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NANOSPONGES: A NOVEL TECHNIQUE USED FOR TARGETED DRUG DELIVERY SYSTEM–AN OVERVIEW

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ABSTRACT

The emergence of nanotechnology has led to many drug formulations being invented. For a long time, successful targeted drug delivery systems have been a dream, because of many major disadvantages, a realistic approach for the formation of discrete functionalized particles, called 'nanosponge', has been developed. A novel colloidal carrier, the invention of Nanosponges, has the ability to solve these problems. Nanosponge is a modern and emerging technology that can reliably control the release rates of managed drug delivery for topical use. The development of nanosponges has been a crucial step in solving these challenges. Small, virus-sized sponges that can be filled with a wide variety of drugs are nanosponges. These small sponges can circulate across the body until they enter and bind to the surface of the specific target site and continue to release the drug in a controlled and predictable manner. Nanosponge technology has been explored for various uses, such as enhancing the bioavailability of drug molecules and the delivery of drugs to the topical, oral and parenteral routes.

Keywords: Nanosponges, targeted delivery cyclodextrin, solubility, preparation

INTRODUCTION

Targeting drug delivery system has overcome by a number of limitations such as enzymatic degradation, gastrointestinal mucosal irritation and first-pass metabolism effect. A new nanotechnology used for the Nanosponges (NSs) using drug delivery of targeting site. For a prolonged period of time, effective targeted drug delivery systems are a dream, but the complex chemistry that's involved in the development of recent years. The invention of nanosponges has been an excellent step in solving these problems. Nanosponges are tiny sponges with the size of a few virus (0.25 μm), which may be stuffed with a wide range of drugs. These tiny sponges can circulate across the body until they reach a certain targeting site and bind to the surface and being to release the drug in a controllable and predictable manner **[1]**. Because the drug is released at the particular targeted site rather than circulating throughout the body it will be more effective for a specific given dosage. Another significant feature of these sponges is their aqueous solubility, which makes it possible to effectively use these structures for poorly soluble drugs **[2]**. Nanosponges are a brand-new class of materials made from microscopic particles with few 'large cavities' of nanometres in which a large variety of substances are encapsulated. Such particles have the ability to hold both lipophilic and hydrophilic compounds and to increase the solubility of molecules that are poorly water-soluble. Nanosponges are small mesh-like structures that can revolutionise the treatment of the many diseases and early results indicate that this technique is 3 to 5 times more efficient than conventional approaches to breast cancer delivery of drugs **[3]**. The nanosponges are around the size of a virus with a "backbone"(a scaffold structure) polymer that is naturally degradable. In a solution of tiny molecules called cross-linkers with an affinity for certain parts of the polyester, the long-length polyester strands are fused. To form a spherical shape which has many pockets (or cavities) where drugs are stored, they "cross link" polyester segments. The polyester has biodegradable characteristics, so release of drug happens when it breaks up in the body **[4]**. Nanosponges technology provides the entrapment of components and is assumed lead to decreased side effects controlling the release of drug, increased elegance, enhanced stability, and increased flexibility in formulation. The system of nanosponges they are non- irritating, non-mutagenic and non-toxic **[5]**.

Figure 1: Diagram of nanosponges

MERITS OF NANOSPONGES:

i. Increase aqueous solubility of the poorly water-soluble drug.

ii. Nanosponges can release the drug molecules in a predictable fashion.

iii. The bacteria cannot penetrate through nanosponges because of their tiny pore size (0.25 µm), and they act like a self-sterilizer.

iv. Nanosponges system is non-irritating, non-mutagenic and non-toxic.

v. The toxic and venom substance from the body can be removed with the help of nanosponges and minimize side effects.

vi. Increase formulation stability and flexibility enhancement.

vii. It reduces the dosing frequency, better patient compliance.

viii. Nanosponges complexes are stable over wide range of pH (i.e. 1-11) and temperature – 130 °C **[6-8]**.

DEMERITS OF NANOSPONGES:

i. Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.

ii. Dose dumping may occur at times **[9]**.

iii. The loading capacity of nanosponges depends mainly on degree of crystallization.

iv. Different loading capacities can be shown by Para crystalline nanosponges.

IDEAL PROPERTIES OF DRUGS SUITABLE FOR NANOSPONGES:

i. The molecular weight of drug candidates should be in the range about 100 to 400 Daltons

ii. The maximum of five condensed rings is more preferred for a drug molecule.

iii. Maximum Solubility in water should be below 10 mg/ml.

iv. Most common choice for nanosponges is BCS class II drugs.

v. Melting point of the substance must be below 250 °C **[10-12]**.

Table 1: Materials used in the preparation of nanosponges [13]

Polymers	**Alkyloxy carbonyl-Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone),Poly(valerolactone-allylvalerolactoneoxepane-dione), Ethyl Cellulose and PVA, Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β- Cyclodextrin,**
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.**
Apolor solvents	**Ethanol, Dimethylacetamide, Dimethyl formamide**

METHODS OF PREPARATION:

Nanosponges formulation may be prepared by solvent method or Emulsion solvent diffusion method or ultrasound assisted synthesis or hyper cross- linked β-cyclodextrin method.

I. Solvent method
II. Emulsion solvent diffusion method
III. Ultrasound assisted synthesiss
IV. hyper cross- linked β-cyclodextrin

I. Solvent Method: [14]

Polymer is mixed with a suitable solvent like Dimethyl Sulfoxide (DMSO), Dimethyl Formamide (DMF)

⇓

This mixture is added to excess quantity of the cross linkers preferably in cross-linker (1:4 ratio)

⇓

Action is carried out at room temperature ranging from 100°C to the reflux temperature of the solvent for the time ranging from 1 to 48hrs.

⇓

After complexation the reaction, the solution is cooled at room temperature and product is added to large excess of distilled water

⇓

The recovery of the product is done by filtration under vacuum

II. Emulsion Solvent Diffusion Method: [15]

Drug + Disperse phase (ethyl cellulose + Dichloromethane)

⇓

Aqueous phase (polyvinyl alcohol + water)

⇓

Above the mixture is stirred at 1000 RPM for 2 hrs at RT

⇓

Formed Nano sponges were filtered and dried at 40°c for 24hrs

⇓

The vacuum desiccator for removal of residual solvent

III. Ultra Sound assisted synthesis: [16]

In this method, reacting polymers with cross-linkers in ultra sound bath, heat at 90°c

⇓

Above the mixture Sonicates for 5hrs

⇓

Then allow the mixture to cool and break the product roughly

⇓

Wash the product with water to remove the non-reacted polymers

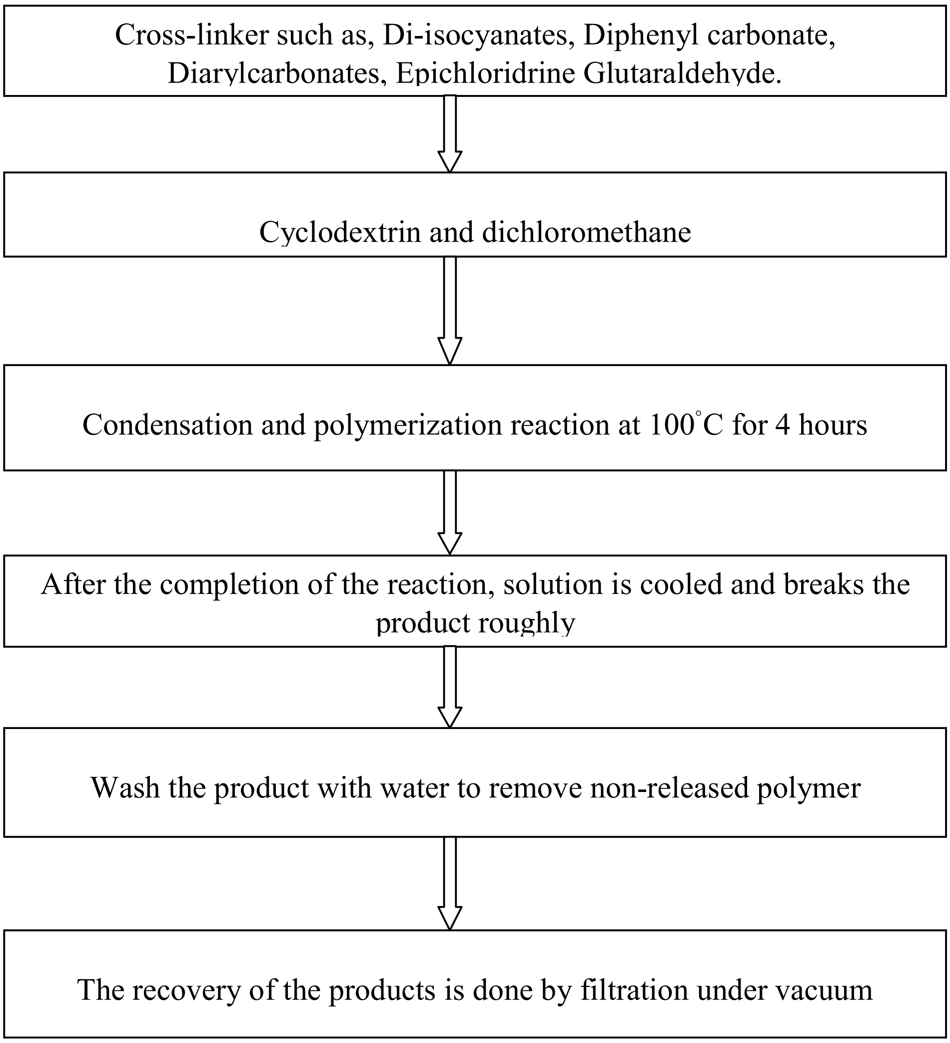
⇓

Subsequently purify by prolonged Soxhlet extraction with ethanol

⇓

The recovery of the product is done by filtration under vacuum

IV. HYPER CROSS-LINKED B-CYCLODEXTRIN: [17]



Loading of Drug into Nanosponges: [18]

Nanosponges are dissolved or suspended in water and sonicated to avoid the presence of accumulation.

↓

Then centrifuged the suspension to obtain colloidal fraction

↓

Separate the supernatant and dry the Nanosponges by freeze dying

↓

Prepare aqueous suspension of NSs and disperse excess amount of drug is added to suspension

↓ Continuously

Maintain the suspension under constant string at specific time for complexation

↓

After complexation, separate the uncomplexed (undissolved) drug by centrifugation.

↓

Above the Obtained solid crystal structure of Nanosponges by solvent evaporation or freeze drying

FACTORS INFLUENCING IN THE FORMULATION OF NANOSPONGES:

1) **Type of polymer:**

The type of polymer used can affects both the formulation and performance of nanosponges. The cavity size of nanosponges should be appropriate for complexity to carry a drug molecule of a suitable size.

2) **Type of drug:**

Drug molecules to be complexed with nanosponges must have certain features mentioned below they are **[19]**:

i. The molecular weight of drug candidates should be in the range about 100 to 400 Daltons
ii. The maximum of five condensed rings is more preferred for a drug molecule.
iii. Maximum Solubility in water should be below 10 mg/ml.
iv. Most common choice for nanosponges is BCS class II drugs.
v. Melting point of the substance must be below 250 °C.

3) **Temperature:**

Temperature changes can affect the complexity of drugs / nanosponges. In general, the rise in temperature decreases the stability of the drug / nanosponges complex due to the interaction forces of drug / nanosponges.

4) **Method of preparation:**

The technique of loading the drug into nanosponges can affect the complexity of the drug / nanosponges. However, a method's efficacy depends on the type of drug and polymer was found to be the most effective freeze drying for drug complexation in many cases **[20]**.

5) **Degree of substitution:**

The nanosponges' complexation potential can be significantly influenced by the type, number and position of the substituent on the parent molecules **[20]**.

VARIOUS METHODS FOR CHARACTERIZATION OF NANOSPONGES:

1. **Microscopic studies:**

The difference in the crystalline state of the raw materials and formation of inclusion complexes can be measured by using scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

2. **Entrapment efficiency:**

The weighed quantity of loaded complexes of nanosponges should be dissolved in suitable solvent and then sonicated after suitable dilution to break the complexes and then analyzed by UV spectrophotometer or High-Performance Liquid Chromatography (HPLC).

3. **Production yield:**

The production of the nanosponges can be determined by calculating initial weight of raw materials and final weight nanosponges.

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

4. **Loading efficiency:**

The loading efficiency (%) of nanosponges can be determined by:

Loading efficiency = actual drug content / theoretical drug content

5. **Solubility studies:**

The phase solubility method described by Higuchi and Connors, which investigated the effect of a nanosponges on the solubility of the substance is most commonly uses approach to analyze inclusion complexation. The phase solubility diagrams demonstrated the degree of complexation.

6. **Particle size:**

Particle size of the nanosponges can be determined by using Dynamic light scattering (DLC) using 90 PLUS particle size determining software.

7. **Polydispersity index (PDI):**

The Dynamic Light Scattering Instrument can calculate PDI. The monodisperse sample has a lower PDI value, where a higher PDI value shows the sample's large distribution of particle size and polydisperse existence. By using the following equation, PDI can be calculated:

PDI=▲d/davg

where.

▲d=width of distribution

8. **Zeta potential:**

zeta potential of nanosponges can be measure by using zeta meter. Zeta potential measurements can be made by using an additional electrode in particle size instrument. The stability of the colloidal dispersion shows the Zeta potential **[21-23]**.

APPLICATION OF NANOSPONGES:

1) **Targeted drug delivery:**

Nanosponges circulate throughout the body until they reached the surface of the tumor cell, bind to the surface and continue to release the drug in a controllable and predictable manner. The controlled release rate of the nanoparticle system used peptide targeting that recognized degradation induced cell surface receptors. This targeting agent paired a nanoparticle with recombinant peptide encapsulating paclitaxel directly targeting irradiated tumor by increasing apoptosis and tumor-growth. When anticancer drug filled with nanosponges it suppresses tumor growth and this delivery method is 3 to 5 times more effective than parenteral.

2) **Oral drug delivery:**
The complex may be dispersed in a matrix of excipients, diluents, lubricants, and anti-caking agents suitable for capsule or tablet preparation during oral administration. For the preparation of nanosponges for the oral delivery system, acetyl salicylic acid (ASA), a non-steroidal anti-inflammatory drug primarily associated with BCS class III drugs, has been developed **[24]**.

3) **Cancer therapy:**
Cancer therapy the use of hydrophobic drugs that do not dissolve readily in water is allowed in the nanosponges of an anticancer drug. For current, these drugs would be combined with adjuvant reagents, which may theoretically decrease the potency of the drug or induce side effects. The drug used in animal experiments was paclitaxel, an active ingredient in taxol anticancer treatment. Researchers also reported the response, with single doses, to two separate types of tumor, slow-growing human breast cancer and fast-acting mouse glioma. In both cases, it was found that delivery by nanosponges increased the death of cancer cells and decreased tumour growth compared to other chemotherapy techniques **[25]**.

4) **Proteins drug delivery:**
Bovine serum albumin (BSA) was used as a model to study the encapsulating capability of β-cyclodextrin-based nanosponges. The bovine serum albumin (BSA) protein solution is not stable and is contained in a lyophilized form. From its native structure, proteins can transform to denatured lyophilization. The major disadvantage of protein formulation and development is that it maintains its native structure and long-term storage during and after processing **[26]**.

5) **Solubility enhancement:**
Wetting and solubility of molecules with very low aqueous solubility in water can be improved by nanosponges. Inside the nanosponge structure, drugs may be molecularly dispersed and then released as ions, preventing dissolution. Consequently, it is possible to increase the apparent solubility of the drug. By improving the solubility and dissolution rate of the

substance, several problems with formulation and bioavailability can be overcome, and nanosponges can greatly increase drug solubility **[27]**.

Table 2: Application of nanosponges as a drug carrier [28-42]

Drug	Drug category	Nanosponge vehicle	Study conducted
Econazole Nitrate	Antifungal	Ethyl cellulose, PVA	Irritation study and adsorption
Isoniazid	Anti-tubercular	Ethyl cellulose, PVA	Drug release
Norfloxacin	Antibiotic	Betacyclodextrin and Diphenylcarbonate	Bioavailability
Cephalexin	Antibiotic	Ethyl cellulose, PVA	Drug release and stability
L-Dopa	Parkinson's Disease	Betacyclodextrin	Drug release
Fenofibrate	Fibrate	Maize starch, SDS	Solubility and bioavailability
Nifedipine	Calcium channel blocker	Betacyclodextrin	Solubility
Glypizide	Sulfonylurea	Betacyclodextrin	Drug release
Ibuprofen	NSAID	Ethyl cellulose, PVA	Drug release
Resveratrol	Antioxidant	Cyclodextrin	Stability, cytotoxicity and permeation
Paclitaxel	Antineoplastic	Betacyclodextrin	Bioavailability
Camptothecin	Antineoplastic	Betacyclodextrin	Stability and solubility
Tamoxifen	Antiestrogen	Betacyclodextrin	Solubility
Celecoxib	NSAID	Betacyclodextrin, N, N- methylene bisacrylamide	Solubility
Griseofulvin	Antifungal	Cyclodextrin	Enhance oral bioavailability

CONCLUSION

Nanosponges have been found to be much more efficient at delivering drugs to the specific site, it can be easily concluded that nanosponges can provide better drug release than other nanotechnology carriers. Nanosponges have been tested to encapsulate to both hydrophilic and lipophilic drug. nanosponges carrier opens new challenges and opportunities for the development of novel improved therapies. Nanosponges are interesting and innovative drug delivery system in a field of pharmaceutical technology and drug delivery in recent years.

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