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A REVIEW ON NANOSPONGES: AN ASCENDANCE OF POTENTIAL NANOCARRIER FOR EMERGING DRUG DELIVERY

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ABSTRACT

The targeted delivery of drug molecule is been always strenuous. This can be accomplishedthrough the specialized drug delivery system without affecting the efficacy and quality of the drug. With the advancement of nanotechnology and to overcome this problem "Nanosponge" has been developed. Few new drugs cannot be effectively delivered in a conventional dosage form. Nanoparticles are fragments in the 1 – 100 nm range. These nanoparticles are used in polymeric nanoparticles, nanosponges, nano-emulsions, carbon emulsion tubes, etc. Nanosponge is a nanosized particle of virus sized filled with a variety of drugs. Nanosponge is formulated by crosslinking cyclodextrin with cross polymers. It is used to control the release rate of drug delivery. These tiny sponges circulate into the body until they encounter the target site and stick on the surface and initiate to release of drugs in a predictable manner. It also helps to overcome certain problems like poor bioavailability, and drug toxicity, decrease side effects, etc. another characteristic of nanosponges is their aqueous solubility. Due to its porous structure, helps to entrap the various drug molecule into it. Nanosponges are delivered in various forms such as oral administration, topical administration, and parental administration. Nanosponges are synthesized by various methods like emulsion solvent diffusion method, ultrasound-assisted method, solvent method etc. Nanosponge drug delivering system has evolved as one of the most prominent fields used in cancer therapy, protein drug delivering, used as adsorbent for poison etc.

KEYWORDS: Targeted delivery, Nanosponge, Nanoparticle, Porous, Cancer therapy.

INTRODUCTION

Currently, targeted drug delivery is a huge problem faced by researchers.[2] In the field of therapeutics targeting intended drug administration with enhancing the efficiency, decrease in side effects and required dosing system can be the leading trends. Targeted drug delivery states for selective and effective pharmacologically important active substance pinpointed atchosen target in sufficient therapeutic concentration. While inhibiting its contact to non- target normal cellular lining and hence reducing its lethal effect and maximizing therapeutic effect of drug.[1, 3] To obtain desired therapeutic response, required amount of drug that needsto be transported to the site of action with consequently to control the rate of drug release. Distribution of drug besides target tissues seems unnatural and wasteful thus main cause of toxicity.[1, 3] Focused drug delivery is the transport of a drug to receptors, organs or can be other parts of the body to which a person desires to deliver the drug to its target.[1] Effectivetargeted drug delivery system has been a long dream but faces difficulty due to its complex chemistry that is required to develop a new system. The advancement in a new and complex molecule called nanosponge has potential to solve the current problem.[1,5]

Nanosponges are small sponges that are about size of virus having a diameter below 1 µm, packing them with a drug and attaching-special chemical linkers that can bind profoundly to the property that is found only on the surface of tumour cells and then injecting them into the body. These small sponges circulate readily around the body until they run to the surfaceof the tumour cell, there they bind to surface and starts the release of their potent drug in required and observable manner.[1] The diameter of a nanosponge is nearly between 10 – 25µm with void extent of 5 – 300 µm as compared to the microsponges which has a diameter less than 1 µm, thus nanosponge provides an advantage over the microsponges.[6,7] These 3D printing techniques will helps in providing the changes according to our needs in nanosponge and also in its development.[6] Nanosponges are "3D network or scaffold", having polyester as a long-length backbone. They are usually dissolved in a medium with small substances call cross-linkers that act as minute clutch hooks to pick out different partsof polymer together. The final effect is to form particles that are spherically shaped filled with cavities where drug substances can be

stockpiled. Biodegradable polymers are used; thus, it easily breaks gradually inside the body. The nanosponge can be changed to bigger or smaller (Based on the structure of nanosponges). Studies has shown that drug delivery system are thinner than 100 nm, the nanosponge particles which are currently in use are nearly 50 nm in size.[2, 4]

Nanosponge are nanoscopic mesh–like structure that reforms the treatment of several diseases and use of this technology has proven five times more beneficial as it is highly effective at transporting drugs in case for breast cancer than other traditional methods.[1, 4] Nanosponge is formed from diminutive particles with little nanometre-wide spaces, onto which various large-scale substances can be filled.[4] The foreseeable release is one of the most important merit of this system when compared to other nanoparticle delivery system. Many different delivery systems by nanoparticles mostly unpack most of their drug in rapidand unmanageable manner. This is also known as the burst effect and makes it problematic to find out the required dosage ranges, this situation is not in the case of nanosponge, managed release of nanoparticle drug delivery system, thus can be a refine delivery method for anticancer therapies.[1] The nanosponge are enfolding type of nanoparticle which encapsulate the drug molecule in its core.[1, 4]

Nanosponge can exhibit magnetic property when they are prepared in presence of magneticsubstances.[1, 3] They are tiny spherical substances with huge porous surfaces. They are evenused as docile target for cosmetic agents to skin even they provide merits such as reduction of net dose, dosage form retention on skin and ducking systemic absorption. The nanosponges can effectively engulf onto topical formulation for extended release and skin retention thus lessen the variation in drug absorption, toxicity even enhance consistency of patients by prolonging intervals for dosing. Moreover, nanosponge can act without decreasing their effect even though majorly reducing the irritation of drugs. They are solid in nature and even be formulated as Parenteral, Oral, Inhalation or Topical dosage forms.[5]

The well–known engineering revolution is nanotechnology since the industrial era. Nanotechnology can be defined has altering or modifying the materials at minute scale to create product that has improved properties. A meter of billionth equals a nanometre. A physical material that has a minimum proportion of 1 – 100 nm range. Nanoparticle are fractions between 1 – 1000 nm in size with a nearby interfacial layer.[6]

The Research which provided effective method for preparation of nanosponge based nanoscopic sized carries with different cavities as well as potential to hold more than two active pharmaceutical ingredients that goes along with various physiochemical properties. They have three five–membered heterocyclic compounds linkers held in the nanosponge rally also supports the supramolecule binding capability to bioactive substances. Furthermore, the mixture is checked for antiproliferative capacity.[6] An advance vision for nanoparticulate system is given to nanosponge. Nanosponge are not particularly sponge like structured shape, it is more likely to be network of molecules in 3D. When dispersed in water. They form suspension hence forming matrix assembling complex in aqueous medium, letting it freely transfer of engulfed drug molecules and carryon the release of drug. Naturallydegradable polyester is backbone of polyester nanosponge.[8] Nanosponge can form both encompass and non-encompass complexes.[9]

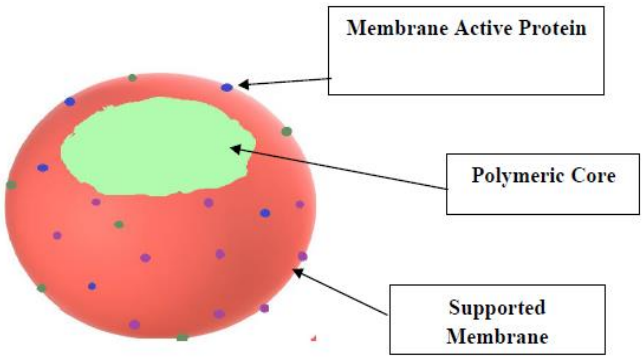

Fig. 1: Structure of Polymer based Nanosponge.[1]

Classification of nanoparticles[1, 4]

By method of linking with drugs, the nanoparticles can be classified as:

1. **Encapsulating nanoparticles**: Mainly shown by nanosponges and nano capsules. Nanoparticles like alginate nanosponge has many cavities that transfer the drug molecule. Nano capsules such as poly (isobutyl-cyanoacrylate) (IBCA) are also confining nanoparticle. They can enmesh drug molecules in its aqueous core.
2. **Complexing nanoparticles:** Here, electrostatic charges play role as nanoparticle attractmolecules via these charges.
3. **Conjugating nanoparticles:** In this type, the nanoparticles are associated to drug molecules via strong covalent bonds.

Types of nanosponges[6]

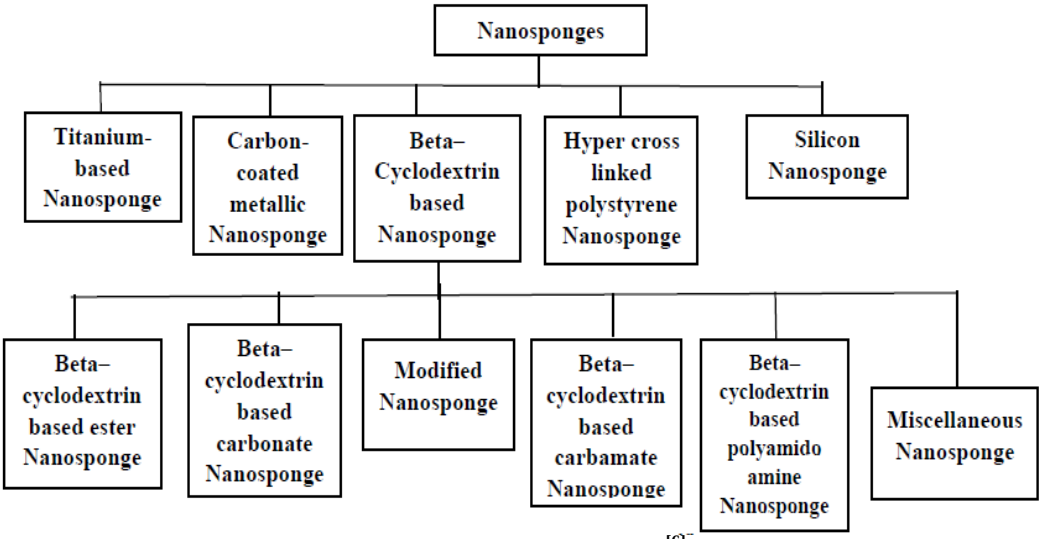

Fig. 2: Types of nanosponges.[6]

Table 1: Formulation of nanosponges prepared.[7]

Name of author	Studies carried
Moura and Lago et al.	Catalytic development of carbon nanotubes and nanofibers on vermiculite was examined in order to make floatable hydrophobic"nanosponges" for oil spill remediation.
Alongi et al.	Reported novel flame retardants containing cyclodextrin nanosponges and phosphorous compounds to enhance ethyl vinyl copolymercombustion properties.
Lee et al.	As electrocatalysts for the oxygen reduction reaction, graphite- nanofiber-supported porous Pt–Ag nanosponges and mesoporous platinum nanosponges were prepared. One of the most difficult subjects in modern photochemistry is the precise regulation of chiral photoreactions, often known as photochirogenesis. A supramolecular approach to photochirogenes is a practical and promising method for facilitating
Wong et al	Three-dimensional nanosponges have been reported to play an essential role in the fractionalization of peptides for proteomicapplications.
Arkas et al.	It has been reported that nanosponges can encapsulate organic contaminants from water. These nanosponges can be impregnated into ceramic porous filters, resulting in hybrid organic/inorganic filter modules. These hybrid filter modules were evaluated for successful water purification using a variety of water contaminants. It has been demonstrated that polycyclic aromatic hydrocarbons can be eliminated with high efficiency (greater than 95%). Pollutants such as trihalogenomethanes, monoaromatic hydrocarbons, and pesticides (simazine) can also be eliminated (>80%).
Liang et al.	For the first time, pyromellitate-linked cyclodextrin nanosponges were used as supramolecular reaction media for sensitising the enantiomer differentiating photoisomerization of (Z) – cyclooctene and (Z, Z) – 1, 3 – butadiene. The photochirogenesis behaviour of cyclooctadiene was markedly different from that of ordinary sensitizer-modified cyclodextrins.
Alongi et al.	The photooxidation of polypropylene exposed to UV radiation has been studied using cyclodextrin nanosponges and two different ultraviolet stabilisers (specifically 2-hydroxy-4 (octyl oxy)-benzophenone and triphenyl phosphate). In the presence of β cyclodextrin in nanosponges, the oxidation induction time was significantly reduced.
Yang et al.	Using silicon substrates as the backbone, researchers created noncytotoxic scaffolds with nanometer resolution. An optics-based strategy was combined with chemical reformation to change thesurface properties of an IC–compatible material from hydrophilicity to hydrophobicity. They created hydrophobic oxidised silicon nanosponges using this nanofabrication-based method. This study highlighted the potential applications of using the silicon based nanopatterns, such as altering cellular behaviour at specified regions on a micro or nanometer scale.

Advantages of nanosponges

- Targeted site-specific drug delivery.[1]
- This nanosponge technology offers entrapment of wide variety of ingredients and reduced side effects.[1]
- This system helps to improve stability, increased elegance and enhanced formulationflexibility.[1]
- These systems are non-irritating, non-mutagenic,

non-allergenic and non-toxic.[1]

- Extended release action up to 12 hours can be achieved.[3]
- Helps to minimizes the irritation and it gives better tolerance which lead to better patientcompliance.[1]
- Improves material processing as liquid is converted to powder.[3]
- These formulations are stable at a wide range (pH 1 – 11).[3]
- It is also stable at higher temperature up to 130ºC.[1]
- These are the self-sterilizing as their average pore size is 0.25 µm so bacteria cannotpenetrate.[1]
- These are free flowing and cost effective.[1]
- They have better thermal, physical and chemical stability.[1]
- These particles are soluble in water, so encapsulation can be done within the nanospongeby the addition of chemical called adjuvant reagent.[1]
- Improve aqueous solubility of lipophilic drug.[4]
- It is used to protect the molecules and develop drug delivery systems for various administration routes.[4]
- It masks the unpleasant flavours.[4]
- Biodegradable in nature.[5]
- Improved bioavailability.[5]

Disadvantages of nanosponges

- Para crystalline as well as crystalline form can be available in nanosponge. These Para crystalline nanosponge shows different loading capacity hence the loading capacity depends on degree of crystallization.[9]
- Nanosponge can entrap only small sized molecules.[9]
- Due to their small particle result in limited drug loading hence dose dumping may occurat times.[9]
- Nanosponges have ability to encapsulate small molecule, not favorable for large molecules.[2]
- Drug loading capacity is also affected by the degree of crosslinking, the crosslinking estimates the void space available in nanosponges which can be used in drug loading. There is a chance of dose dumping due to early dissolution of crosslinker.[2, 6]

Characteristics of nanosponges:

Nanosponge are those which enclose nanoparticle which can hold the drug substance in thecore.[6] The functional group which is present and its concentration in the cross-linker plays an important role as it affects the porosity of the nanosponge and gives changeable polarity.[6] Nanosponge of changeable polarity and of a specific size can be synthesized by altering thecross-linker to polymer proportion.[4] The cavity in the framework can be made with the crosslinkers present which even modifies the drug release pattern.[6]Nanosponges have a range of dimension 1 µm or can be less than that.[4] Nanosponge are unswerving at increased temperatures up to 300°C, they are non-poisonous and porous particles insoluble in most of the organic solvents.[4] Nanosponge in the formulation are durable over a pH range of 1 – 11and a temperature range of up to 130^{0}C. [4] They form a clear and pearly suspension in water as well as they can be reproduced by simple thermal desorption, extraction with solvents, by the use of microwaves and ultrasound.[4] Nanosponges have 3D structure which enables them to transport, capture and specific release of huge variety of substances. They have competency to bind with different functional group and hence can be targeted to different sites. Especially chemical linker helps nanosponges to bind specifically to target site. They form inclusion and non-inclusion complexes with different drugs.[4] They could be either in crystalline or para-crystalline form, as per the given process situation. Crystal complexes of nanosponge are needed for complexation with the drug. Degree of crystallization is decided by the drug-loading capacity of nanosponges. Various drug loading capability is exhibited by para-crystalline nanosponge.[4] Inhalational, topical, parenteral, and oral formulations are currently available as nanosponge preparations.[6]

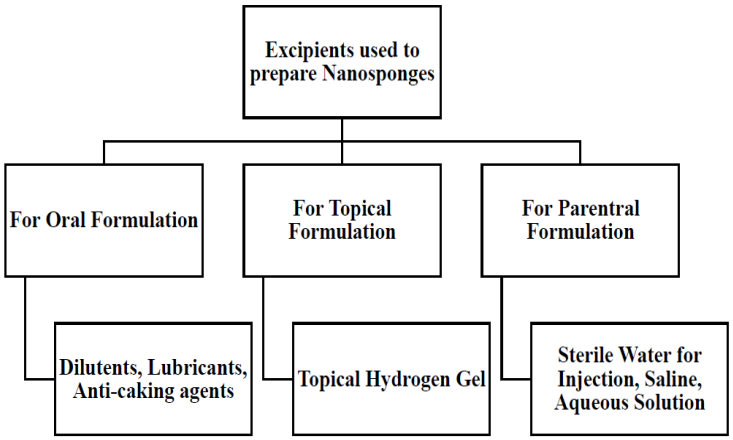

Fig. 3: Excipients used to prepare nanosponges.[6]

The nanosponges have adherent capability thus controlled drug release with a predictable manner can be achieved due to the property of adhering to the surface by nanosponges.[4] The drug has release pattern for 12 hours and thus provides an opportunity for the alliance with immiscible liquid which enhances material processing, which can later be transformed to powder. Nanosponges have good water solubility which helps in administrating poor aqueous soluble drugs.[6] They can transfer both hydrophilic (water-loving) and hydrophobic(oil-loving) drugs. They even possess minute side effects and are profoundly stable and refined. Nanosponge cannot cause cancer as well as allergies.[6] Outer Magnetic area can enhance the release of the drug by adding magnetic particles in presence of ferrite into the mixture during preparation.[6]

Table 2: Material used.[6,18]

Various Polymers Used for Nanosponge Formulations			
Polymers	**Co-polymer**	**Crosslinker**	**Polar Solvent**
Hyper cross-linked polystyrenes Cyclodextrin (alkoxycarbonyl cyclodextrins)	Poly (Valero lactone ally Valero lactone)	Carbonyl diimidazole	Ethanol
Methyl β– cyclodextrin	Poly(Valero lactoneally Valero lactone oxy panedione)	Carboxylic acid dianhydrides	Dimethylacetamide
Poly Valero lactone	Ethyl cellulose	Diarylcarbonates	Dimethylformamide
Eudragit RS100	Polyvinyl alcohol	Dichloromethane	
Acrylic Polymer		Di isocyanates	
		Glutaraldehyde	
		Pyromellitic anhydride	
		2, 2–bis(acrylamide) Acetic acid	

Methods for the preparation of nanosponges

1. Solvent method:

Mix the polymer with a suitable solvent, preferably a polar aprotic solvent like dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). Then, in an excess amount, add this combination to the cross-linker; the optimal cross-linker/molar ratio is 1:4. The reaction was carried out at temperatures ranging from 100°C to the solvent's reflux temperature, over periods varying from 1 to 48 hours. Dimethyl carbonate and carbonyl diimidazole are two cross-linkers that may be preferred. When the reaction is finished, the solution is allowed to cool at room temperature before the product is added to a significant excess of bi-distilled water and recovered by filtration under vacuum before being purified by lengthy Soxhlet extraction with ethanol. Finally, the product is vacuum-dried and ground in a mechanical mill to obtain a homogenous powder.[2, 6]

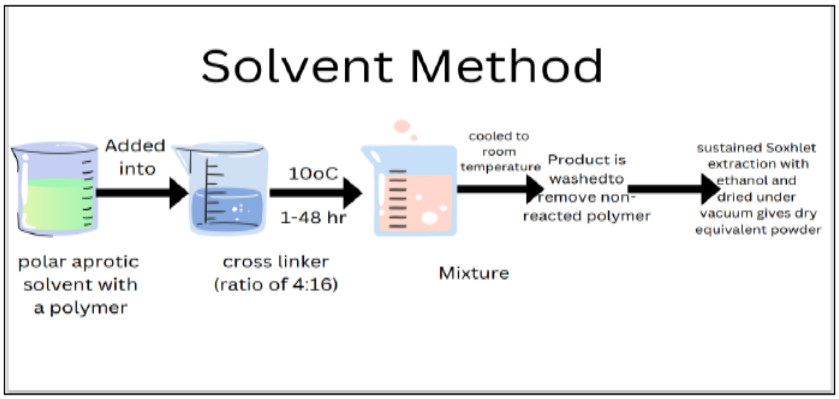

Fig. 4: solvent Method.[6]

2. Melting (Fusion) Method:

Cyclodextrin reacts with a suitable crosslinker in the melt technique, such as dimethyl carbonate, diphenyl carbonate, isocyanates, diaryl carbonates, carbonyl diimidazole ($C_7H_6N_4O$), carboxylic acid anhydrides, and 2, 2–bis (acryl amide) Acetic acid. All the ingredients are properly combined and placed in a 250 ml flask heated to 100°C with a magnetic stirrer for 5 hours. Allow the mixture to cool before breaking it down and rinsing it with a suitable solvent to eliminate any unreacted excipients.[17]

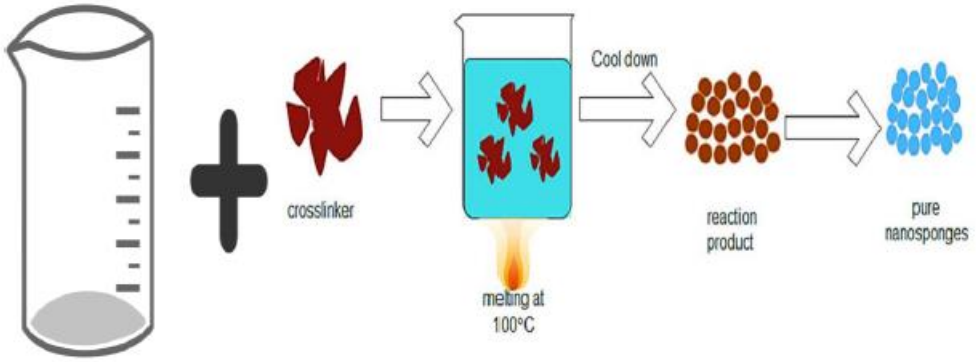

Fig. 5: Melting (Fusion) Method.[6]

3. Emulsion solvent diffusion method:

Nanosponges can be created by varying the amounts of ethyl cellulose (EC) and polyvinyl alcohol (PVA). The dispersed phase including Ethyl cellulose and medication was dissolved in 20 ml dichloromethane before being slowly added to a specific amount of polyvinyl alcohol in 150ml of aqueous continuous phase. For 2 hours, the reaction mixture was agitated at 1000 rpm. Filtration was used to collect the produced nanosponges, which were then dried in an oven at 400ºc for 24 hours. The dried Nanosponges were stored in vacuum desiccatorsto ensure the elimination of remaining solvents.[1,2,11]

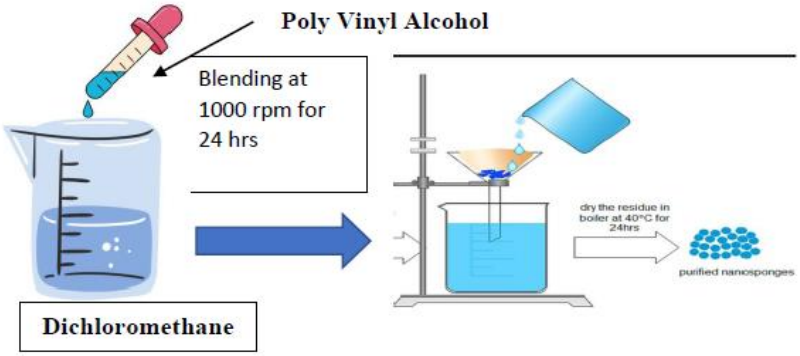

Fig. 6: Emulsion solvent diffusion method.[6]

4. Nanosponges prepared from Hyper Cross–linked β–Cyclodextrins:

Cyclodextrin can be utilized as a carrier for drug delivery system. By reacting with cyclodextrin, nanosponges can be prepared by using a cross linker. As a result, 3D networksare produced, which may be a roughly spherical structure about the size of a protein with interior channels and pores. When cyclodextrin reacts with a cross-linker such as diisocyanates, diary carbonates, and so on, the size of the sponge is controlled by porosity and surface charge density for attachment to diverse molecules. Nanosponges can be made in neutral or acidic forms. An average diameter of nanosponge is less than 1 m, however, fractions smaller than 500 nm can be chosen. They are used to improve the aqueous solubilityof poorly water-soluble medications. They are made up of solid particles that have been crystallized.[6, 11, 13]

5. Ultra sound assisted method:

The polymer ultrasonics junction is used in the ultrasound-assisted method of synthesis. Crosslinking happens without the use of a solvent, and polymer crosslinking occurs as a result of ultrasonic vibrations. Polymer and crosslinker were mixed in a flask at an appropriate molar ratio. An ultrasound bath was utilized to place the flask during the ultrasonication procedure, at a temperature of 90°C for 5 hours. Following sonication, the temperature of the collected mixture was decreased, and the product was forcefully divided and cleaned to extract unreacted polymer and reagents with an excess volume of water. Soxhlet extraction was used to purify the washed solid with ethyl alcohol. The filtered nanosponges were vacuum dried and properly treated before additional drug loading. [5, 13]

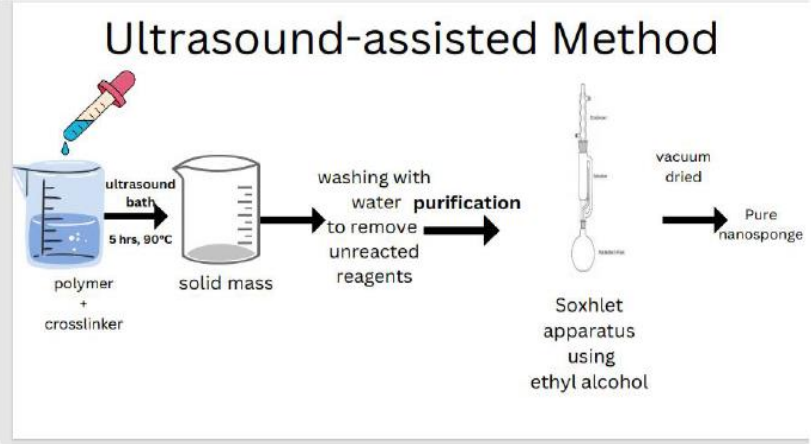

Fig. 7: Ultra sound assisted method.[6]

6. Bubble electrospinning:

A conventional and typical electrospinning arrangement comprises principally of a syringe, as stated in numerous literatures, a syringe pump, a high-voltage supply, and a grounded collector. The amount of production of nanofibers, however, is one of the key restrictions that limits their applicability. Polyvinyl alcohol can also be utilized as a polymer in bubble electrospinning. The solution of polymer (10%) was organized by adding distilled water to it, which was then moved at 80 – 90 °C for 2 hours to form a one-phase mixture. It was thenleft to achieve with the polymer solution at room temperature before being employed to manufacture nano porous fibers.[6]

7. Synthesis using microwave radiation:

This is the concise method of microwave irradiation synthesis of cyclodextrin nanosponges that markedly decrease the reaction time. These nanosponges show high crystallinity levels. Preparation of nanosponge by microwave radiation showed a four-fold decrease in reaction time compared to traditional heating methods. Moreover, a homogenous particle size distribution with consistent crystallinity was created. Singireddy et al. preformed an experiment to determine beneficial effects of microwave-assisted heating in comparison to conventional heating during synthesis of cyclodextrin based nanosponges. The outcomes ofresearch suggested that nanosponge prepared by microwave-assisted synthesis has doubled the drug holding capacity for the model drug. The result of high resolution-transmission electron microscopy showed that nanosponges were highly crystalline, and showed increased degree of complexity along with narrow size distribution. The advantage of synthesis utilizing microwave irradiation is that it delivers direct energy to the targeted molecules, allowing energy to be delivered precisely. The energy is not lost by heating the container walls or the liquid next to the reactant molecules, thus the entire effect is visible as the reaction progresses towards completion. Zainuddin et al. , used microwave synthesizer to synthesis β–cyclodextrin in Para crystalline nature and used diphenyl carbonate for crosslinking.[6]

8. Quasi emulsion solvent method:

The nanosponges can also be made utilizing the quasi-emulsion solvent diffusion approachand various polymer quantities. Eudragit RS100 was dissolved in a suitable solvent to prepare the inner phase. The drug can then be added to the solution and dissolved using ultrasonication at 35^0C. The inner phase was poured into the poly viny alcohol solution in water (outer phase) and stirred for 1 hour before filtering to separate the nanosponges. The nanosponges are dried in an air heated oven at 40^0C for 12 hours. [16, 17]

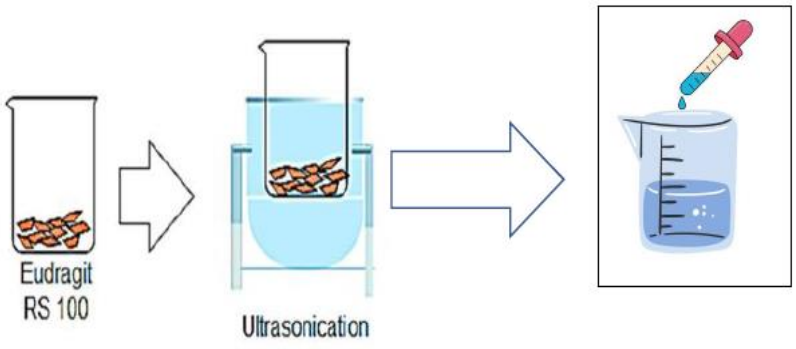

Fig. 8: Quasi emulsion solvent method.[6]

9. Polymerization:
A non-polar drug solution is generated in the monomer, to which an aqueous phase containing surfactant and dispersant to promote suspension is added. Polymerization occurs after establishing suspension with distinct droplets of the required size by activating the monomers via catalysis or increased temperature. The polymerization process results in the production of a reservoir-type system with pores at the surface. [16, 17]

Loading of drug:
As per the process of loading of drug into a nanosponge, the nanosponge must first be, processed to get the particle size smaller than 500 nm. To achieve this range, the nanospongeis suspended in water. Thus, these suspended ns can get accumulated hence to prevent this, they are strenuously sonicated. Then to produce a colloidal fraction the suspension is centrifuged. The floaty layer is isolated and the sample is dried with the help of a freeze dryer. Thus, the watery suspension of nanosponge is prepared. Further, the superfluity of thedrug is added to the suspension and stirred uninterruptedly for a certain period for complexation to take place. After it has taken place, the remaining uncomplexed drug is separated with the help of centrifugation. The crystals of nanosponge can be obtained by evaporating the solvent or with the help of a freeze-dryer. The solid crystals of nanosponges have a critical role in the complexation of a drug. The crystalline nanosponge has more drug loading capacity when compared with Para crystalline nanosponge. The loading of the drug occurs as a mechanical mixture in frail crystalline nanosponge.[2]

Developed nanosponges are suspended inside drug dispersions and freeze-dried along with the drug substance. Loading of drugs can also be carried out by using the solvent evaporation method, in this technique the drug particles are dissolved in an appropriate organic solvent. In the above dispersion of the drug, now the prepared nanosponges are added and titrated till the solvent gets evaporated. The solubility of the drug decides the Drug/nanosponge ratio. For instance, itraconazole was mixed with dichloromethane to form a solution. To the above solution, a nanosponge with copolyvidonum was added and triturated till the solvent gets evaporated. The ratio of 1:1:1 is maintained while adding of the drug, nanosponge, copolyvidone. Furthermore, the acquired solid dispersion was dried overnight in the oven (at 50^0C and at atmospheric pressure) to exclude any traces of dichloromethane. The ratio ofcyclodextrin and crosslinker can also be differed during preparation to enhance the drug loading and to achieve a smart release profile.[10]

Mechanism of drug release from nanosponges
The nanosponge is open structured that is they do not have any incessant membrane in its surroundings, thus active ingredient is mixed into the vehicle via the encapsulated form. Moreover, the encapsulated active material can flow freely from the particles into the agent until the agent (vehicle) gets flooded thus equilibrium is achieved. Unsaturation due to disruption in equilibrium in a vehicle having an active substance is observed when the product is applied to the skin. Hence, flow occurs of active substances from the nanospongeinto the epidermis till the vehicle is dried up. The release of active materials is uninterrupted for a longer period in the skin even though the nanosponge particles accumulated in the skin surface at the stratum corneum.[2]

Factors affecting drug release[18]
- Chemical and physical effects of entrapped active ingredients.
- Capability of vehicle in which the sponges are diffused finally.
- The properties like pore diameter, pore volume and resiliency of sponges.
- Pressure (rubbing) can release active material from nanosponges into the skin.
- Pore characteristics as well as composition even particle size is considered as crucialparameters.
- External parameters like pressure and solubility of active material, temperature.
- Temperature because few entrapped entities can be too viscous at room temperature to flow, hence, to increase flow spontaneously from sponge to skin then the temperature of skin or its environment must be increased which results in higher flow rate indirectly drug release.
- Solubility is also important because certain release of materials occurs in presence of water. For instance, sponges filled with water-soluble ingredients like antiperspirantsand antiseptics release the material in presence of water.

Factors affecting nanosponge formulation
1. **Type of polymer:** The type of polymer used can affect how successfully nanosponges form and function. The cavity size of a nanosponge for complexation should be adequate to fit a drug molecule of a specific size.[3, 5] The pre-formulation is impacted by the polymer utilised in the creation of nanosponges.[2] The formation of nanosponge is influenced by the type of polymer used, the type of cross-linking agent and ratio of polymer to cross-linker and affect the rate of drug release from nanosponges.[9] Molecular nanocavities are transformed into a 3D nano porous structure by a very effective cross-linker polymer.[17] It depends on the crosslinker type utilised whether thenanosponge will dissolve in water or any other solvent.[6]

Hydrophilic nanosponges: A cross-linker called epichlorohydrin is used to make a hydrophilic nanosponge. Hydrophilic nanosponges are an efficient drug carrier becausethey can alter the rate of drug release even in formulations for immediate release and improve drug absorption through biological barriers.

Hydrophobic nanosponges: To create hydrophobic nanosponges, crosslinkers such as diphenyl carbonate, pyromellitic anhydride, di isocyanates, and carbonyl diimidazole can be used. For drugs that are water soluble, like peptides and proteins, they serve as sustained release carriers.[6]

2. **Type of drug:** The following characteristics for drug molecules that will be complexed with nanosponges should be present. The molecular weight of drug should range from 100 to 400 Dalton. Less than five condensed rings make up the average drug molecule. Less than 10 mg/ml of solubility is required in water. The melting point of drug must be below 250°C. [15, 16]

3. **Temperature:** Temperature variations affect a stability constant of nanosponge complex. The stability constant and temperature rise are inversely proportional. In general, increasing temperature decreases the magnitude of the stability constant of nanosponge/drug complex may be due to the result of reduction of nanosponge interaction forces, such as Vander-Waal and hydrophobic forces with increase in temperature. [16]

4. **Method of preparation:** The method of loading of drug can affect the drug or nanosponge complexation. The effectiveness of a method will depend on the nature or characteristics of drug and polymer; however, freeze-drying was found to be most effective for drug complexation. [1, 5, 15]

5. **Degree of substitution:** The number, type, position and substitution of the substituents on the parent molecule affect the complexation ability of nanosponges. Because there are different types of B–cyclodextrin derivatives available with varying functional groups on their surface, the type of substitution is important. When complexed together with the help of a crosslinker, different functional groups yield different types of complexed material such as β cyclodextrin nanosponges, β cyclodextrin carbamate nanosponges, β cyclodextrin carbonate nanosponges, etc. The degree of crosslinking is directly related to the number of substitutions that are present; the more substitutions, the more likely it undergoes crosslinking. A greater degree of crosslinking will result inhighly porous nanosponges because more connections between the polymers will create a mesh-like network. The production condition depends on position of substitution.[1,2,3,16]

Evaluation of nanosponges

1. **Loading efficiency:** The formed nanosponge its loading efficiency is determined by subtracting the un-trapped drug from the total amount of the drug. The drug entrapment efficiency will be determined by separating un-entrapped drugs which are estimated by any method of analysis. Some of the methods are gel filtration, dialysis, and ultra-centrifugation. The amount of the drug loaded into the nanosponge can be estimated using a UV spectrophotometer and a high-performance liquid chromatography method for the nanosponges. The following equation can be used to determine the loadingefficiency of the nanosponge. [2]

$$\text{Loading Efficiency} = \frac{\text{Actual Drug Content in Nanosponges} \times 100}{\text{Theoretical Drug Content}}$$

2. **Microscopic studies:** For the analysis of topography and microscopy aspects of the drug surface, nanosponges and the product(drug/nanosponge complex), a Scanning Electron Microscope(SEM) and Transmission Electron Microscope (TEM) can be used. The difference between the state of crystallization shown by initial materials and the resultants were observed under the microscope which suggests that inclusion complexes are formed. The NS surface morphology was determined using JEOL JSM-5610LV scanning electron microscope for 30 kV transmissions. JEOL JFC-1600 auto fine coater helps with covering products with gold-palladium under an argon atmosphere at room temperature. In another analysis, TEM JEOL 1400 was used at transmissions of 60 kV where approximately 10 µL of nanosponge sample was diluted with Milli-Q water to 100 µL. To visualize the sample, 5 µL of the watery mixture, the sample was held on a network then held on a glass plate for a microscope and then observed. [3, 6]

3. **Particle size and Polydispersity Index (PDI):** Dynamic light scattering can be used to assess particle size utilizing a 90 Plus particle sizer loaded with MAS OPTION particle sizing software or laser light diffractometry or Malvern Zeta sizer. The measurements were made at a fixed angle of 900 at a temperature of 25^0C. Each sample is then analysed in triplicate. DLS is defined as a technique used to find out the size distribution profile of nanoparticles. The polydispersity index (PDI) and mean hydrodynamic diameter (Dh) can be measured from dynamic light scattering instruments. The PDI measures the width, spread, or variance of the particle size distribution. A monodisperse sample has a lower PDI value; whereas a higher value of PDI indicates a wider particle size distribution and polydisperse nature of the nanosponge. Particles larger than 30 µ can impart a gritty feeling and hence particle size should be between 10 and 25 µ are preferred in the final topical formulation. [3, 9]

4. **Zeta potential:** The surface charge of the nanosponge is measured by a zeta sizer. It is possible to measure it with an additional electrode in particle-size equipment. Zeta potential is defined as the difference of potential between two layers

(dispersion medium and immobile layer) of fluid locked up with dispersed particles. high zeta potential will prevent particle-particle agglomeration. If the zeta potential is greater than 30mV the dispersion will be stable. To determine the zeta potential, samples of nanosponge dispersions were diluted with a KCl solution of 0.1 mmol/L and placed in an electrophoretic cell, at an electric field of about 15 V/cm. The higher the value of the zeta potential of a colloidal dispersion more is its stability. [2, 10]

5. **Fourier Transform Infrared (FTIR) Analysis:** It was conducted to verify the interactions of chemical bonds between drug-polymer complex, drugs, blank nanosponges, and drug-loaded nanosponges and the possible interactions. The range detection is from 4000 to 650 cm^{-1} and black carbon reference. It also helps in the detection of hydrophilic and hydrophobic sites in nanosponge. In hydrophobic drugs, ifthe functional groups are not visible implies that the functional groups have complexed with cyclodextrin or its cavity. [6, 10]

6. **In-vitro drug release study:** The release of drug from the nanosponge formulation can be studied using a multi-compartment rotating cell with dialysis using Franz Diffusion cell with a diffusional area of 2.26 cm^2 with 25 rpm. An aqueous phase dispersion of nanosponges (1 ml) containing the drug is placed at the donor compartment, while the receptor compartment separated by a hydrophilic dialysis membrane is filled with phosphate buffer at pH 7.4 or pH 1.2. it is carried out for 24 hr and the receptor buffer is completely withdrawn and replaced with a fresh buffer then analysed by UV spectrophotometer.[1, 5]

7. **Drug release kinetics:** The release data was analysed using the Zero order, first order, Higuchi, Korsmeyer–Peppas, Hixon Crowell, Kopcha, and Makoid–Banakar models to study the mechanism of drug release from the Nanosponge. The graph pad prism software can be used to analyse the data. The software calculates the parameters of a nonlinear function that gives the best fit between experimental data and the nonlinear function. [1, 16]

8. **Solubility studies:** Higuchi and Connors created a method for studying inclusion complexation known as the phase solubility method, which investigates drug solubility in nanosponge. The degree of complexation is indicated by phase solubility diagrams. The Erlenmeyer flask was employed in this approach. The drug is introduced to the flask along with an aqueous solution containing varying percentages of nanosponges. After stirring the Erlenmeyer flask on a mechanical shaker at room temperature until it reached a steady state, the suspension was centrifuged using a 3000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 U.S.A). High performance liquid chromatography was used to determine the medication concentration in the solution. [2, 16]

9. **Resiliency (Viscoelastic properties):** The resiliency (viscoelastic characteristics) of sponges can be altered to produce beadlets that are softer or stiffer depending on the final formulation's requirements. Crosslinking causes the rate of release to slow down. As a result, the resiliency of sponges will be evaluated and modified as needed by considering release as a function of cross-linking with time. [3, 11]

10. **Dissolution test:** The dissolving profile of nanosponges can be examined using the dissolution apparatus USP XXIII with a modified basket made of 5 m stainless steel mesh and a rotation speed of 150 rpm. To achieve sink conditions, the dissolution medium is chosen with active solubility in consideration. Samples from the dissolution media can be evaluated using an appropriate analytical method. [3, 16]

11. **Porosity:** A porosity analysis is carried out to determine the extent of the produced nanochannels and nanocavities. A helium pycnometer is used to measure the porosity of nanosponges because helium gas may penetrate material inter- and intra-channels. The helium displacement method determines the true volume of material. Nanosponges havemore porosity than the parent polymer utilised to make the system due to their porous nature.[11,12]

$$\% \text{ Porosity} = \frac{\text{Bulk Volume} - \text{True Volume}}{\text{Bulk volume}} \times 100$$

12. **Thermo analytical methods:** This method states that the will the drug substance undergo change former to the thermal degradation of the nanosponge. Changes observed can be melting, decomposition, oxidation or polymorphic transition and evaporation. The complex formation will be indicated via the change in drug substance. The Thermogram received will be studied for immerging of new peaks or disappearance of certain peaks and shifting as well as broadening even weight decrement can prove the formation of inclusion complexes.[1]

13. **Thin layer chromatography:** In this parameter the value Rf of drug reduces to certainapplicable manner which helps in knowing the complex formation between the drug and nanosponge. The inclusion complex between both molecules is reversible phenomenon. Thus, there can be separation in of both molecules which will appear separate in chromatographic process and only spots of individual molecules are found on TLC plate.[1]

14. **Infra-Red Spectroscopy:** It estimates the interaction between ns and the drug molecule which are in solid state. This technique involves by assigning band however, the method is not able to detect the inclusion complexes and less dependable than other method. Its application is restricted to the drugs having few characteristic bands, like carbonyl even sulfonyl groups. This study provides information related to involvement of hydrogen in various functional groups. Due to this it shift the absorbance band to lower frequency, increment in intensity and broadens the band caused by stretching vibration of group which were involved in making of hydrogen bonds . Largest shift will be observed dueto H-bond at hydroxyl group. [1]

15. **X–Ray Diffractometry:** To find inclusion complexation (solid state) powder x-ray diffractometry is used. In case of drug molecule being liquid (liquids do not have diffraction pattern of their own) then diffraction pattern observed will be completely differ from uncomplexed ns. While, for solid material, a comparison must be made between the diffractogram of assumed complex that to the mechanical mixture of polymer and drug molecule. Sum of each component gives diffraction pattern of physical mixture. While, new solid phase obtained by diffraction pattern of complex which vary for each constituent. Chemical decomposition and complex formation can be determined by diffraction peaks of mixture of compounds. The complex formed between drug and ns can vary the diffraction pattern and even change the crystalline nature of drug. Furthermore, the complex formation helps in sharpening of existing peaks, new peak formation and changing of certain peaks. [1]

16. **Single Crystal X–Ray structure analysis:** Single crystal x-ray structure analysis method is used to determine the complicated structure and mode of interaction. Accurate geometrical relation can be obtained if the interaction between the host and guest molecules can be known. The viable knowledge acquired during analysis leads to know about the formation of complex. [15]

Table 3: Examples of Nanosponges.[1,18]

Various Drugs Formulated in Nanosponge Formulations				
Drug	**Polymer**	**TherapeuticUse**	**Study**	**In–vitro /In–vivoModel**
Anti-sense oligonucleotides	Sodium alginatePoly L-lysine	Cancer therapyViral infectionPathologic disorder	Pharmacokinetic studies	Mice
Tamoxifen	β-cyclodextrin	Breast cancer	Cytotoxicity	MCF7 cell line
Resveratrol	β-cyclodextrin	Inflammation, Cardiovascular disease Dermatitis Gonorrhoea Fever hyperlipidaemia	Accumulation ofdrug in the buccal mucosa of rabbit Ex- vivo study Permeation study	HCPC-I cellline Rabbit buccal mucosa Pig skin
Paclitaxel	β-cyclodextrin	Cancer	Bioavailability Cytotoxicity	Sprague Dawley ratsMCF7 cell line
Itraconazole	β-cyclodextrin Copolyvidonum	Antifungal	Saturation solubility study	Higuchi model
Camptothecin	β-cyclodextrin	Cancer	Haemolyticactivity	Diluted blood HT-29 cellline
Dexamethasone	β-cyclodextrin	Brain tumor	Drug release experiment	Dialysis bag technique In-vitro
Econazolenitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat
Temozolomide	Poly (Valero lactone allyl, Valero lactone), Poly (Valero lactone allyl valerolactone-Oxepanedione)	Brain tumours	Drug releasestudy	In-vitro andIn-vivo studies
Bovine Serum Albumin	Cyclodextrin based Poly (Amidoamine)	Protein Supplement	Drug releasestudy Stability study	In-vitro release modulation and stability
Voriconazole	Ethyl cellulose, Polymethyl	Anti-fungal	Drug release Experiment	Rat
	methacrylate,Poly Vinyl Alcohol			

Table 4: Biopharmaceutical Classification System Class – II Drugs can be used to Formulate Nanosponge Formulations.[1,18]

Category	Drug
Antianxiety drugs	Lorazepam
Antiarrhythmic agents	Amiodarone hydrochloride
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
Anticoagulant	Warfarin
Anticonvulsant	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
Antidiabetic and Antihyperlipidemic drugs	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
Antiepileptic drugs	Phenytoin
Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole
Antihistamines	Terfenadine
Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene,Tamoxifen, Temozolomide, Topotecan
Antioxidant	Resveratrol
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
Antiulcer drugs	Lansoprazole, Omeprazole
Anthelmintics	Albendazole, Mebendazole, Praziquantel
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Diuretics	Chlorthalidone, Spironolactone
Gastroprokinetic agents	Cisapride
Immunosuppressants	Cyclosporine, Sirolimus, Tacrolimus
Non-Steroidal Anti-Inflammatory Drugs(NSAIDs)	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
Steroids	Danazol, Dexamethasone
Miscellaneous	Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone

Applications of nanosponges

Nanosponge because of biocompatibility and versatility have several applications in regards to pharmaceutical field. They may be used as excipients in preparation of pellets, granules, suspension, capsules, tablet even solid dispersion and topical dosage form.

1. **Nanosponges as controlled drug delivery:** The pattern of modified release is mostly purposed to optimize the treatment schedule by providing slow, steady delivery of drug over entire dosed interval. Hence, it also reduces the dose administered and change in pharmacokinetic profile even decreases side effects. By using compatible polymers and crosslinkers prolonged drug release from nanosponge can be achieved. Substance like volatile oil for instance, antiviral agents like acyclovir is used for treating infection by herpes simplex virus. The agent is absorbed in GIT at slow rate and is incomplete even highly variable. The in vitro release sate of acyclovir from various types of ns showed sustained release of drug. The release of agent (acyclovir) from nanosponge and carb- nanosponge after 3hrs of administration were about 70% and 22% respectively. As drug was not adsorbed on the surface of nanosponge and even no initial burst effect was observed.[4]
2. **Nanosponges as to enhance aqueous solubility:** Nanosponges are also known as nano porous structures that can carry both hydrophilic and lipophilic drugs. There will be formation of inclusion complex with several drugs which will enhance the aqueous solubility of poorly water-soluble drugs. The complexes are also used to enhance dissolution rate, stability of drug substance and to mask unpleasant odour as well as to convert liquid materials to solid. As compared to direct injection the polymer based nanosponge can deliver the drug molecules to target site 3 to 5 times more efficiently. Even the drug that are specifically critical for formulation in terms of their solubility can efficiently delivered by loading into the nanosponge. The nanosponge are solid in nature can be coined into Oral, Parenteral, inhalation or topical dosage forms. For oral formulation the complex is diffused into matrix of excipients like lubricants, diluents and anticaking agents compatible for formulation of capsules and tablets. For Parenteral formulation the complexation is usually done in sterile water, saline

or other aqueous solution. For topical formulation, they are indulged in topical hydrogel. Due to tiny shape of nanosponge it enables them for pulmonary and venous delivery of nanosponge. The pores present in nanosponge enhances the rate of solubilization of poorly soluble drug by entrapping that drug moiety in the pores. Because they nano sized, they have huge surface area and high rate of solubilization. For instance, the drugs under BCS class – II have low solubility thus when formulated with ns they exhibit improved solubility and convenient drug release property. [5, 9]

3. **In cancer therapy:** Nanosponge can also be used in anticancer drug delivery system. The claim was made that it is three to five times more effective at decreasing growth of tumor than direct injection of drugs. The small nanosponge are filled with a drug and exposed to site having targeting peptides that binds to radiation induced cell surface receptors present on tumor. The cell is encountered by sponges and they stick to surface and are triggered to release their cargo. The merits of targeted drug delivery include more effective therapy with same dose and lesser side effects. Studies conducted on animals with paclitaxel as sponge load. Plant alkaloid (camptothecin) and effective antitumor agent, has little therapeutic capability due to its poor aqueous solubility also lactone ring instability and potent side effect. Cyclodextrin based ns are novel cross-linked derivative of cyclodextrin. They are used as to enhance poorly soluble actives, to protect fluctuating groups and to release in controllable manner. Study was aimed at making complexes of camptothecin with β-cyclodextrin based nanosponges.[5]
4. **Nanosponges as topical drug delivery system:** The delivery system of n is distinctive technology due to its control release of tropical agents with prolong release and retention of drug onto the skin. There are some which can readily form topical ns such as, local anaesthetics, antifungal and antibiotic. The active ingredients penetrate the skin thus leads to rashes or even more potent side effect. On other hand, this technique allows even and sustained release, decreasing irritation also maintain its efficacy. Several substances can be indulged into formulated products like gel, lotion, liquid and even powder also creams and ointment. Econazole nitrate is used tropically which is antifungal agent to give relief from the symptoms of superficial candidiasis, versicolor, dermatophytosis and in skin infections they are available in cream and solution, ointment, lotion. For effective therapy the econazole is applied on skin with higher concentration of active ingredients and here adsorption is not significant. Hence, econazole nitrates ns is trumped up byemulsion solvent diffusion method and ns are being filled with hydrogel for sustained drug release.[5]
5. **Nanosponges as antiviral agents:** Due to vast application of its administration in nasal, ocular, pulmonary route. Thus, with the use of nanocarriers to selective delivery of antiviral drugs or small interfering RNA (siRNA) to nasal epithelia and lungs can be achieved to target viruses like respiratory syncytial virus, influenza virus & rhinovirus. They may use for human immunodeficiency viruses, herpes simplex virus and hepatitis B. The drugs which are used now a days in nano carrier system are zidovudine, saquinavir, interferon–α, acyclovir (Eudragit based). [5]
6. **Encapsulation of nanosponges using gases:** The three gases which were used in cyclodextrin based carbonate nanosponge are 1–methyl cyclopropene, oxygen and carbon dioxide. For biomedical application the complexation of oxygen and carbon dioxide can be useful. In several diseases, supply of oxygen done by nanosponge filled with oxygen to the hypoxic tissues. Due to huge porous structure, it is effective gas carrier. Nanosponge formulation has capability to stock and release oxygen in controllable manner. In upcoming eras, nanosponge can be important tool for carrier of some important gases. [5]
7. **Nanosponges as chemical sensors:** Nanosponge which are used as chemical sensor are"metal oxides'' they are highly sensitive for detection of hydrogen with the nanosponge titania. Because the structure of nanosponge has no initial point of contact so lesser resistance to electron transport and it gives higher 3D parallel nanosponges titania which is tactful to Hydrogen gas. [5]
8. **Nanosponge in protein drug delivery:** Bovine serum albumin (BSA) protein is stored in lyophilized form because it is unsteady in solution form. Expandable cyclodextrin based polymer nanosponge has stability for proteins like BSA. Nanosponge is also used for enzyme immobilization, protein encapsulation with stabilization and controlled delivery. [5]
9. **Nanosponges as a transporter for biocatalysts:** They act as transporter in delivery of enzymes, vaccines, antibodies and proteins. There are several drawbacks of industrial process involving chemical transformation certain non- specific reaction tends to provide lesser yield and requires higher temperature and pressure which consumes huge energy, this all drawbacks are eliminated with usage of enzymes as biocatalyst. These enzymes are highly specific even have high reaction speed with requirement of mild reaction conditions. They have positive effect on environment as they lessen the energy consumption and production of pollutants. There is huge increment in industrial application for this and even in development of genetic engineering have improved stability, specificity of enzymes and economy. [5]
10. **As absorbent in treatment of poison in blood:** Nanosponge can absorb the poison in body thus helps in elimination of dangerous poison from blood. Alternate of using antidotes, if we engulf

nanosponge with injection into blood nanosponge can absorb the toxins. It can absorb toxins in bloodstream via attacking it due to they appear as red blood cells. Number of molecules it can absorb depends on the toxin. [2]

11. **Miscellaneous:** The microporous hyper cross-linked nanosponge are used for specific separation of inorganic electrolytes by size elimination chromatography. 3D nanosponge in fractionalization of peptides for proteomic administration. Nanosponge based cyclodextrin can forcefully bind organic molecules and eliminate them from water evenat low concentration. Nanosponge as transporter of gases like oxygen and carbon dioxide. It is also used in biomedical application. Nanosponge can absorb biomarker for diagnostic purpose. The nanosponge can collect rare cancer marker from blood.[5]

CONCLUSION

In skin the nano sized colloidal transporter can easily penetrate. Furthermore, they are having small size and porous nature thus they can bind poorly water soluble drugs in their matrix and enhance bioavailability of drug. Even poorly soluble drugs solubility is enhanced by nanosponge. Nanosponge have capability to include either lipophilic or hydrophilic drug and release them in manageable and predictable manner at its target site. The release rate can be modified via controlling the ratio of polymer to cross-linker and particle size. The active moiety of insoluble drug can be protected from physicochemical degradation by nanosponge. Due to their small size and spherical shape are can be formulated in various dosage forms like aerosol, parenteral, topical and tablets. Nanosponge can be efficiently retained on skin when incorporated in tropical drug system. Nanosponge has tiny mesh like structure thus it can used in treatment of several diseases. Nanosponge has 5 times more effective for delivery of drug in the treatment of life threatening diseases such as cancer. Theaverage pore size of a nanosponge is 0.25 µm thus bacteria could not penetrate hence they are self–sterilizing.

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