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NANOSPONGES-REVOLUTIONIZING TARGETED DRUG DELIVERY SYSTEM

Rushikesh Ruprao Gawai[1]* and Gauri Pramod Gawande[2], Swati P. Deshmukh

[1]Lecturer Shraddha Institute of Pharmacy, Kondala Zambre, Washim-444505.
[2]Student of Bachelor of Pharmacy, S.G.S.P.S Institute of Pharmacy, Kaulkhed, Akola-444002 (MS). India.

***Corresponding Author: Rushikesh Ruprao Gawai**
Lecturer Shraddha Institute of Pharmacy, Kondala Zambre, Washim-444505.

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ABSTRACT
Nanosponges are small, porous particles with 1-2 nanometer pores suitable for drug delivery, detoxification, and environmental cleanup. They are non-toxic, stable at high temperatures, and can selectively release chemicals due to their 3D structure. Composed of polymer, surfactant, drug substance, and solvent with advantages like compatibility, self-sterilization, free flow, extended-release action, oil control, high entrapment effectiveness, and improved product performance. Nanoparticles are materials with various properties and applications, including titanium dioxide (tio2), silicon, hyper-cross-linked polystyrene, cyclodextrin nanosponges (cdns), and polyamidoamine nanosponges. They are biodegradable, specific polyester structures that release drugs over time. Preparation methods include melt, solvent, ultrasound-assisted synthesis, quasi-emulsion diffusion, drug loading, and emulsion solvent diffusion. Nanosponges are a cutting-edge drug delivery system that improves the solubility of poorly water-soluble medications. They offer high solubility. Nanosponges can enhance drug solubility by over 27 times, and polyvinyl pyrrolidone adds 55 times, resulting in faster drug dissolution profiles. They are also used for drug delivery, protein delivery, cancer therapy, antiviral applications, gas delivery systems, water purification, biomedical engineering, drug release modulation, enzyme immobilization, targeted delivery, and diagnostic applications. Nanosponges have potential therapeutic and diagnostic applications, including treating cardiovascular disease a atherosclerotic plaques. In conclusion, nanosponges are a promising method for treating cancer, improving site-specific drug delivery, and enhancing the effectiveness of medications. Future advancements in healthcare could follow nanosponge technology, which could be a valuable tool for preventative care. With its prolonged and safe actions, nanosponges have a keen interest in contemporary medicine and research.

INTRODUCTION
Nanotechnology has become an advantage in developing new dosage forms for controlled drug delivery and targeting mechanisms. Nanosponges, a type of nanoparticle, are small, porous particles with pores ranging from 1-2 nanometers, making them ideal for drug delivery systems, detoxification processes, and environmental cleanup. They are often synthetically manufactured but can also include natural materials to improve efficiency. Nanosponges are insoluble in water and organic solvents, porous, non-toxic, and stable at high temperatures up to 300°c. They can catch, transport, and selectively release a wide range of chemicals due to their 3d structure with nanometric-sized cavities and variable polarity. They can be easily regenerated through various treatments, such as washing with environmentally friendly solvents, stripping with hot gases, light heating, or modifying ph or ionic strength. Nanosponges can be used in various applications, including the cosmetic and pharmaceutical industries, to improve water solubility, protect degradable compounds, and develop drug delivery mechanisms other than the oral route. The fundamental chemistry of polymers and cross-linkers presents few preparation hurdles, and this process can be rapidly scaled up to commercial production levels. Nanosponges can be magnetized and distributed both pulmonary and venous due to their small size.

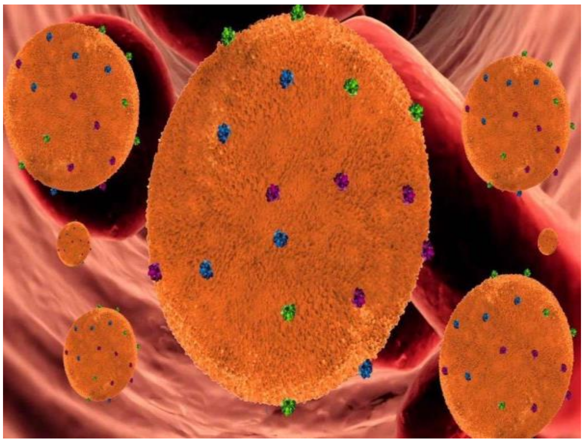

Fig. 1: Nanosponges.

Composition

Nanosponges are complicated structures made of long linear molecules that are folded into a spherical form roughly the size of a protein by cross-linkers. Nanosponges are made up of five major components.

A) Polymer
B) Cross-linking agent
C) Surfactant
D) Drug substance
E) Solvent

A) Polymer

The polymer utilized can have an impact on the production and release rate of nanosponges. Active medicinal compounds can be contained in polymers or interact with them. The cavity size of the nanosponge should be large enough to allow the complexation of a specific-size medicinal molecule. A polymer's potential to cross-link is determined by the functional and active groups that are substituted in it. To offer tailored drug release, the polymer should be able to connect to certain ligands.[4]

Examples: Ethylcellulose, polymethyl methacrylate, eudragit rl-100.

B) Crosslinking agent

The crosslinking agent chosen is determined by the drug chosen and the chemical structure of the polymer. For topical treatments, the most often used crosslinker is dichloromethane. Because the viscosity of the internal phase decreased as the volume of the internal phase grew, particle size and drug entrapment in the polymers did not follow any particular pattern. When 20 ml of dichloromethane was employed, higher entrapment efficiency nanosponges were formed.[5]

Examples: dichloromethane, ethanol, methanol.

C) Drug substance

Certain properties of drug compounds that are to be formed as nanosponges are listed below:

- Molecular weight ranges from 100 to 400 daltons.
- A drug molecule should have a maximum of five condensed rings.
- Water solubility of molecules should be less than 10 mg/ml.
- The active moiety's melting point should be less than 250°c.[4]

D) Surfactant

Polyvinyl alcohol is a commonly used surfactant in the preparation of nanosponges and plays a crucial role in the formation of nanosponges with reduced particle size. The particle size was found to increase with the increase in the concentration of surfactant. Foaming is observed at higher concentrations of surfactants, this resulted in the formation of aggregates. The drug entrapment efficiency was reduced at increasing surfactant concentration. This may be due to insufficient polymer concentrations for that particular drug for particle encapsulation.[5]

Examples: Polyvinyl alcohol, Ethanol, Dichloromethane.

E) Solvent

Water is the only solvent used in the manufacturing of nanosponges. The solvent quantity and temperature are crucial variables in the last step of nanosponge production because they affect both the pore diameter on the surface of the nanosponges and their yield.[4]

Polymers	Hyper cross-linked polystyrenes, cyclodextrins and its derivatives like methyl β- cyclodextrin, alkyloxycarbonyl-cyclodextrins, 2-hydroxy propyl β-cyclodextrins and copolymers like poly (valerolactone - allylvalerolactone), poly (valerolactone- allylvalerolactoneoxepane-dione), ethyl cellulose and pva
Cross-linkers	Diphenyl carbonate, diarylcarbonates, di-isocyanates, pyromellitic anhydride, carbonyl-di-imidazole, epichloridrine, glutaraldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamide) acetic acid and dichloromethane.
Apolar Solvents	Ethanol, dimethylacetamide, dimethyl formamide

Advantages

a. Nanosponges are compatible with a wide range of vehicles and substances found in formulations.
b. These formulations are self-sterilizing due to their 0.25m pore size, which prevents germs from penetrating the formulations.
c. Product elegancy and formulation flexibility can be greatly improved: they are designed to deliver an active component efficiently at the lowest possible dose while also improving stability, reducing side effects, and changing the drug release profile.
d. It has a high entrapment effectiveness of the chemicals, which decreases adverse effects and enhances stability.
e. It increases the thermal, chemical, and physical stability of compositions.
f. Nanosponges are not irritating, mutagenic, allergenic, poisonous, or biodegradable.
g. Extended release: they have a non-collapsible structure that allows active chemicals to be released Regulated and Predictable manner.[6]

Disadvantages

a. They must be carefully synthesized.
b. It depends upon the loading capacities
c. Dose dumping.
d. May retard the drug release.
e. It includes a capacity to encapsulate small molecules only.
f. The manufacturing must be done in safer

environments.

g. The stickiness of the powder makes the final product contaminated.[6]

Classification of nanosponges

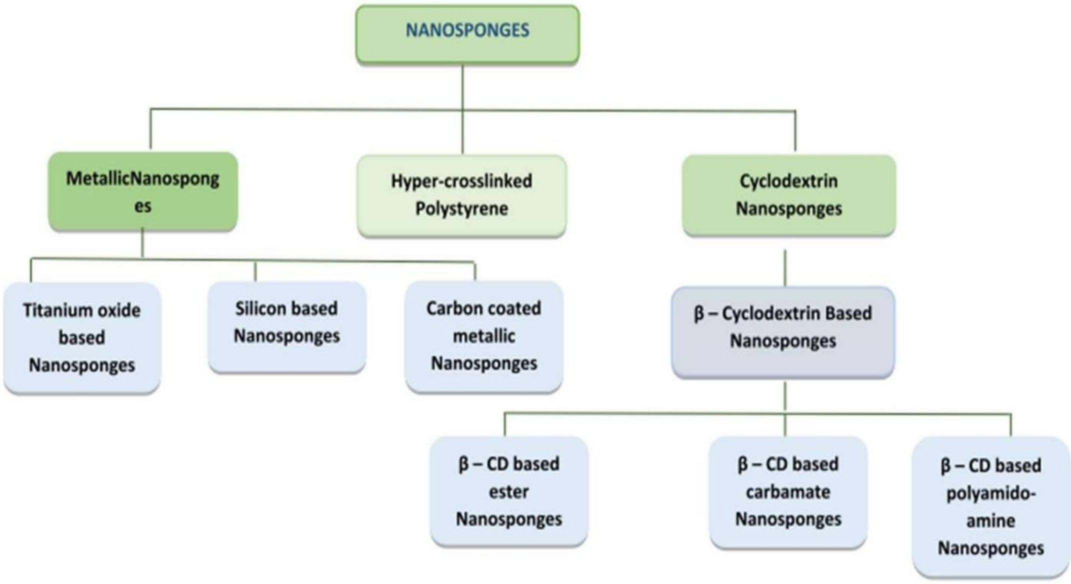

Fig. 2: Classification of nanosponges.

a. Metallic nanosponges

Titanium dioxide (tio2) nanosponges

Titanium dioxide (tio2) nanoparticles are porous metal oxide nanoparticles with pronounced physical and chemical properties. They have higher surface area, mass transfer, and electron mobility. Synthesis methods include functional polystyrene nanodispersion, carbon sphere synthesis, and bimetallic ns like tio2/ag, vo2/tio2, and pt-tio2. Tio2 ns are explored for various applications, including photocatalytic properties, high-performance supercapacitors, hydrogen chemical sensors, and recyclable oil absorbents.[7,8]

Silicon nanosponges

Porous silicon particles are sponge-like structures formed by chemical or electrochemical etching of bulk si. Since their discovery in 1990, they have been explored for various applications, including microelectronics, chemical and biological sensors, and photoluminescence. They are commonly prepared by electrochemical etching under ultrasonic agitation, with methods like tasciotti et al. Using heavily doped p++ type silicon wafers coated with silicon nitride, and chadwick et al. Using metallurgical grade silicon powder.[9]

b. Hypercross-linked polystyrene nanosponges

Nano-structured nanoparticles (ns) are biodegradable, specific polyester-like structures that release drugs over time. They are made of hyper-cross-linked polystyrene, a low-density, microporous material with high absorption capacity. Ns is used in implant materials, drug delivery systems, and diagnostic systems, particularly in cancer drug delivery.[10]

c. Cyclodextrin nanosponges

Cyclodextrin nanosponges (cdns) is crosslinked β-cyclodextrin with organic diisocyanates, enhancing entrapment efficiency in liposomes, microparticles, and nanoparticles. They consist of β-cyclodextrin, γ-cyclodextrin, and -cyclodextrin, with hydrophilic cds harmless at moderate dosages.[11]

Cyclodextrin-based carbamate nanosponges

Cds are treated with diisocyanates at 70°c for 16-24 hours, removing dmf, and producing cross-linked polymer powder. These carbamate nanosponges bind to organic compounds, enabling water filtration with loading capabilities of 20-40 mg per cm3.[11]

Cyclodextrin based ester nanosponges

Nanosponges are manufactured using dianhydride, including pyromellitic anhydride, for cross-linking. Exothermic cross-linking occurs at room temperature, combining cd with dianhydride in dmso with organic bases. These nanosponges can hold non-polar organic compounds and cations simultaneously.[11]

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 an aqueous medium (Shows ph-dependent action).[11]

Mechanism of drug release from nanosponges

Since the nanosponges have an open structure (in the surroundings of nanosponges they do not have any continuous membrane), the active substance is added to the vehicle in an encapsulated form. The encapsulated active substance can move freely from the particles into the vehicle until the vehicle gets saturated and the equilibrium is obtained. As soon as the product is applied on to the skin, the vehicle containing the active ingredient gets unsaturated causing a disturbance in the equilibrium. Thus, the flow of active substances from nanosponge particles into vehicles starts in the epidermis until the vehicle is either absorbed or dried. Even after the retention of the nanosponge particles on the surface of the skin i.e., the stratum corneum, the release of active substance continues to the skin for a long period.as its complexation.[12]

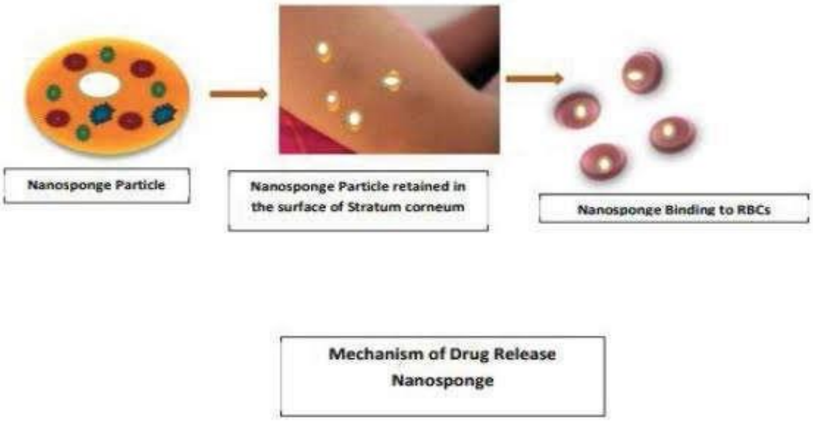

Fig. 3: Mechanism of drug release from nanosponges.

Method of preparation

Methods for the preparation of nanosponges are given below

A. Melt method
B. Solvent method
C. Ultrasound assisted synthesis
D. Quasi-emulsion diffusion method
E. Loading of drug into nanosponges
F. Emulsion solvent diffusion

A. Melt method

Cd-ns are prepared by melt technique. Ns was developed by reacting β-cyclodextrin with crosslinkers like dimethyl carbonate, diphenyl carbonates, diisocyanates, carbonyl diimidazole, diaryl carbonates, etc. The cd was heated along with a cross-linker and solvent such as dimethylformamide (dmf) at 100°c for 5 hr on a magnetic stirrer in a 250ml flask. The product obtained was then brought to room temperature, and washed to remove basic unreacted components and by-product using solvent. It was followed by purification which is the most important step to avoid the toxicity caused due to by-products.[13]

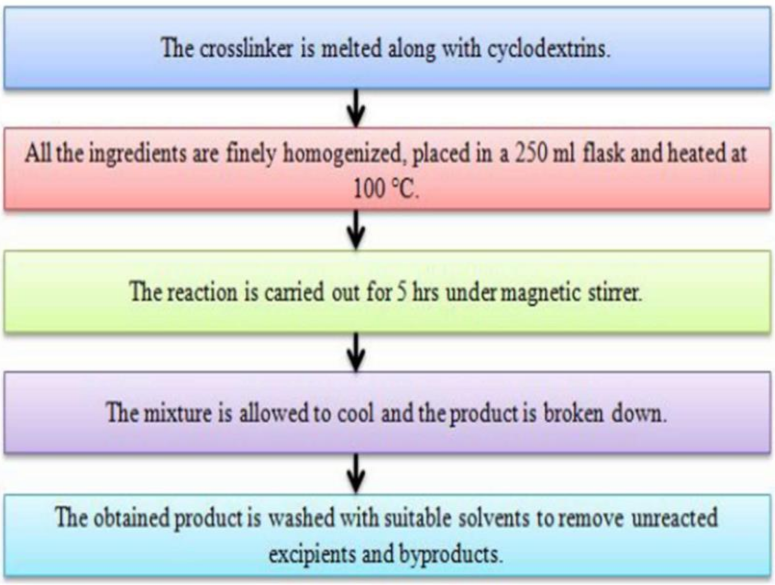

Fig. 4: Melt method.

B. Solvent method

In this method, the crosslinker is solubilised in solvents like dimethylformamide or dimethylsulfoxide (dmf/dmso) and the melting step is eliminated. Particularly a polar aprotic solvent is generally used for mixing with the polymer which is followed by addition of this mixture to an excess quantity of the crosslinker. Optimization of the process is performed by varying the crosslinker/polymer molar ratio. The reaction is carried out at temperatures ranging from 10 °c to the reflux temperature of the solvent, for 1 to 48 hrs. The carbonyl compounds such as diphenyl carbonate (dpc), dimethyl carbonate (dmc) or carbonyldiimidazole (cdi) are the cross-linker required for the reaction. The product is acquired by adding the cooled answer for an expansive overabundance of distilled water. The item is recovered by filtration under vacuum and the thing is moreover washed down by deferred soxhlet extraction.[14]

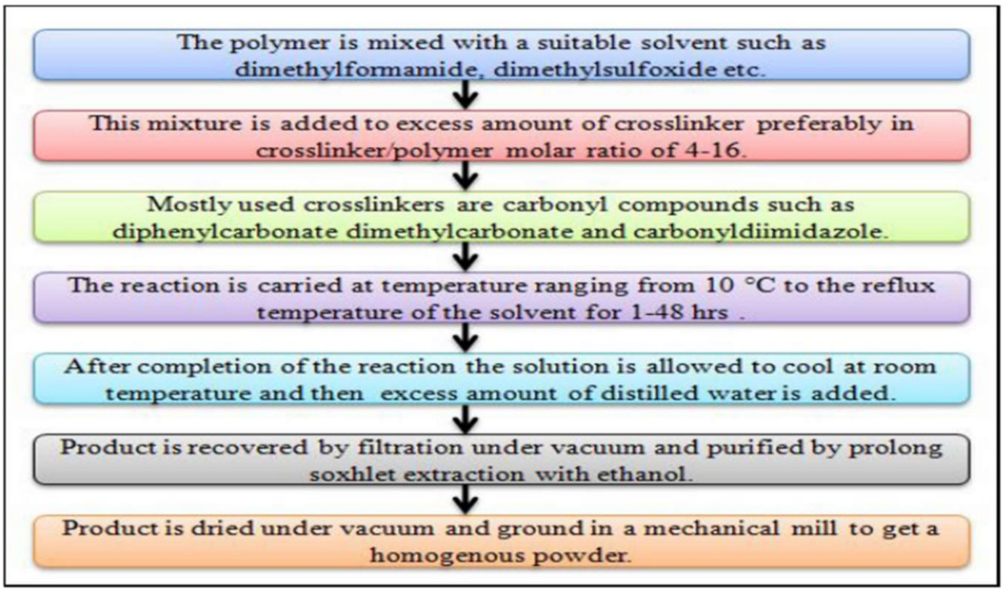

Fig. 5: Solvent method.

C. Ultrasound assisted synthesis

The ns were obtained by sonication of polymers and crosslinker, without using solvent.[50] The ns obtained by this technique were uniform in size i.e., 0.5µ and they are spherical. Cross-linker used in this method is diphenyl carbonate and pyro metallic anhydride. Cds were added in a specific amount to react in melted di-phenyl carbonate for 5 h at 90°. The product obtained was then extracted through soxhlet extraction method with ethanol and impurities were removed and the obtained ns were stored at 25°c until its use. This method is used for preparation of cd ns and the frequency of ultrasound is 25 to 42 khz.[15]

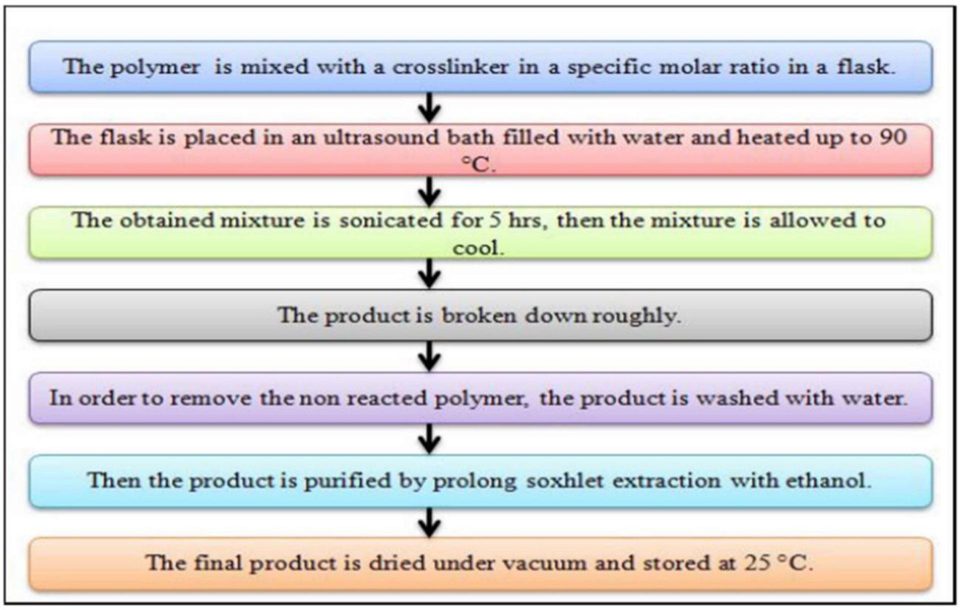

Fig. 6: Ultrasound assisted synthesis.

d. Quasi emulsion diffusion method

The nanosponges prepared using the polymer in different amounts. Eudragit rs 100 is added with a suitable solvent to prepare the inner phase. A drug used provided with a solution and dissolved under ultra-sonication 35ºc. This inner phase added to the external phase containing pva act as an emulsifying agent. The mixture is stirred at 1000-2000 rpm for 3hr at room temperature and dried in an air-heated oven at 40ºc for 12 hours.[16]

e. Loading of drug into nanosponges

Nanosponges for drug delivery should be pre-treated to obtain a mean particle size below 500nm. For this, nanosponges are suspended in water and then sonicated to avoid the presence of aggregates. Further, the suspension is centrifuged to obtain the colloidal fraction. The supernatant is separated and the sample is to be dried by freeze-drying. Aqueous suspension of nanosponge is prepared and dispersed in the excess amount of the drug and the suspension is maintained under constant stirring for a specific time (required for complexation). After complexation, the uncomplexed (undissolved) drug from the complexed drug is separated by centrifugation. Then, the solid crystals of nanosponges are obtained by solvent evaporation or by freeze-drying. The crystal structure of nanosponge plays a very important role in the complexation with the drugs. A study revealed that para-crystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than para-crystalline ones. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than an inclusion complex.[17]

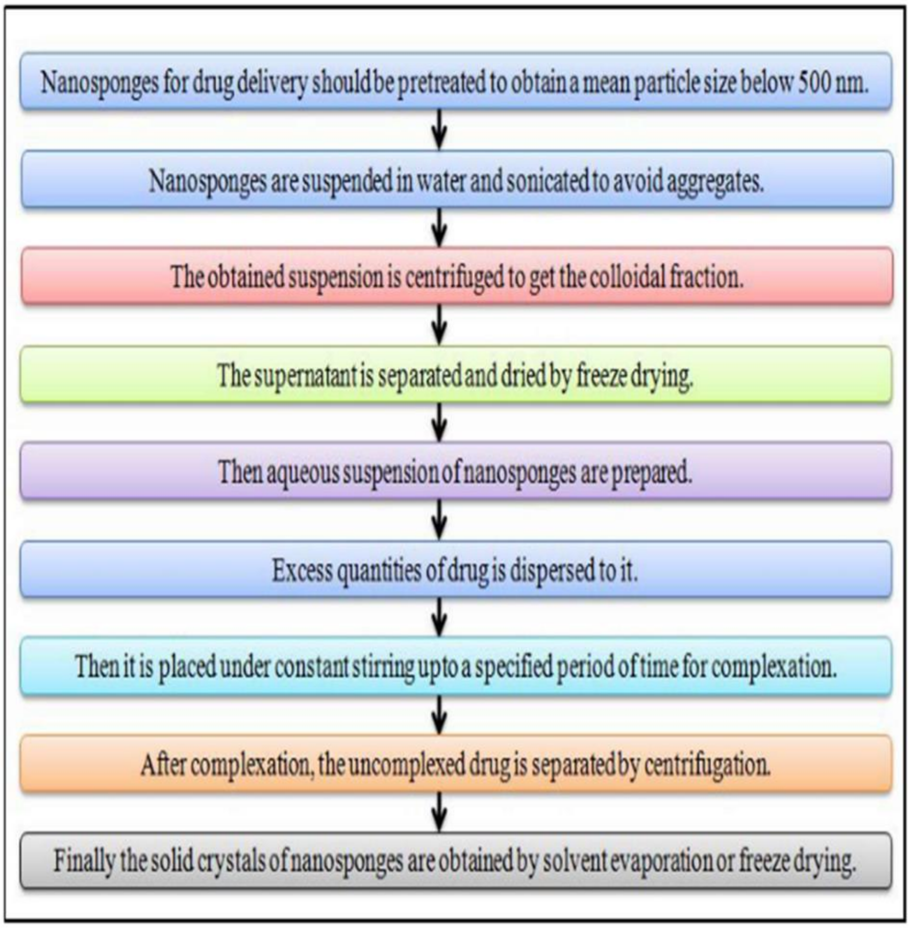

Fig. 7: Loading of drug in nanosponges.

f. Emulsion solvent diffusion method

The emulsion solvent diffusion method is another form of the solvent method of preparation of ns. In this method, the dispersed phase and aqueous phase are the two phases that are used. The dispersed phase has drug and polymer in specified amounts whereas, the aqueous phase has polyvinyl alcohol in a specified amount dissolved in 150 ml of water. Two extents of organic and polymer phases were used in this technique. Organic integrates drug and polymer, whereas the aqueous phase contains polyvinyl alcohol. Drug and polymer were dissolved into proper organic solvent and it is then slowly added to the aqueous phase and agitated at 1000rpm at 2 h using a magnetic stirrer. The ns were obtained, washed, and dried in air at room temperature.[18]

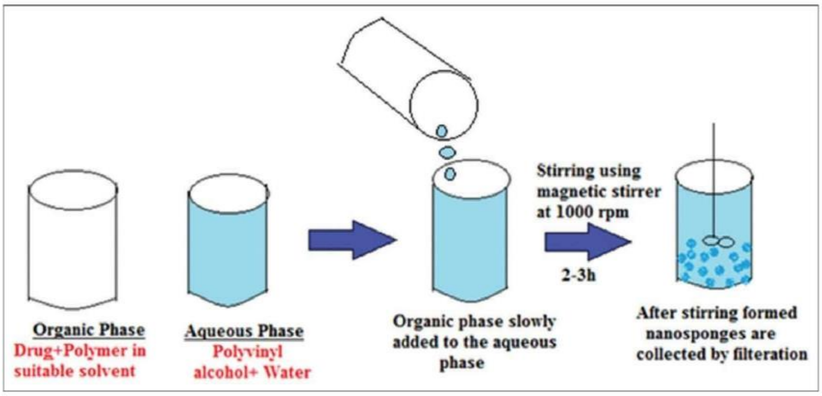

Fig. 7: Fabrication of nanosponges by emulsion solvent diffusion technique.

Factors affecting nanosponges formulation[19]

Some factors which influence the formulation of nanosponges are given below

A. Type of drug
B. Type of polymer
C. Temperature
D. Method of preparation of nanosponges
E. Degree of substitution

A. Type of drug

The drug molecules to be complexes with nanosponges should have certain characteristics bellowed:

a. Solubility in water is less than 10 mg/ml. (bcs class ii drugs are most commonly used)
b. Molecular weight between 100 and 400 gm/mole.
c. The structure of the drug molecule should contain no more than five condensed rings.
d. The melting point of the drug should be below 2500 c

B. Type of polymer

The polymer which is used in the formulation can affect the formation as well as the performance of nanosponges. The cavity size of nanosponge should be suitable to accommodate a drug molecule of a particular size for the complexation. Hydroxy propy1 βcyclodextrin possesses a good affinity to form inclusion complex as compared to other.

C. Temperature

The temperature variation can affect the formation of nanosponges. An increase in the temperature, decreases the magnitude of the apparent stability constant of the drug/nanosponge complex may be due to a result of possible reduction of drug/nanosponge interaction forces, with a rise in temperature.

D. Method of preparation of nanosponge

The method of nanosponge formulation affects the loading drug into nanosponge and complexation. The effectiveness of the method depends on the nature of drug and polymer used in the formulation.

E. Degree of substitution

The type, number, and position of substituent on parent molecule can affect the nanosponge formation as well its complexation.

Application of nanosponges

A. Solubility enhancement

Low water solubility in pharmaceuticals hinders their clinical application. Nanoparticles (ns) can improve the wetting and solubility of molecules with low solubility in water, increasing drug apparent solubility. Encapsulation of β-cd ns increases drug solubility by over 27 times, and polyvinyl pyrrolidone (pvp k-30) adds 55 times, resulting in faster drug dissolution profiles. This approach can solve formulation and bioavailability issues.[20,25]

B. Nanosponges for drug delivery

Nanosponges are versatile dosage forms containing telmisartan, paclitaxel, and econazole nitrate, with varying biological effects. They offer high solubility and in vitro drug release, suitable for various applications.[26]

C. Nanosponges for delivery of protein

Protein formulation development faces challenges in maintaining native protein structure. Swaminathan et al. Synthesized nanosponges 10 and 11 using β-cyclodextrins and polyamidoamine chains. These nanosponges were stable at 300°c and demonstrated high protein complexation capacity.[27]

D. Nanosponges for cancer therapy

Nss are effective in reducing tumor cell growth by loading a drug and exposing it to a radiation-induced targeting peptide. 5-fluorouracil, a cancer drug, was improved with a 5-fu ns tablet, increasing drug release to 96.66% in vitro. Camptothecin, an anticancer drug, was encapsulated in β-cd ns to improve its inhibitory effect on du145 prostate tumor cell line and pc-3 growth.[28]

E. Role of nanosponges for treatment of fungal infections

Fungal infections are a global concern, and econazole nitrate is an effective antifungal drug. Nanosponges were fabricated to increase itraconazole solubility by cross-linking β-cyclodextrine with carbonate bonds.[29]

F. Antiviral application

Ns deliver antiviral drugs to lung and nasal epithelium, inactivating respiratory infections like influenza and rhinovirus. Carbonylated β-cd ns improve solubility and bioavailability of acyclovir, prolonging release kinetics and releasing 20% after 3 hours.[30]

G. Gas delivery systems

Cd ns are developed as oxygen delivery systems, storing and releasing oxygen slowly, providing oxygen to hypoxic tissues in diseases. They can be permeable to silicon membranes and encapsulate 1-methyl cyclopropane, oxygen, and carbon dioxide.[31]

H. Purification of water

Cd ns effectively removes organic pollutants from water, forms hybrid filters with ceramic porous filters, and has high oil sorbency potential for oil spill disasters.[32]

I. Biomedical engineering

Nanostructured silicon substrates are being used for micropatterning mammalian cells, adhering to breast cancer cells, and developing selective protein binding and glucose biosensors.[33]

J. Modulating drug release

Modulated drug release dosage forms offer advantages over conventional formulations, enabling continuous delivery, reducing dose, pharmacokinetic profile, and side effects.[34]

K. Enzyme immobilization

Enzymes immobilized on ns improve catalytic activity and stability. Boscolo et al reported high-catalytic performance of pseudomonas fluorescenslipase adsorbed on cd-based carbonate ns, achieving structural and functional stabilization even at high temperatures. Acinetobacterradio resistance s13 catechol 1,2-dioxygenases showed improved activity and stability at various ph and temperature profiles.[35]

L. Targeted Delivery and Diagnosis

Nanocarriers have potential therapeutic and diagnostic applications, including treating cardiovascular disease and addressing unstable atherosclerotic plaques. Recent studies show higher cell-toxicity and negative signal in cells, proving their therapeutic and diagnostic capabilities.[36]

Marketed nanosponges preparation[37]

Sr. No	Drug	Drug category	Administration route	Dosage form	Trade Name
1.	Alprostadil	Erectile dysfunction	Intravenous	Dosage form	Prostavasin
2.	Dexamethasone	Anticancer	Dermal	Ointment	Glymesason
3.	Iodine	Antiseptic	Topical	Solution	Mena-gargle
4.	Piroxicam	Anti-inflammatory	Oral	Capsule	Brexin

CONCLUSION

Nanosponge is cutting-edge method for treating cancer that delivers site-specific drug delivery. They can also transport medicinal compounds that are hydrophilic and lipophilic. The use of nanosponge, a drug delivery system with small particle size and shape, enhances the effectiveness of medications supplied topically, parenterally, and orally in the treatment of cancer. The medicine is contained via nanosponge technology, which also improves stability, increases elegance, and increases formulation flexibility. Thus, site-specific drug delivery for the treatment of cancer is made possible by nanosponge technology, which also increases patient compliance. According to the findings presented, nanosponges are a cutting-edge type of drug delivery systems that are used to improve the solubility of medications that are poorly water soluble.

Future advancements in healthcare could be followed by the nanosponge, which could be a valuable tool for preventative care. Due to its prolonged and safe actions, it is therefore a future that looks optimistic with increased patient compliance and acceptability. They therefore have a keen interest in contemporary medicine and research.

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