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A Comprehensive Review Article on Nanosponges

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ABSTRACT:
The technologies who involved in the formulation of pharmaceutical products to alter drug release profile, absorption, distribution and elimination for the benefit of enhancing product efficacy and safety, as well as patient compliance targeting the delivery of drug is a biggest problem facing by the medical scientists. The developments of new and complex molecules called Nano-sponges have the capacity to solve this problem. Nanosponge are tiny sponges with size is about a virus, which can be filled with wide verity of drug. And these tiny sponges can circulate around the body until they encounter the specific site and stick on the surface and release the drug in an control and predictable manner.Another important character of these sponges is solubility they allow the use of drug who is poorly soluble and the nanosponges are solid in nature and can be formulated as oral, parenteral, topical and inhalational dosage forms.

KEYWORDS: Nanosponges,Targeted drug delivery

I. INTRODUCTION:

The delivery of the drug to the body is only possible by the drug delivery system. The drug delivery system provides the drugs to the body to achieve the desired therapeutic effect/effect of drug.The novel drug delivery system has reawakened interest in drug delivery by targeting the drugs to appropriate site/right area. Targeting the drugs to the appropriate site has long been a challenge for medical researchers. The need for targeting drug therapy is to control the release of drug, to maximize the therapeutic effect/efficacy and to minimize the toxicity/toxic effects of the drugs. Nanosponges which are novel and sophisticated molecules have the ability to alleviate these challenges.Nanosponges are a novel class of material that is used as a carrier in drug delivery system. They are made up of microscopic particles having some nanometer wide cavities that can encapsulate a large variety of drug substances. These particles can contain both lipophilic and hydrophilic compounds as well as improve the solubility of molecules that are poorly water soluble.

Nanosponges are tiny/microscopic mesh like structures/bodies that have the potential to revolutionize the treatment of numerous diseases. Early trials reveal that this technology is up to five times more successful than traditional methods for delivering medications to patients with breast cancer. This system allows excellent delivery/administration of topical drugs.

The nanosponges are about the size of virus having a scaffold structure called backbone that is made up of naturally long length degradable polyester. The polyester strands are mixed in the solution of small molecules called cross-linkers. These cross-linkers have the affinity for certain portions of the polyester. The segments of these cross-linker polyester forms a spherical shape that has many cavities/pockets where the drug particles/molecules can be stored. As the biodegradable polyester gradually breaks down in the body, the loaded drug can be released in a predictable schedule[1-8].

ADVANTAGES OF NANOSPONGES:

1. The formulation of nanosponges is biodegradable as they are made up of degradable polyesters.
2. These types of formulations are non-mutagenic, non-irritating and non-toxic in nature.
3. Solubility of both lipophilic and hydrophilic drugs may be improved.
4. Enhanced flexibility of formulations with increased elegance and stability up to 13^0C.
5. Cost effective formulations that can be used commercially.
6. Nanosponges are also useful as toxins (such as snake venom- by quickly elimination of harmful substances from the blood stream).

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7. As they provide therapeutic effect for longer duration, chances of dose dumping are low.
8. Particle size can be increased or decreased by changing the cross-linker to polymer.
9. Due to their average pore size of 25nm, bacteria can't penetrate hence they are called self-sterilizing.
10. They can be used to convert liquid substances to solids and to mask unpleasant flavors.
11. The nanosponges are solid in nature and can be formulated as oral, parenteral, topical and inhalational dosage forms.

DISADVANTAGES OF NANOSPONGES:

1. Only small molecules are encapsulated by nanosponges.

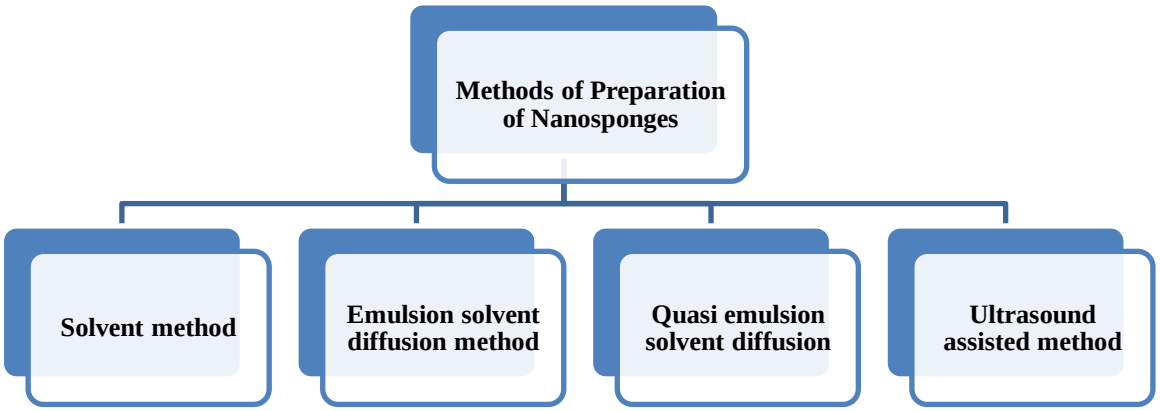
2. Loading capacity of nanosponges are very low that's why they depends on the loading capacity[9-12].

II.TYPES OF NANOSPONGES:

- Cyclodextrone Based Nanosponges
- Titanium Based Nanosponges
- Silicone Nanosponges
- Hyper-Crosslinked Nanosponges
- Cd Based Carbamate Nanosponges
- Cd Based Carbonate Nanosponges
- Cd Based Ester Nanosponges
- Polyamid Nanosponges
- Modified Nanosponges

III.METHODS OF PREPARATION OF NANOSPONGES:

Methods of preparation of nanosponges shown in figure.



Methods of preparation of nanosponges

Emulsion solvent diffusion method

The main polymers used in this method are ethyl cellulose and polyvinyl alcohol in varying proportions. The dispersed phase is formed by adding ethyl cellulose and the available drug which is dissolved in 20ml of dichloromethane. The drop wise addition of continuous phase is by prepared by dissolving polyvinyl alcohol in 150 ml of distilled water. Then the mixture is allowed to stir for 1000rpm for about 2 hrs. The obtained Nano sponges are collected, filtered and dried in oven for around 1 day and stored in desiccators[13].

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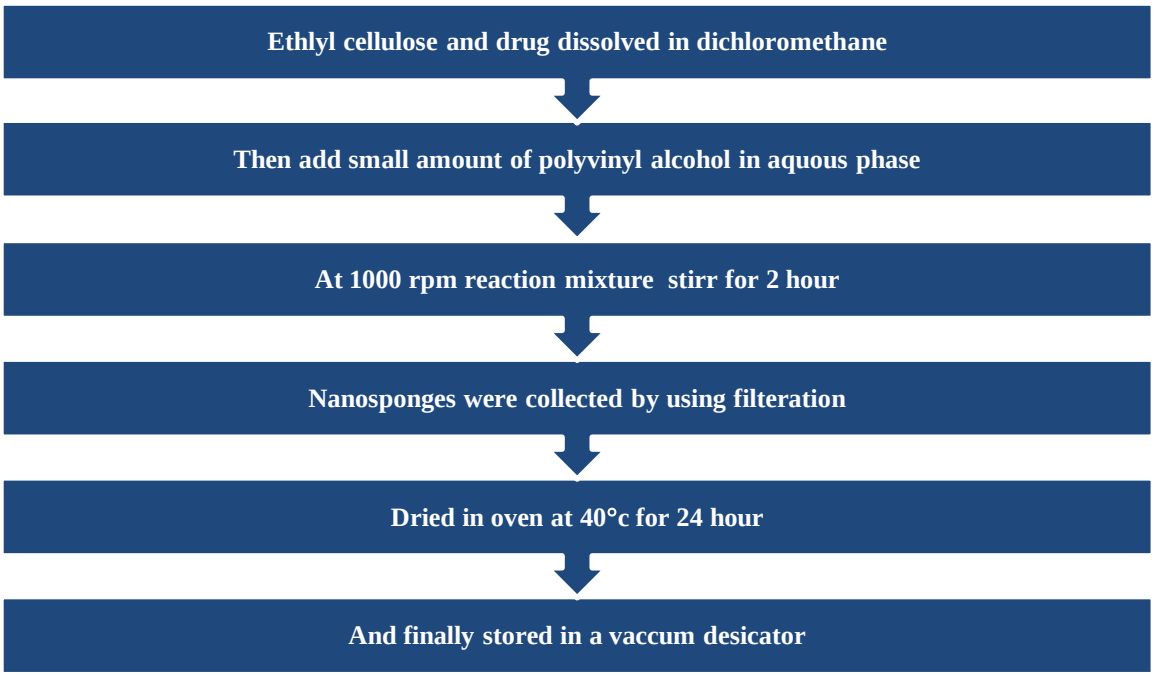

Flow chart preparation of nanosponge by emulsion solvent diffusion method

Solvent method:

Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide. Then add this mixture to excess quantity of the crosslinker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 10^0C to the reflux temperature of the solvent, for time ranging from 1 to 48 hrs. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyldi imidazole). After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bi distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet [14].

Quasi-emulsion solvent diffusion:

The nanosponges arranged utilizing the polymer in various sums. The inward stage is readied utilizing Eudragit RS 100 and added to a reasonable dissolvable. Medication utilized gave an answer and broke down under ultra-sonication at 35ºC. This inward stage included into outside stage containing PVA go about as emulsifying operator. The blend is mixed at 1000-2000 rpm for 3hr at room temperature and dried in an air-warmed stove at 40ºc for 12hr[15].

Ultrasound assisted synthesis:

In ultrasound-assisted synthesis, polymers mix with cross-linkers in absence of solvent in a flask and place the flask in ultrasound bath field with water and heat it for 90^{o}C and sonicate for 5 hours. Allow mixture to cool and break the mixture roughly. Wash the mixture with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol and dry the product under vacuum and stored at 25^{o}C until further use[16].

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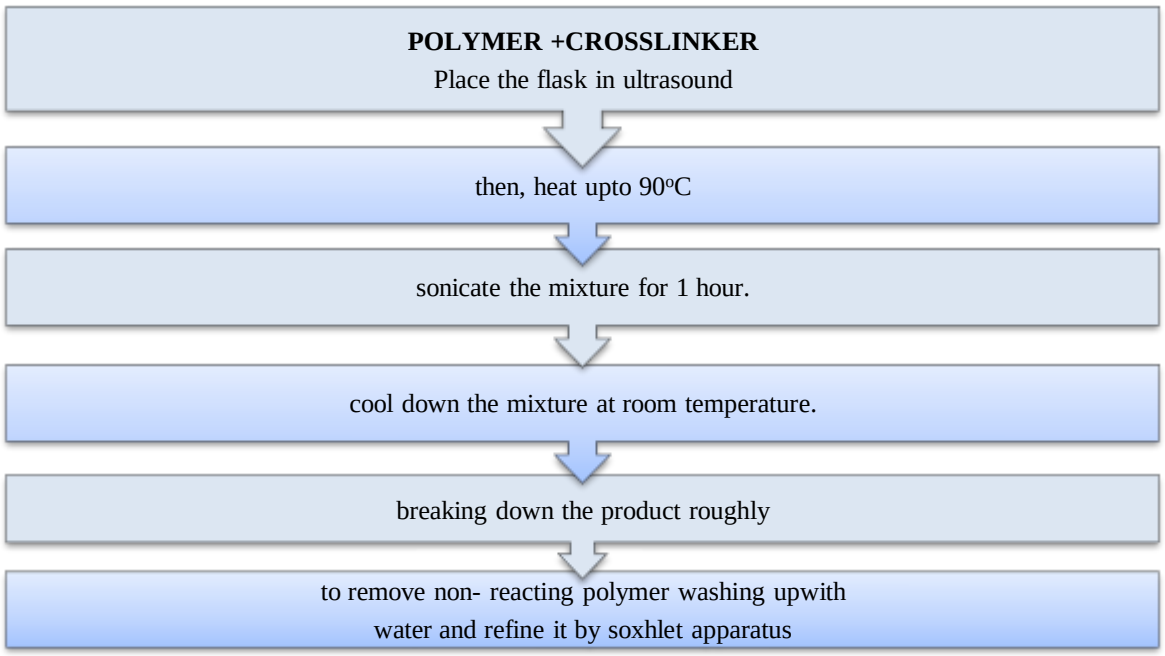

Flow diagram for the preparation of nanosponges by using ultra-sound synthesis method.

IV. FACTORS INFLUENCING NANOSPONGE FORMULATION

Types of polymer

The formation of nanosponges depends upon the selection of suitable polymer. The cavity or pore size of the nanosponges should be able to accommodate the drug molecule of suitable size.

Types of drug

The drug molecule structure should contain less than five condensed rings. The molecular weight is 100- 400 Daltons. The solubility in water should be less than 10 mg/ml. The melting point of the drug substance should be less than 250 °C [17].

Temperature

The change in temperature can affect the drug/nanosponges complexation. The increase in the temperature decreases the magnitude of the apparent stability of the Nanosponges complex which may be due to a result of possible reduction of drug/ nanospongesInteraction forces, van der Waals force and hydrophobic forces with rise of temperature[18].

Method of Preparation

The method of preparation of drug loaded nanosponges can affect drug/nanosponges complexation. However, the effectiveness of a method depends on the polymer and nature of the drug, in many cases freeze drying was found to be most effective for drug complexation[19].

Degree of Substitution

The formulation nanosponges may be deeply affected by the number, type and position of substituent on the parent molecule[18].

V. EVALUATION OF NANOSPONGE:

Production Yield

The production yield can be determined by calculating initial reading of row material and final reading of nanosponges**.**

(Production yield=practical mass of nanosponges/theoretical mass (drug +polymer)*100)

The percentage yield of different nanosponges was determined by weighting after drying**.**

Drug Entrapment Efficiency-

The entrapment efficiency is calculating by accurately Weight the Quantity of Nanosponges (10mg) with 5ml of methanol in a volumetric flask and shaken for 1 min using vortex mixer.

The volume was made up to 10ml. then the solution was filtered and diluted and the concentration of drug was determined spectrophotometrically by wavelength.

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(Loading Efficiency=Actual Drug Content of Nanosponges /Theoretical Drug Content*100)

Determination of Drug Content

To study the amount of drugs fused in the nanosponges. The drug was extracted from Nanosponge by dissolving them in 25ml of methanol. The resulting solution was filtered. The drug content in the methanolic extracts was analyzed by using a UV-Visible spectrophotometer at a wavelength against methanol in blank.

(% Drug Content = Actual Drug Content/Theoretical Drug Content *100)

size and polydispersity index: The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software or laser light diffractometry or Malvern Zeta sizer. From this, the mean diameter and polydispersity index can be determined values of polydispersity index are given in table[20]

Part icle

Polydispersity index	Type of dispersion
0-0.05	Monodispersed standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Midrange polydispersity
>0.7	Very polydisperse

Table : Polydispersity index

Resiliency:

Resiliency (viscoelastic properties) of sponges can be modified to produce beadlets that are softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time[20].

Solubility studies:

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nanosponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation[21].

Zeta potential determination

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment[22].

Loading efficiency

The loading efficiency (%) of the Nanosponges can be calculated according to the following equation[23,24],

$$L.E = \frac{\text{loading efficiency actual drug in Nanosponges}}{\text{Theoretical drug concentration}} \times 100$$

Microscopy studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes[25] .

Thermoanalytical methods

Thermoanalytical methods determine whether the drug substance undergoes some changes before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The

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thermogram obtained by differential thermal analysis and differential scanning calorimetry can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes[26].

Thin layer chromatography

The Rf values of the drug molecule diminish to considerable extend in thin layer chromatography and this helps in identifying the complex formation between the drug and nanospsonge formulation[27].

In-Vitro Drug Release Study

The in-vitro drug release study is performed by using USP Paddle method at 50 rpm and temperature in between 37± (0.2)°c in 900ml ml of pH buffer(pH=6.8). In the formulation 100 mg nanosponges used for each experiment. The sample is taken at interval of 1 hour at every 10 hours. The sample is measured spectrophotometrically and the latest dissolution medium was filling up each time when the sample is withdrawn to compensate the volume[28].

Fourier-Transform Infrared Analysis

To confirm the formation of nanosponges, FTIR spectroscopy were used and for study potassium bromide pellets method. If any interaction found between the drug and the polymer the mixture were scanned by using FTIR Spectroscopy and the spectra is compare with the pure drug and polymer. The Spectra is recorded in the wave number 4000-500cm^{-1}[29].

Stability Study

The most widely used approach to study inclusion complexation is the phase solubility method.This method is described by higuchi and corners. As per the standard protocol, the samples must be analyzed at 0, 1,2,3,4 and 6 months' time points. The stability studies were performed for the final optimized formulation. Samples were analyzed at 1, 2 mo. time points[30,31]

VI. APPLICATIONS OF NANOSPONGE:

Nanosponge As Chemical Sensors

Nanosponge is a type of metal oxide and act as a chemical sensor which is used highly detection of hydrogen using Nanosponge Titania. The nanosponges structure initially have no point of contact so there is less hindrance to electron transport and the result in higher 3D Higher Interconnect Nanosponge Titania.[32,33]

Nanosponge As Topical Agent

Nanosponge delivery system is a unique technology for the control release of topical agent. This formulation can be used in gels, cream lotion, ointment, or powder. The ability of nanosponges to increase the uptake of the guest molecule by the skin can be attributed to the capacity to increase solubility at the surface of skin.[34]

In Anti-Cancer Therapy

The researchers found that the delivery of drug through Nanosponge increase the death of cancer cells and delayed tumour growth compare with other chemotherapy approaches[35]

In Anti-Mycotic Therapy

The Nanosponge also used as an antifungal agent for topically relives the symptoms of candidiasis, dermatophsis and skin infections and the preparation is available in cream, ointment and lotion[36].

For Antiviral Therapy

Nanosponges provide specificity to deliver antiviral drug to lungs or nasal route through Nano-carriers .Which may cause infection to RTI (such as-influenza virus, rhino-virus) and antiviral nanosponges administered through nasal and pulmonary route. The drug used as Nano carrier are-Saquinavir, Ziddovudine[37].

For Solubility Enhancement

Beta-Cyclodextrin based nanosponges of Itaconazole have increased the solubility of poorly-soluble drug. The solubility increased by 50 folds compare to ternary dispersion system. Some drug such as ketoconazole, paclitaxel, and tomoxifen are difficult to formulate due to its poor solubility can be easily formulated as nanosponges by enhancing their solubility[36].

Nanosponges for Protein Delivery

The major obstacle in protein formulation development is the maintenance of the native protein structure both during the formulation process and upon the long term storage. Swaminathan et al. reported the new swellable cyclodextrin based poly (amidoamine) nanosponges named nanosponges 10 and nanosponges 11, were synthesised by cross-linking β-cyclodextrins with either 2, 2-bis-acrylamido aceticacid or a short polyamido-amine chain

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deriving from 2, 2-bisacrylamido acetic acid and 2-methyl piperazine respectively. The prepared β-cyclodextrin based poly (amidoamine) nanosponges were found to be stable at 300 °C and high protein complexation capacity was also observed[38] .

Nanosponges as a carrier for delivery of gases

In diagnostic, treatment purpose gases play a key role in medicine. Hypoxia (deficiency of adequate oxygen supply) is related to various pathologies, from inflammation to cancer. Sometimes it can be difficult to deliver oxygen in appropriate form and doses in clinical practice. Cavalli et al. developed nanosponge formulations as oxygen delivery systems for topical application which were having the ability to store and to release oxygen slowly over time[39].

Nanosponges in drug delivery

Due to nonporous nature they are used as carriers for water-insoluble drugs (Biopharmaceutical classification system class-II drugs)[40]. These complexes can be used to increase the dissolution rate, solubility and stability of drugs as well as to mask the unpleasant flavors. β-Cyclodextrin based nanosponges are reported to deliver the drug to the target site three to five times more effectively than direct injection[41]. List of BCS-II drugs which can be incorporated into nanosponges are given in table 3. Nanosponges can be formulated as oral[42,43] . Parental, topical or inhalation dosage forms. For oral administration the complexes can be dispersed in matrix of excipients like diluents, lubricants and anti-caking agents suitable for production of capsules and tablets. For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions[44]. For topical administration they can be effectively incorporated into topical hydrogel. Nanosponges used topically have the advantages in reducing skin irritation while maintaining efficacy. They can be formulated topical gels, lotions, creams etc[45,46].

Table : List of BCS-II drugs which can be incorporated into nanosponges

Antianxiety drugs	Lorazepam
Antiarrhythmic agents	Amiodarone hydrochloride
Antibiotics	Azithromycin, Ciprofloxacin
Anticoagulants	Warfarin
Anticonvulsants	Carbamazepine, Clonazepam
Antidiabetics	Glibenclamide, Glipizide
Antiepileptic drugs	Phenytoin
Antifungal agents	Econazole nitrate, Griseofulvin
Antihistamines	Terfenadine
Antihypertensive drugs	Felodipine, Nicardipine
Antineoplastic agents	Camptothecin, Docetaxel
Antioxidants	Resveratrol
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir
Cardiac drugs	Carvedilol, Digoxin
Diuretics	Chlorthalidone, Spironolactone
Gastroprokinetic agent	Cisapride

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Immunosupressants	Cyclosporine, Sirolimus
NSAIDs	Dapsone, Diclofenac, DiflunisalSteroids

VII. CONCLUSION

Nanosponge is the best novel drug delivery system. Who have the ability to Include Both Either Lipophilic or Hydrophilic Drugs and Release them in a Control and Predictable Manner. Nanosponge is useful for improving the dissolution and bioavailability of poorly soluble drugs. Nanosponges can be developed in different dosage form because of their small size and spherical shape. The BCS Class-2 drugs are more suitable drug for formulated into Nanosponge. Nanosponges in prepared by using different formulation method but solvent diffusion method is cost effective and simpler than others. Nanosponges can be formulated in different dosage form such as capsule, aerosol, ointment, lotion, powder and creams, tablets. Nanosponge formulations are non-mutagenic, non-irritating and non-toxic in nature.

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