical etching of bulk Si. Since the discovery of their room temperature photoluminescence by Canham in 1990, porous Si particles have been created for variety of applications. Their use in microelectronic, as chemical and biological sensors is well described. The major roles of Si NS are in areas of photoluminescence and cellular patterning on account of luminescence and light emitting properties of Si. Si porous particles are commonly synthesized by electrochemical etching of Si particles under ultrasonic agitation to get ordered pore structure. The method reported by Tasciotti et al involves use of heavily doped p++ type silicon wafer used as the substrate coated with silicon nitride. They are made into a porous Si using photolithography. The porosity of the synthesized particles was adjusted by changing in the current density and ratio of hydrofluoric acid and ethanol. Another method reported by Chadwick et al involves use of metallurgical grade silicon powder and its chemical etching in mixture of nitric acid and hydrofluoric acid [5].

3. Polystyrene Based Ns

Nanosponges are tiny mesh-like structures and are the size of virus with a naturally degradable polyester. The long chain polyesters are mixed in solution with cross linkers that have an affinity for certain portions of the polyesters. The drug is stored within the cross-link segments of the polyester to make a spherical shape that has numbers of cavities, where the nanoscale materials are sufficiently small to be significant in passing through or attached to the cell membranes. The NS are synthesized in a specific size and release drugs over time and not just in the fast mode, like other delivery methods. The engineering capacity of nanosponge is due to the relatively simple chemistry of its polyesters and linking material (peptides). The polyester is biodegradable, hence they breaks in the body, the drug is released in a prescribed manner. Hyper cross-linked polystyrene has a low density, micro porous and transparent material that has an inner surface area measuring approx 1000 m2/g and have high absorption capacity. For the easy of mass transfer, they are also subjected with transport pores which are opaque. Hyper cross-linked polystyrene sorbents are used in large scale adsorption of organic compounds from aqueous gaseous medium. They are also used in solid-phase extraction of trace compounds. The formation process of this type of nanosponge is relatively different. A long polymeric chain first extends from the initial solution and remains strongly solvated through the entire period of network formation. Then the cross-linking bridges emerge through the volume of the reacting system with a uniform distribution . Polystyrene NS are used in implant material, drug delivery system and diagnostic system. Polystyrene NS were developed for drugs delivery of cancer drugs like paclitaxel and temozolomide[5].

4. Cyclodextrin (CDs)

CDs and their derivatives have been used form couple of years to make inclusion complexes with variety of the drug molecules for solubility improvement or controlled release of the drug. CDs are a family of sugar compounds that are bound together in a cyclic ring (cyclic oligosaccharides). Cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers which causes enzymatic degradation of starch**.** They were first discovered by a Villers which was further

explained by Schrodinger who described two crystalline compounds, β dextrin and α dextrin. CDs are non-reducing, crystalline, water-soluble, cyclic oligosaccharides composed of 5 or more anhydrous -D-glucopyranoside units (AGU) linked together by an a-1,4-bond. Six, seven, or eight are generally present in CD and are known as α, β, and γ-CD, respectively. CDs have a cylindrical cone with a cavity of about 7.9–8 × 10–10 m deep and 5–10 × 10–10m in diameter, which is depends upon the number of glucose units. Beta-CD (β-CD) based NS are hyper cross-linked cyclic oligomers which have nanochannels in which both hydrophilic and hydrophobic drugs can be encapsulated. This porous network has a colloidal size with a diameter of less than 1 μm and this is available in crystalline or amorphous forms. NS can be prepared by using variety of the cross-linking agents' carbonyl diimidazole, triphosgene, diphenyl carbonate, etc [5].

CHARACTERISTICS:

- Nanosponges provide a range of dimensions (1 μm or less) with tunable polarity of the cavities.
- Nanosponges of specific size are formulated by changing in the crosslinker and polymer ratio.
- They occurs in paracrystalline or crystalline forms, depending on the process conditions.
- Crystal structure ofnanosponges plays a vital role during the complexation with drugs.
- Drug loading capacity of Ns mainly depends on the degree of crystallization.
- Variety of drug loading capacities is shown by paracrystalline nanosponges.
- Ns are nontoxic, porous particles, insoluble in most of organic solvents and stable at temp upto 300 ℃.
- Ns are stable at the pH range of 1-11.
- They form clear and opalescent suspension in water.
- They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
- Their three-dimensional structure allows capture, transportation and selective release of a variety of substances.
- They can be sited to different target sites because of their capacity to link with different functional groups.
- Chemical linkers permit nanosponges to bind preferably to the target site.
- By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.
- By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges [12, 13, 18].

ADVANTAGES:

- Improve aqueous solubility of lipophilic drugs.
- To protect the molecules and to develop drug delivery systems for various administration routes.
- They mix with water and are used as a transport for fluid.
- To mask unpleasant flavors.
- The chemical linkers enable the NSs to bind specifically at the target site.
- These formulations are stable over range of pH 1 to 11.
- These formulations are stable at higher temperatures.
- These formulations are compatible with most vehicles and ingredients.
- These are self-sterilizing as their average pore size is 0.25μm where bacteria cannot penetrate.
- These formulations are free flowing and can be cost effective.
- Nanosponges are non-irritating, non-mutagenic, non-allergic, and non-toxic.
- Allows for the incorporation of immiscible liquids, which improves material processing by converting liquids to powders.
- Commercial production is easy to scale up.
- Nanosponges can be regenerated using eco-compatible solvents, inert hot gases, mild heating, and changing strength.
- Nanosponges help to remove the toxic and venom substance from the body.
- Reduce dosing frequency.
- Better patient compliance. [12,13,17,18,22]

DISADVANTAGES

- Nanosponges could be either paracrystalline or in crystalline form.
- The loading capacity of nanosponges depends mainly on degree of crystallization.
- Paracrystalline nanosponges can show different loading capacities
- Nanosponges can only hold encapsulated molecules and are therefore unsuitable for bigger molecules.
- Dose dumping is a possibility. [5,12,13,17,22]

PROPERTIES

- Nanoporous structures have been broadly classified into nanoporous membranes, nanoporous hydrogels and nanoporous particles.
- NS fall into the category of nanoporous particles.

- CD-NS have been reported as white fine powders, insoluble in water and common organic solvents.
- The academic studies and pharmaceutical industry have found nanosponges to be effective drug delivery systems.
- Nano-sized carriers have recently been applied for adsorption, separation, and catalysis due to their considerable internal surface areas and pore volumes.
- The thin line of distinction among nanoparticles and NS is the difference in porosity and size.
- Nanoparticles have size in nanometer whereas NS have pores in nanometers while their overall size can extend up to micrometers, and are usually smaller than 5 μm.
- CD-NS have colloidal dimensions which form clear or opalescent suspensions in water depending on their concentration.
- NS show different domains in their structure, since they have both hydrophobic and hydrophilic groups [21]

COMPOSITION OF NANOSPONGES

Polymer

The selection of polymer can impact the formation along with the frunctioning of Nanosponges. The cavity size must be appropriate in size to incorporate the particular drug molecule. The polymer selection is depends upon the required release and drug to be enclosed. The selected polymer should have the specificity to attach with particular ligands [17]

Cross linking agent

The cross linking agent selection can be carried out based upon the structure of polymer and the drug which is to be prepared [17]

Drug substance

- Molecular weight between 100-400 Daltons.
- Solubility in water is less than 10 mg/ml.
- Drug molecule consists of less than five condensed rings.
- Melting point of substance is below 250 °C[17]

Table no. 1. List of polymer and crosslinkers used in Nanosponges

Polymers	Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA
Crosslinkers	Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2- bis(acrylamido) Acetic acid and Dichloromethane

TECHNIQUES FOR PREPRATIONS OF NANOSPONGE

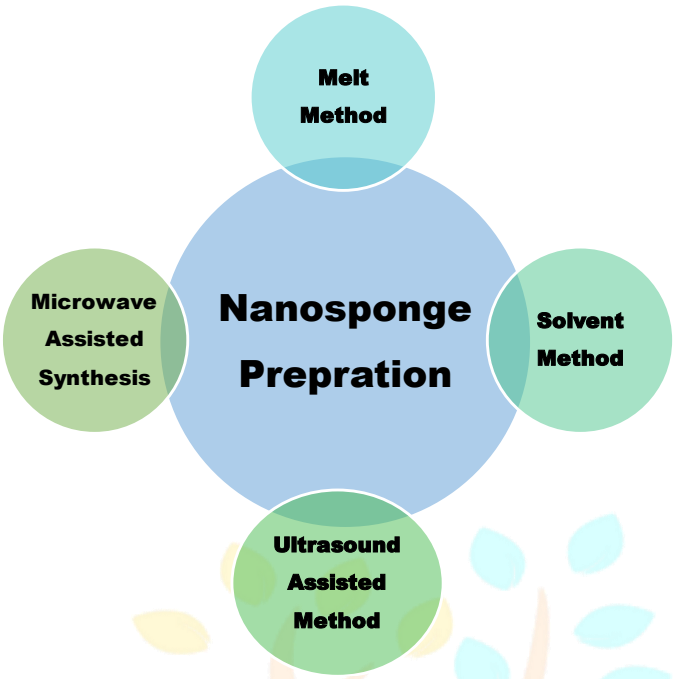

Figure 4 Techniques for preparations of nanosponges.

1. Melt method[22]

In melt method, cyclodextrin reacts with a appropriate crosslinker like as dimethyl carbonate, diphenyl carbonate, isocyanates, diaryl carbonates, carbonyldiimidazole (C7H6N40), carboxylic acid anhydrides, and 2, 2-bis (acrylamide) acetic acid. All of the ingredients are appropriately integrated and placed in a 250 mL flask heated to 100°C for about 5 hours with the help of magnetic stirrer. The mixture is allowed to cool before the resulting product is broken down and washed with a particular solvent to remove nonreacted excipients.

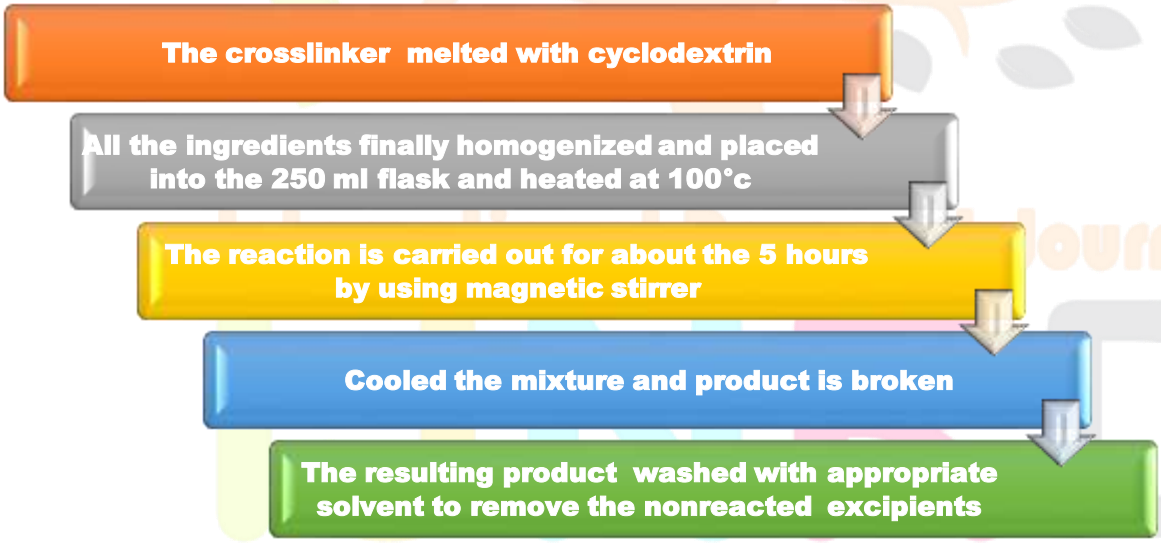

Figure 5 Schematic Representation of Melt Method.

2. Solvent Method[1]

In this method, a polar aprotic solvent, such as dimethyl formamide or dimethyl sulfoxide, is mixed with a suitable polymer , in a molar proportion of 4–16, this blend is blended with the excess quantity of crosslinker. The reaction is followed at temperatures ranging from 10°C to the solvent's reflux temperature for period of about 1 to 48 hours. Carbonyl compounds like as the dimethyl carbonate and carbonyl diimidazole (C7H6N4O) are mostly used crosslinkers. On finalization of the reaction, the mixture is allowed to cool at room temperature, after which the chemical is united with an plenty of distilled water, enhanced by percolation under vacuum, and immedistely purified by prolong Soxhlet extraction with ethanol, and finally dried under the vacuum. The dry product is crushed in a mechanical mill to make a uniform fine powder.

3. Microwave assisted synthesis [33]

It is the simplest method for formulating the CDNS by microwave irradiation, remarkably slow down the reaction time. The formed Nanosponge acquire higher degree of crystallization in comparison with the common melt method, microwave assisted fabrication had showed four time reduction in reaction time. The process lead to production of particles of homogeneous distribution and crystallinity.

4. Ultrasound Assisted Method [1]

Nanosponge is prepared by the reacting polymers with cross-linkers in the absence of solvent and under sonication in this process. This path will produce spherical and uniformly sized nanosponges. In a flask, combine the polymer and cross-linker in a correct molar ratio. Heat the flask to 90 ºc in an ultrasonic bath filled with water for about the 5 hours, sonicate the mixture. Allow the mixture to cool before breaking the resulted into pieces. washed the product with excess water to remove the unreacted polymer, then purify with ethanol after a prolonged soxhlet extraction. Dry the finished product under vacuum and keep it at 25℃.

LOADING OF DRUG INTO BLANK NANOSPONGE

For drug delivery NS should be digested to get a mean particle size below 500nm. Put the nanosponges in water and sonicate to avoid the formation of aggregates and then centrifuge the suspension to get the colloidal fraction. Separate out the supernatant and dry the sample using freeze drying. Prepare the aqueous suspension of Nanosponge and add the much quantity of the drug and maintain the suspension at constant stirring for specific time necessary for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of NS by solvent evaporation or by freeze drying[8] .Crystal structure of nanosponge plays a major role in complexation with drug. A study explained that paracrystalline nanosponges showed different loading capacities as compared to crystalline nanosponges. The drug loading capacity is greater in crystalline nanosponges than paracrystalline [34]

FACTORS AFFECTING NANOSPONGE FORMATION

1. Type of polymer [22]

The type of polymer used can have an influence on the prepration and functioning of NS. The cavity size of a nanosponge should be enough to incorporate a drug molecule of a particular size for complexation. The type of polymer used in nanosponges can have an influence on their prepration and functioning. A cross-linker polymer with high efficiency create molecular nanocavities into a 3D nanoporous structure.

a) Hydrophilic Nanosponge: Epichlorohydrin is used as a cross linker to prepared hydrophilic nanosponge. Even in fast release formulations, hydrophilic nanosponges can change the drug release and boost drug absorption across biological barriers, assess them as effective drug carrier.

b) Hydrophobic Nanosponge: As a crosslinker, diphenyl carbonate, pyromellitic anhydride, diisocynates, and carbonyl diimidazole can be used to formulate hydrophobic nanosponges. They serve as sustained release carriers for water-soluble drugs such as peptides and proteins.

2. Type of drugs and Medium Used for Interaction [35]

Certain properties of drug compounds that will be complexed with nanosponges are listed below.

a) Molecules with a molecular weight of 100 to 400 Daltons

b) The drug molecule is made up of no more than five condensed rings.

c) Water solubility is less than 10 mg/ml.

d) The substance's melting point is less than 250℃.

3. Temperature [36]

Drug/Nanosponge complexation is affected by changes in temperature. The ennormity of the stability constant of the Drug/Nanosponge complex decreases with increasing temperature; this is because of reduction in drug/nanosponge interaction forces such as van der Waal forces and hydrophobic forces. Due to the drug/nanosponge interaction forces are reduced as temperature rises, the apparent stability constant decreases in ennormity. As a result, when making nanosponges, it's essential to keep the temperature under control.

4. Method of preparation [36]

Drug/Nanosponge complexation can be influenced by how the drug is loaded into the nanosponge. However, because the success of a method is dependent on the nature of the drug and polymer, freeze drying has been shows the most successful approach for drug complexation in many conditions.

5. Degree of substitution [37]

The type, number, and position of the substituent on the parent molecule may have a significant influence on the NS capacity to complex. There is a direct relation between the number of substitutions present and the degree of cross linking; the more substituent's present, the greater the possibility of higher cross linking. Because of additional linkages between polymers forming a mesh like network, higher degrees of cross linking will give highly porous NS. The position of substitution is determined by the conditions of production of NS. Because of occupancy of a different position by the functional group on the parent molecule, a change in prepration method will resulted in materials which have different physicochemical properties.

EVALUTION OF NANOSPONGES

1. Particle size and polydispersity index [22]

Dynamic light scattering, using a 90 Plus particle sizer with MAS OPTION particle sizing software, or laser light diffractometry, using a Malvern Zetasizer can be used to estimate particle size. The mean diameter and polydispersity index can be calculated using this information.

2. Morphology and surface topography[22]

By coating the drug, nanosponges, and the product (drug/nanosponge complex) with gold–palladium under an argon environment at room temperature, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) can be used to analyze the morphology and surface topography of the drug, nanosponges, and the product (drug/nanosponge complex). The production of inclusion complexes is shown by the difference in crystallization states of the raw materials and the finished product as observed under an electron microscope.

3. Thermo analytical methods[22]

Before the nanosponge is thermally destroyed, thermoanalytical methods are used to see whrer the drug alteration occurs. A drug substance alteration involves melting, evaporation, disintegration, oxidation, and polymorphic transitions. The formation of a complex is implied by the presence of in the alteration of drug substance. The thermogram produced by DTA and DSC can identify broadening, shifting, the formation of new peaks, and the elimination of certain peaks. Weight loss changes can also be employed to support the formation of inclusion complexes.

4. Single crystal X-ray structural analysis and X-ray diffractometry [17]

Inclusion complexation in the solid state can be measured using powder X-ray diffractometry. The crystalline character of the drug is changed by the complicated synthesis of the drug in nanosponges, which alters the diffraction patterns. The complicated creation causes existing peaks to sharpen, the creation of a few new peaks, and the shifting of some summits. The complex development is shown by the variation in diffraction patterns are useful in determining the chemical decomposition and complicated development of a mixture of chemicals. The exact inclusion structure and manner of interaction can be measured by single crystal X-ray structural analysis. The interaction between the host and guest molecules and exact geometrical relationship can be identified.

5. Infra-Red spectroscopy [1]

The interaction between nanosponges and drug molecules in the solid state is determined using infrared spectroscopy. When the fraction of the guest molecules encapsulated in the complex is less than 25%, bands that may be assigned to the included part of the guest molecules are easily obscured by the bands of the nanosponge spectrum. The technique is less correctively than other techniques and is not generally used for detecting inclusion complexes.

6. Thin Layer Chromatography [39]

The Rf values of a drug molecule decrease significantly in Thin Layer Chromatography, which help in determining the complex formation between the drug and nanosponge.

7. Loading efficiency and production yield [8]

The following equation can be used to measure the loading efficiency (%) of nanosponges.

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

After determining the exact start weight of the raw materials and the final weight of the nanosponge obtained, the following equation can be used to calculate the production yield of nanosponges.

$$\text{Production yield} = \frac{\text{Practical mass of NS}}{\text{Theoretical mass}} \times 100$$

8. Resiliency [40]

Sponge resiliency (viscoelastic characteristics) can be altered to generate softer or firmer beadlets depending on the final formulation's requirements. The rate of release is slowed by increased cross linking. As a result, the resiliency of sponges will be investigated and optimized in accordance with the requirements, taking into account release as a function of cross-linking with time.

9. Solubility studies [38]

The phase solubility method proposed by Higuchi and Connors, which evaluates the effect of a nanosponge on drug solubility, is the most commonly used method for studying inclusion complexation. The degree of complexation is indicated by phase solubility diagrams.

10. Zeta potential [35]

Surface charge is measured by the zeta potential. An additional electrode in the particle size equipment can be used to measure it. Nanosponges containing materials were extracted and diluted with 0.1mol/l KCl before being placed in an electrophoretic cell with a 15V/cm electric field applied. After averaging the complete measurement, the mean hydrodynamic diameter and poly dispersity index were computed.

11. Dissolution test [39]

The dissolution profile of nanosponges can be analyzed using modified USP XXIII dissolving equipment with a 5m stainless steel mesh basket rotating at 150 rpm. To achieve sink conditions, the dissolution medium is chosen while considering the solubility of the actives. Analytical methods can be used to analyze samples from the dissolving media.

12. Microscopy studies[40]

The microscopic aspects of the drug, nanosponges, and the result (drug/nanosponge complex) can be studied using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The production of complex

formation is shown by the difference in crystallization states of the raw materials and the finished product as observed under an electron microscope.

13. Drug release kinetics [22]

The release data was analyzed using Zero order, First order, Higuchi, Korsemeyer-Peppas, Hixon Crowell,Kopcha, and Makoid-Banakar models to examine the mechanism of drug release from the Nanosponge.Graph pad prism software can be used to analyze the data. The software calculates the parameters of a nonlinear function that gives the best match between experimental data and the nonlinear function.

APPLICATIONS

Applications of Nanosponges

Nanosponges have the ability to incorporate drugs within their structure, generally as inclusion complexes or as non-inclusion complexes. By virtue of their biocompatibility and versatility, nanosponges have many applications in the pharmaceutical field.

1. Solubility enhancement [36]

For the development of various pharmaceuticals the greatest limit is the low water solubility of many drugs. About 40% of new drugs are poorly soluble in water, which influence their clinical application. To make a formulation of poorly water-soluble drugs constitutes a problem that is difficult to solve. Nanosponges can increases the wetting and solubility of molecules with very poor solubility in water. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be improves. The bioavailability problems of many formulations can be solved by increasing the solubility and dissolution rate of a substance, and nanosponges can greatly improves the drug solubility.

2. Sustained delivery system [42]

To formulate a modified-release product is generally intended to improve the treatment regimen by providing slow, continuous delivery of the drug over the entire dosing intervals. This makes it possible to decrease the dose administered, change the pharmacokinetic profile, and decrease side effects. The drug release kinetics from nanosponges can be obtained with a prolonged release profile over time by using suitable polymers and cross linking agents. Nanosponges can be used to keep and prolong the release of volatile molecules, such as essential oils, following their encapsulation.

3. Oral delivery systems [42]

The dissolution rate of a solid drug is a limiting factor for oral bioavailability. For hydrophobic drugs, the dissolution process acts as the rate-determining step and therefore, determines the rate and degree of absorption. As a result, many hydrophobic drugs show variable and incomplete absorption from the gastrointestinal tract. For the oral administration, the complexes may be dispersed in a matrix of excipients, diluents and lubricants suitable for the preparation of capsules or tablets.

4. Topical delivery systems [8]

Conventional dermatological and personal care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short-term overmedication followed by long term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy. Nanosponges can encapsulated a wide variety of substances, and then be incorporated into a formulated product such as a gel, lotions, cream, ointments, liquid or powder. Nanosponges can be used in gels or creams for topical application. The ability of nanosponges to improves the uptake of the guest molecule by the skin can be attributed to the capacity to enhance solubility at the surface of the skin.

5. Protein delivery [22]

A novel synthetic route was used to generate swellable cyclodextrin-based nanosponges for protein delivery. New swellable cyclodextrin-based poly (amidoamine) nanosponges (PAA-NS) were formulated by cross-linking -cyclodextrin with either 2,2-bis(acryl amidoacetic acid) or a short polyamido-amine chain derived from 2,2-bis(acryl amidoacetic acid) and 2-methylpiperazine, respectively. Using the high pressure-homogenization approach, PAANS was reduced in nanosuspensions. The pH of the surrounding media was found to affect the swellable nanosponges.

6. Gas delivery [22]

Nanosponge formulations can be used to store a variety of gases. The ability of -CD nanosponges to kept substantial volumes of carbon dioxide,

1 methylcyclopropene, and oxygen has been demonstrated. Many biomedical applications could useful from the complexation of oxygen or carbon dioxide. The oxygen-filled nanosponges, in particular, could provide oxygen to hypoxic regions found in a variety of diseases. As oxygen encapsulating formulations, three distinct cyclodextrin nanosponges were produced by cross linking α-, β-, or -cyclodextrin with carbonyl di-imidazole. Both in the presence and absence of ultrasound, the nanosponges were able to release oxygen (US). A nanosponge/hydrogel combination technique was used to achieve oxygen penetration across a silicone membrane.

8. Removal of Organic Pollutants from Water[43]

B-cyclodextrin Nanosponges are completely insoluble in water, have the property of encapsulating organic pollutants from water. Ceramic porous filters can be saturated with these Nanosponges resulting in hybrid organic/inorganic filter

modules. These hybrid filter modules were tested for the effective purification of water, employing a variety of water pollutants. It has been established that polycyclic aromatic hydrocarbons (PAHs) can be removed very efficiently (more than 95%). Representatives of the pollutant group of trihalogen methanes (THMs), monoaromatic hydrocarbons (BTX), and pesticides (simazine) can also be removed (>80%).

9. Nanosponges for cancer therapy [44]

Because of their limited solubility, anticancer drug distribution is one of the most difficult tasks in the pharmaceutical industry now a day. The nanosponge complex is three times more effective than direct injection in reducing tumour growth. The complex of the nanosponge loads a medicine and exposes a targeting peptide that binds strongly to the tumour receptor's radiation-induced cell top layer. When nanosponges come into contact with a tumour cell, they adhere to its surface and begin to release medication molecules. Targeting drug delivery has the advantage of providing a more effective therapeutic impact at the same dose with fewer side effects.

10. As absorbent in treating poison in blood [44]

By absorbing the toxin, nanosponges can remove the hazardous harmful chemical from our blood. Instead of utilizing antidotes, we can use nanosponges injected into the bloodstream to absorb the toxins. The nanosponge imitates a red blood cell in the bloodstream, fooling toxins into attacking it and then absorbing it. The toxin determines how many poison molecules each nanosponge can absorb.

11. Biomedical applications [45]

Both hospitals and the medical industry depend primarily on oxygen, which can be difficult to store at times.Carbonate nanosponges based on cyclodextrin were designed to form inclusion complexes with several gases such as carbon dioxide, methylcyclopropene, and oxygen in a novel attempt to overcome this difficulties. These oxygencarrying nanosponges can be used to provide oxygen in hypoxic conditions.

12. To provide stability [45]

Nanosponges have the ability to selectively trap a few families of protein molecules from the blood, allowing them to be protected from enzymatic breakdown.

FUTURE PERSPECTIVES

Due to the unique characteristics of the nanosponge drug delivery system holds a promising approaches in variety of pharmaceutical applications in the upcoming future; which makes it flexible to design and develop a novel product forms. The actual difficulties in future are the development of the delivery systems for oral peptide and other susceptible biomers. The use of biocompatible and biodegradable polymers for drug delivery is allow it for the safe delivery of the actives by various routes. As these porous systems have also been studied for drug delivery through pulmonary route; which represents that, these system has effective drug release even in the short supply of the dissolution fluid, thus colon targeted delivery may be able to expand like such as never before. Nanosponge particles can also be used in cell culture media.

EXAMPLES OF NANOSPONGES [18]

Drug	Nanosponge Vehicle	Category of drug	Study
Celecoxib	Betacyclodextrin, N, N-methylene bisacrylamide	NSAID	Solubility
Erlotinib	Betacyclodextrin	Tyrosine kinase inhibitor (Anticancer)	Solubility, bioavailability and In-vitro cytotoxicity.
Econazole Nitrate	Ethyl cellulose, PVA	Antifungal	Irritation study, Adsorption
Isoniazid	Ethyl cellulose, PVA	Anti-tubercular	Drug release
Cephalexin	Ethyl cellulose, PVA	Antibiotic	Drug release and Stability
Norfloxacin	Betacyclodextrin and Diphenylcarbonate	Antibiotic	Bioavailability
L-Dopa	Betacyclodextrin	Parkinson's Disease	Drug release
Fenofibrate	Maize starch, SDS	Fibrate	Solubility and Bioavailability
Nifedipine	Betacyclodextrin	Calcium channel blocker	Solubility
Glypizide	Betacyclodextrin	Sulfonylurea	Drug release
Ibuprofen	Ethyl cellulose and PVA	NSAID	Drug release
Resveratrol	Cyclodextrin	Antioxidant	Stability, cytotoxicity and permeation
Paclitaxel	Betacyclodextrin	Antineoplastic	Bioavailability
Camptothecin	Betacyclodextrin	Antineoplastic	Stability and solubility
Tamoxifen	Betacyclodextrin	Antiestrogen	Solubility
Temozolmide	Poly(valerolactineallylvalero lactone) and poly	Antitumour	Drug release

	(valerolactoneallylvalero lactone oxepanedione)		
Dexamethosan e	Betacyclodextrin	Antitumour	Drug release
Gamma-Oryzanol	Betacyclodextrin	Antioxidant	Stability
Telmisartan	Carbonated crosslinkers	Antihypertensive	Dissolution rate
Lysozyme	Cyclodextrin-based poly(amidoamine)	Enzyme	Solubility and drug release
Itraconazole	Betacyclodextrin, and copolyvidonum	Antifungal	Solubility

CONCLUSION

Evolution on the existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety and efficacy. In the form of a Novel Drug Delivery System an existing drug molecule can get a new life. An appropriately designed Novel Drug Delivery System can be a major advance for solving the problems related towards the release of the drug at specific site with specific rate. Nanosponge has been recently been developed and proposed for specific side drug release, they can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability . Due to their small particle size and spherical shape these can be developed as different dosage forms like oral, parenteral and topical preparations. Nanosponges are a novel type of formulation made up of biocompatible cross-linked polymer with a flexible and cost-effective manufacturing method. This method allows substances to be entrapped, which reduces adverse effects, improves stability, and enhances elegance. Aside from drug delivery, they have potential use in cosmetics, biomedicine, bioremediation processes, agro-chemistry, and catalysis, among others. Drugs supplied in the form of nanosponges can be proven to be safe and effective.

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