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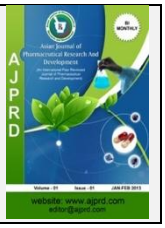

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Review Article

Systematic Overview on Nanosponges

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A B S T R A C T

Nano sponges are the most recent advancements in nanotechnology. The original goal of nanosponge delivery technology was to deliver topical medications. Water soluble and bioerodible polymers can now be used to administer medications orally. Nano sponges are permeable structures with a diameter of less than 1m, comparable to viruses in size. Because of their small size and porous nature, nanosponges can bind to poorly soluble medicines and increase their bioavailability. These nanosponges can bind to specific target sites and travel throughout the body. Begin the controlled release of the drug at the intended site. For the fabrication of nanosponges, numerous methods have been reported, including the melt method, solvent diffusion method, solvent method, ultrasound assisted approach, and sonication. Nanosponges for targeted medication delivery. A particular kind of nanoparticle is a nanosponge, which is often a synthetic polymer containing carbon. Because of its porous nature, which has pores ranging in size from 1-2 nanometers, they can be used to absorb trace amounts of material or toxins. In medicine, nanosponges are frequently employed as targeted drug delivery vehicles, detoxifying techniques, or post-injury damage management measures. They can also be employed in environmental applications, such as water purification or metal deposit removal, to improve ecosystems. Because of their microscopic size, they can move swiftly through liquids like blood or water, effectively locating and eliminating undesirable material. In order to increase their effectiveness when injected into the body, natural elements are frequently added to synthetically made nanosponges. The best are nanosponges. The prefix Nano implies that items of this size are measured on a scale of meters.

KEYWORDS: Small Size, Better Solubility, Controlled Delivery, and Nanosponge.

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INTRODUCTION:

Nanosponges, colloidal carriers, have been developed and proposedfor use in drug delivery. Nanosponges are microscopic structures that look like mesh. These are small, spherical, spongy, porous polymeric structures that release medication in a controlled and predictable manner. The average diameter of a nanosponge is less than 1m. Nanosponges can contain a diverse range of molecules due to the formationof inclusion and non-inclusion complexes. These particles can work with both hydrophilic and lipophilic materials. These are novel colloidal structurescomposed of solid nanoparticles with colloidal and nanoscale cavities based on hyper crosslinked polymers. They have hydrophilic branching on the outside and a hydrophobic chamber on the inside. The cross linker connects the polyester strand at specific points.by the cross linker to create a frame structure. To regulate the pore size, use the small size sponges can circulate all over the body until interact with the specific target site and stick on the surface and start releasing the drug in the control manner. they are free flowing, self-sterilizing, cost effective and stable over the range of Ph 1 -11 and temperature up to 130degree Celsius.**1,2**

Advantages of Nanosponges:

- Because nanosponge particles are water soluble, the hydrophobic drug can be encapsulated within the nanosponge.
- Targeted site-specific drug delivery.
- Less harmful side effects.
- These formulations are pH stable from 1 to 11.
- These formulations are temperature stable up to 130°C.
- It can be used to mask unpleasant flavors as well as to solidify liquid substances
- Biodegradable.
- By varying the proportion of cross linker to polymer, particles can be made smaller or larger.

- Consistent release.
- These are self-sterilizing due to their 0.25micron average pore size, through which bacteria cannot penetrate.
- Enhanced formulation flexibility, improved stability, and elegance.

Disadvantages of nanosponges:

- They can also be either paracrystalline or crystalline
- The degree of crystallization mostly determines the loading capacity of NSs.
- Only tiny molecules can be included in the Nanosponges
- Different loading capacities can be displayed using paracrystalline NSs

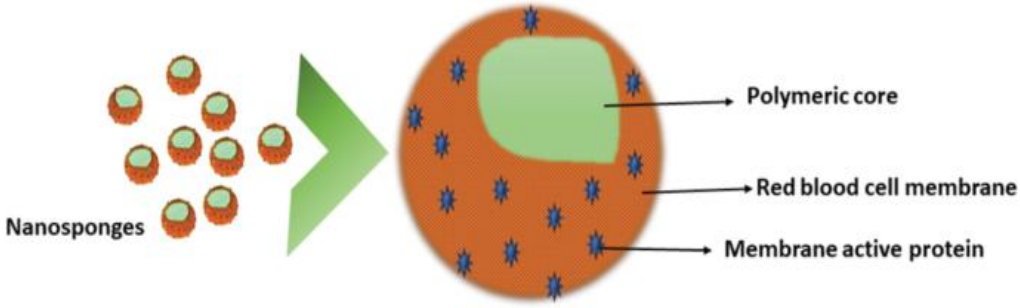

Figure 1: Nanoparticles

Characteristics of nanosponges:

- Because of their high aqueous solubility, NSs are primarily used to encapsulate poorly soluble drugs.
- They can transport both lipophilic and hydrophilic drugs and protect the drug from physicochemical degradation.
- By forming inclusion and non-inclusion complexes, NSs can encapsulate various types of molecules.
- They can remove organic contaminants from water.

Classification of Nanosponges

Materials Used:

A) **By method of associating with drugs.**

1. Encapsulating nanoparticles: Nanosponges are used to represent encapsulating nanoparticles. Nanosponges are sponge-like nanoparticles with many holes in their aqueous core that carry drug molecules.
2. Nanoparticle Complexation:Electrostatic charge attracts the molecules.
3. Nanoparticle conjugation: Nanoparticles form covalent bonds with drugs.

Table 1: Material Required for the Preparation of Nanosponges

Polymers	Hyper cross-linked polystyrene, cyclodextrin and its derivatives like methyl β-cyclodextrin, hydro propyl β-cyclodextrin
Cross linkers	CH-Diphenyl Carbonate, Diary carbonateDiisocyanatos, Pyromellitic anhydride, Carbonyl diimidazoles, Epicloridrine, Glutaraldehyde, Carboxylic acid dianhydrades,2,2-bis(acrylamide) Acetic acid and Dichloromethane
Copolymer	Ethyl cellulose (EC), Polyvinyl Alcohol (PVA)
Polara protectsolvent	Dimethyl sulfoxide (DMSO), Dimethyl formamide (DMF)

Method of Preparation of Nanosponges:

1] Melt Method:

By reacting cyclodextrin with a cross-linker, nanosponges are created. Widely used cross-linkers include dimethyl carbonate, diphenyl carbonate, diisocyanates, diaryl carbonates, carbonyl diimidazoles, carboxylic acid anhydrides, and 2,2-bis(acrylamido) acetic acid. All of the ingredients are finely homogenized before being placed in a 250ml flask and heated to 1000 degrees Celsius. The reaction was carried out over several hours, and the reactant mixture was uniformly mixed using a magnetic stirrer. The mixture was allowed to cool and the product was broken down. To remove any unreacted excipients, the finished product was washed with a suitable solvent. Wrightia tinctoria[3], Naproxen, Ibuprofen[4], Miconazole nitrate[5], etc.

2] Solvent Method:

A polar aprotic solvent, such as dimethylformamide or dimethyl sulfoxide, will be required. The aprotic solvent dissolves the polymer. The cross linker is treated with a polymer-aprotic solvent mixture. The cross linker must be used in large quantities. The cross linker/molar ratio of 4 to 16 is preferred. The reaction is carried out at a solvent reflux temperature and time interval ranging from 1 to 48 hours. The reaction has been completed, and the solution has been allowed to cool to room temperature. The formed product is mixed with an excess of double distilled water and filtered using a vacuum filter. The product is then purified using Soxhlet extraction with ethanol. Finally, the product is vacuum-dried and ground in a mechanical mill to obtain homogeneous powder. e.g., Flurbiprofen[6], Ciprofloxacin[7] etc.

3] Ultrasound Assisted Synthesis:

In the absence of a solvent, the polymer and cross linkers are allowed to interact. The interaction is brought about by ultrasonic waves. This technique will yield a spherical and uniform size. The ratio of polymer to crosslinker used, the temperature maintained in the water bath, and the duration of sonication are all critical parameters that must be optimized.

4] Loading of drugs Into Nanosponges:

The nanosponges should be pretreated to keep the mean particle size below 500nm. Nanosponges were suspended in water and sonicated to remove aggregates and particles before being centrifuged to obtain a colloidal fraction, from which the supernatant was separated and dried by freezing. Following that, an aqueous suspension of nanosponges is prepared, and an excess amount of drug is dispensed for maintaining the suspension under constant stirring for a specific time period for complexation is over, the undissolved drug (uncomplexed condition) is separated from the complexed drug via centrifugation. This method aids in the formation of solid crystals of nanosponges via solvent evaporation or freeze drying. Crystal nanosponges play an important role in drug complexation. When compared to crystalline nanosponges, para-crystalline nanosponges demonstrated different loading capacities.poorly crystalline nanosponges had act drug loading as a mechanical mixture rather than inclusion complex.

Factors influencing Nanosponge formation:

1] Polymers and Crosslinkers:

The formations and the performance of nanosponges depend on the type of polymers and cross linkers used. Nanosponges structures are three dimensional and nano porous. There is a presence of hydrophobic and hydrophilic components which having ability to trap targeted compounds. The rate of drug release which enhance drug absorption across the biological barriers.eg.by using diphenyl carbonate di-isocyanates another cross linker can be formulated and act as a sustained release carriers for water soluble drugs.

2] Types of drugs and medium used for interaction:

Nanosponges have unique properties that allow them to be entrapped in nanocavities. Drug molecules with molecular masses ranging from 100 to 400 Daltons. When the drug is loaded into nanosponges, the M.P. should be reduced. The organic guest molecule will be carried into hydrophobic cavities trapped in nanosponges by the interaction between nanosponges and hydrophilic medium. The polarity, size, hydrophobic EVS, and structural properties of molecules all influence their strong interaction.

3] Complexation temperature:

Temperature has an effect on a complex's stability constant, and these are inversely related. As the temperature rises, the magnitude and apparent stability decrease due to nanosponge interaction.

4] Degree of substitution:

Nanosponges having complexing ability, the number and the position of substituents on the polymeric molecules are affected e.g. The substituents cyclodextrin derivative causes beta cyclodextrin beta derivative in the different forms. The presence of different cross-linking agents, functional groups would yield different types of complex materials. The higher no. of substituents having higher cross-linking abilities, which includes the degree of highly pores nanosponge. These effects caused by the position of substituents.

Characterization of Nanosponges:

The characterization techniques as solubility, porosity, microscopy, drug loading, particle size, polydispersity index, zeta potential, drug release, swelling, differential scanning calorimetry etc. will be used.

Applications of Nanosponges:

Due to nanosponge versatility and biocompatibility nanosponges have many applications. Nanosponges have wide application in drug delivery as to enhance of solubility of poorly water solubility of drugs, delivery of proteins.

A. For Topical Delivery

1. The drug **Itraconazole** is used in combination ofPolyvinyl alcohol, ethyl cellulose and dichloromethane by using Emulsion solvent diffusion method gives the outcome Nanosponge formulation loaded with itraconazole resulted in controlled release of drug. The optimized formulation showed high entrapment efficiency and particle size, polydispersity index was found to be excellent[8].
2. The **Lemongrass oil** is used in combination with Ethyl cellulose, PVA, carbopol940 by using Emulsion solvent evaporation method gives the outcomes The nanosponge drug delivery was developed for Lemongrass oil. Because of its diverse pharmacologic and clinical effects, it is a volatile oil that has become one of the most important natural oils in the pharmaceutical industry. Because of its low aqueous solubility and the instability of its main active constituent,skin irritation is major disadvantage of the lemongrass oil. Ethyl cellulose loaded Lemongrass oil nanosponges with a topical hydrogel were successfully developed for improved therapeutic success[9].
3. The drug **Fluconazole** is used in combination with Ethyl cellulose, PVA, dichloromethane by using Emulsion solvent diffusion method gives the outcomes TheFluconazole hydrogel system based on polymeric nanosponge for improved topical delivery. The oil-in-water (o/w) emulsion solvent diffusion method was used to create nanosponge. The nanosponge drug delivery resulted in improved permeation of the fluconazole across skin[11].
4. The drug **Etodolac** is used in combination with Ethyl cellulose, dichloromethane, Polyvinyl alcohol by using Emulsion solvent diffusion method gives the outcome The work deals with the improvement of solubility of Etodolac; BCS class II drug through development of nanosponge formulation. Nanosponge were prepared by emulsion solvent diffusion method. The results revealed that proportion of Drug 1: Polyvinyl alcohol 3: ethyl cellulose 2 showed nanosized particle, excellent poly dispersibility Index and in vitro release showed significant improvement of the in vitro release than pure Etodolac hydrogel[10].

5. The drug **Tizanidine hydrochloride** is used in combination with βcyclodextrin, diphenyl carbonate, DMSO, triethanolamine, Carbopol 934, propylene glycol by using Solvent evaporation method gives the outcome Tizanidine HCl, central acting skeletal muscle relaxant. It undergoes first pass metabolism and having less BA. Nanosponges were prepared by hyper cross linked β-cyclodextrin method.Formulation and evaluation of nanosponges loaded hydrogel of Tizanidine HCl overcome the limitation of oral bioavailability[12].

6. The drug **Butenafine** is used in combination with Ethyl cellulose, dichloromethane, 0.3 % PVA solution by using Emulsion solvent evaporation technique gives the outcomes The nano-based gel formulation is showed more effective treatment of fungal infections, as drug permeation occurs deeper into skin layer[13].

7. The drug **Ketoconazole** is used in combination with PVA, ethyl cellulose, methanol (99%), triethanolamine, Carbopol 934 by using Emulsion solvent evaporation technique gives the outcomes Nanosponge prepared by using various ratios of ethyl cellulose and finally loaded into Carbopol 934 gel showed excellent controlled drug release kinetics i.e., zero order and Higuchi[14].

8. The drug **Isoniazid** is used in combination Ethyl cellulose, polyvinyl alcohol, dichloromethane, triethanolamine, Carbopol 934, Carbopol 940, HPMC K4M by using Emulsion solvent evaporation method gives the outcome Nanosponges prepared by emulsion-solvent evaporation method resulted in controlled release for Isoniazid as topical delivery[15].

9. The drug **Luliconazole** is used in combination with Ethyl cellulose, polyvinyl cellulose, DMSO, Carbopol 940, HMPC, sodium alginate, acacia, methyl paraben, propyl paraben by using Emulsion solvent diffusion method gives the outcome Luliconazole nanosponge hydrogel is developed as dermatological gel and showed improved therapeutic effect, better dispersibility and good more effective than conventional gel[18].

B. For Oral Delivery Sustained Release

1. The drug **Ciprofloxacin** is used in combination with Ethyl cellulose, polyvinyl alcohol byusing Solvent evaporation method gives the outcomes Ciprofloxacin is acid labile drug so that it is entrapped with ethyl cellulose. Formulated NSs loaded with Ciprofloxacin nanosponge resulted in sustained release.

2. The drug **Naproxen** and Ibuprofen is used in combination with Ethyl cellulose, polyvinyl alcohol buy using Emulsion solvent diffusion method gives the outcome An equal proportion of ethyl cellulose to drug results in nanosponges with the desired particle size, production yield, drug content percentage, and entrapment efficiency. Based on the Higuchi model, the release kinetics of formulations resulted in a sustained release pattern, and drug release follows Fickian diffusion and the Korsmeyer-Peppas model.

3. The drug **Norfloxacin** issued in combination with β-cyclodextrin, diphenyl carbonate by using Melt method gives the outcomes β-cyclodextrin was used as base and diphenyl carbonate as crosslinker agent at 1:2 M/M ratio resulted higher encapsulation efficiency and small particle size. The nanosponge showed mucoadhesive property and due to mucoadhesion results in increased norfloxacin absorption. It ultimately improves the antibiotic activity[22].

4. The drug **Budesonide** is used in combination with Eudragit S-100, polymethyl methacrylate, dibutyl phthalate, PVA by using the emulsion solvent diffusion method gives the outcome Budesonide is an ideal drug for the local therapy because of low oral bioavailability, quick clearance and toxic metabolites. The nanosponge prepared by Quasi-emulsion solvent diffusion showed prolonged transport of drugs for an extended period of time and it reduces application frequency and enhances bioavailability[23].

5. The drug **Cefadroxil** is used in combination with Diphenyl carbonate, β -cyclodextrin by using Solvent diffusion method gives the outcome The solubility of Cefadroxil is improved by development of nanosponge drug delivery[24].

6. The drug **Resveratrol** is used in combination with Carbonyl diimidazole, β-cyclodextrin, Milli Q water by using Solvent diffusion method The Resveratrol shows increase in solubility, stability and permeation by formulating as cyclodextrin based nanosponge[26].

C. For Immediate Release

The drug**Clopidogrel** Bisulphate is used in combination with Ethyl cellulose, glutaraldehyde by using Emulsion solvent diffusion method gives the outcome Clopidogrel bisulphate, BCS class II drug having poor bioavailability by oral route. The nanosponges of clopidogrel bisulphate showed improved solubility of Clopidogrel bisulphate[29].

D. For Enhanced of Bioavailability/ Solubility

1. The drug **Lansoprazole** is used in combination with Ethyl cellulose, PVA, Pluronic F-68, dichloromethane by using Emulsion solvent diffusion method gives the outcome The developed nanosponges of Lansoprazole were further formulated as enteric coated tablet. The drug release from coated tablet was extended up to 12 h[30].

2. The drug **Losartan** is used in combination with β-cyclodextrin, polyvinyl alcohol, Hydroxypropyl βcyclodextrin by using Solvent evaporation method gives the outcomes Losartan is a BCS class II drug, Nanosponge of losartan was prepared by using ethyl cellulose, β-CD and HP-β-CD cyclodextrin. For the optimized nanosponge the entrapment efficiency was found to be more than 95 %[31].

3. The drug **Simvastatin** is used in combination with Dichloromethane, ethyl cellulose, β -cyclodextrin by using Solvent evaporation method gives the outcome Enhancement of solubility of Simvastatin is achieved through development of nanosponge drug delivery[32].

4. The drug**RisedronateSodium**is used in combination with Eudragit RS 100, Eudragit E 12.5, Ethyl cellulose, potassium hydroxide, methanol, dichloromethane, polyvinyl alcohol by using emulsion solvent diffusion

method gives the outcome The Risedronate Sodiumhas poor and erratic absorption. The *In-Vitro* drug dissolution of optimized formulation showed burst release for initial 2 h followed by slow and sustained release up to 24 h. The study revel as better results in improvement of osteoporotic condition[33].

E. For Vaginal Delivery[d]

1 The drug **Miconazole Nitrate** is used in combination with D-phenyl carbonate, β CD by using Melt method gives the outcome The nanosponge formulation were developed using β CD as polymer and D-phenyl carbonate as cross linker in 1:1 ratio. Optimized Nanosponge loaded gel showed better results

Nanosponges for cancer therapy:

Because of their low solubility, anticancer drugs are currently the most difficult to deliver in the pharmaceutical field. According to one article, nanosponges complex is three times more effective than direct injection in slowing tumor growth. The nanosponges complex contain a drug and expose a targeting peptide that binds tightly to a radiation-induced cell upper layer on the tumor receptor. When nanosponges come into contact with a tumor cell, they adhere to the cell's surface and begin to release drug molecules. The benefit of targeting drug delivery is that it provides a more effective therapeutic effect at the same dose while minimizing side effects.

Nanosponges for delivery of protein:

Bovine serum albumin (BSA) was used as a model protein to investigate the encapsulating capacity of -cyclodextrin-based nanosponges. Because the protein solution of bovine serum albumin (BSA) is unstable, it is stored in lyophilized form. Proteins can convert from their native structure to denature lyophilization. The main disadvantage of protein formulation and development is maintaining its native structure and long-term storage during and after processing. Nanosponges can increase the stability of proteins such as Bovine serum albumin (BSA) when delivered with cyclodextrin. Nanosponges have also been used for enzyme immobilization, protein encapsulation, controlled delivery, and stabilization.

Role of nanosponges for treatment of fungal infections:

Skin fungi are one of the most dangerous diseases in the world. Because of benefits such as drug targeting to the site of infection and a reduction in systemic side effects, topical therapy is an appealing option for the treatment of coetaneous infections. Econazole nitrate (imidazole) is a fungicide used topically to treat athlete's foot, ringworm, tinea pityriasis versicolor, jock itch, and vaginal thrush. Cream, ointment, lotion, and solution are the available econazole nitrate products on the market. When applied to the skin, econazole nitrate adsorption is minimal, and effective therapy requires a high concentration of active agents to be combined. As a result, econazole nitrate nanosponges were created using an emulsion solvent method.These econazole nitrate nanosponges were then loaded into a hydrogel for topical delivery for sustained drug release. Itraconazole, another antifungal drug, falls into biopharmaceutical classification system class II and has a slow dissolution rate and low bioavailability. As a result, the goal of this study was to increase the solubility of itraconazole in order to solve the bioavailability problem. If cyclodextrin is cross-linked with carbonate bonds and loaded into these nanosponges, the solubility of itraconazole can be increased.

As absorbent in treating poison in blood:

By absorbing the poison, nanosponges can remove the dangerous poisonous substance from our blood. Instead of using antidotes, we can use nanosponges to absorb toxins by injecting them into the blood. The nanosponge imitates a red blood cell in the bloodstream, tricking toxins into attacking it and then absorbing it. The number of toxin molecules that each nanosponge can absorb is determined by the toxin.

CONCLUSION:

Nanosponges are a novel drug delivery system. It is a biocompatible and versatile drug carrier that transports both hydrophilic and lipophilic drugs by forming inclusion and non-inclusion complexes. They are administered via oral, topical, and parenteral routes [34,35]. Nanosponges deliver the drug to the targeted site in a controlled and predictable manner, increasing the drug's bioavailability. To better suit the application, the particle size and release rate can be adjusted by adjusting the polymer to crosslinker ratio. Nanosponges can be used to improve the aqueous solubility of lipophilic drugs while also protecting them from physicochemical degradation. They have been discovered to be promising materials for immediate technological use in drug development.

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