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# NANOSPONGE DRUG DELIVERY SYSTEM: REVIEW

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**Abstract:**

Drug delivery for a long time has been a major problem in the pharmaceutical field. The development of a new Nano-carrier system called nanosponge has shown the potential to solve the problem. Nanosponge has a porous structure and can entrap the drug in it. It can carry both hydrophilic and hydrophobic drugs. They also provide controlled release of the drugs and can also protect various substances from degradation. Nanosponge can increase the solubility of drugs and can also be formulated into an oral, topical and parenteral dosage form. The current review explores different preparation techniques, characterization parameters, as well as various applications of nanosponge.

**Keywords:** Drug, Nanosponge, preparation techniques, characterization parameters

## INTRODUCTION

The pharmaceutical industry has developed and used nanomaterial to address various problems related to the physical, chemical, and biological treatment of diseases (R. Patel et al. 2010). In 1950, the technology of nanotechnology was dominated. Hence, variants have been made of formulations such as Nanoparticles Nano- capsules, Nan- spheres, Nano-suspension, Nano - crystals. Nanoparticles can be obtained in various ways, including polymer Nano particles, solid lipid nanoparticles, nanosponges, carbon nanoparticles, micellar, dendrimers, etc(laila abdulhussein alwan 2021).

Nano sponge is a novel approach which offers controlled drug delivery for topical use. NS is an emerging technology for topical drug delivery. NS drug delivery system is employed for the improvement of performance of topically applied drugs(Jilsha and Viswanad 2013).

Nano sponge was a modern material form, consisting of small particles with a few nanometers of narrow cavity. Such small cavities can be filled with different materials. The nanosponges are a polyester network which is able to degrade naturally. These polyesters are blended to form Nanosponges with a cross-linking solution(laila abdulhussein alwan 2021).

NS are capable to carry both lipophilic and hydrophilic drugs. They are used to increase aqueous solubility of less water-soluble drugs, to remove pollutants from contaminated water, or as Nano carriers for biomedical applications. NSs are used to remove organic impurities in water(Pawar, Naik, and Jadhav 2016).

Nano sponges are formed in water and organic solvent as pore, non–toxic and stableat high temperatures up to 130Co in comparison with other nanoparticles. Nano sponges (NS) defined as a nanoparticles which formulated as Nano -sized colloidal carriers having the shape of Nano porous biocompatible in nature(S Shivani 2019).

Targeting drug delivery systems to achieve the desired result has been a long-term goal. Nanosponge drug delivery systems were originally only available as a topical administration system, but in the 21stcentury, Nanosponges can now be administered orally as well as intravenously (IV)(Bilal J. et al. 2021).

## CYCLODEXTRIN BASED NANO SPONGES

Cyclodextrin-based nanosponges are a novel nanosized delivery system composed of hyper-cross-linked cyclodextrins connected in a three dimensional network. They form porous nanoparticles with sizes lower than 500 nm, spherical shape and negative surface charge. They show a good capacity for incorporating small molecules, macromolecules, ions and gases within their structure.that have been reported to have a very high solubilizing power for poorly soluble molecules , and they are proposed to form inclusion and non-inclusion complexes with different drugs.The CD cross-linker ratio can be varied during their preparation to improve the drug loading and to obtain a tailored release profile. A previous work dealing with b-CD-based nanosponges focused on the solubilization of molecules for immediate release(Shringirishi et al. 2014).

### The nanoparticles can be categorized into three groups based on how they associate with medicines:

### Encapsulating Nanoparticles:

Nanosponges and nanocapsules are examples of encapsulating nanoparticles. Alginate Nanosponges, which are sponge-like nanoparticles, have multiple hollows that allow drug molecules to pass through.

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Nanoparticles are also encapsulated in nanocapsules such as poly (isobutyl cyanoacrylate) (IBCA). Drug molecules can be located in their aqueous core(Muni Raja Lakshmi, Suma Shree, and Lakshmi Priya 2021).

### Complexion Nanoparticles:

This category comprises compound nanoparticles that use electric charges to attract molecules(S Shivani 2019).

### Conjugating Nanoparticles:

These nanoparticle cominations link or connect to drug substance with covalent bond(Bilal J. et al. 2021).

## ADVANTAGES OF NANOSPONGE

1. Targeted site-specific drug delivery.
2. This method allows for the trapping of chemicals and the reduction of side effects along with improved stability, elegance, and formulation flexibility.
3. Nanosponge systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.
4. A Nanosponge provides continuous action up to 12 hours i.e. extended release.
5. It minimizes the irritation and it gives better tolerance which leads to improved patient compliance.
6. Nanosponges can be regenerated using eco-compatible solvents, inert hot gases, mild heating, and changing strength.
7. Allows for the incorporation of immiscible liquids, which improves material processing by converting liquids to powders.
8. Nanosponges complexes are stable throughout a wide pH range (from 1 to 11) and at 130 °C.
9. They act as a self-sterilizer even though their average pore size is 0.25 µm, in which bacteria cannot penetrate.
10. These are free flowing, highly compatible with wide variety of ingredients and cost effective.
11. They have better thermal, physical and chemical stability.
12. Nanosponge particles are soluble in water, so encapsulation can be done within the nanosponge, by the Addition of chemical called an adjuvant reagent.
13. Nanosponges aid in the removal of harmful and venomous substances from the body and minimize side effects(Raja Narender and Raja Sridhar 2019; Bilal J. et al. 2021).

## DISADVANTAGES:

1. Dose unloading may happen at time
2. Nano sponges have capacity to incorporate just little atoms.
3. Nanosponges can be paracrystalline or crystalline in nature.
4. Dose dumping is a possibility.
5. The stacking limit of nanosponges relies predominantly upon level of crystallization(Shah, Kehinde, and Patel 2021).

## MECHANISM OF DRUG RELEASE FROM NANOSPONGES

Because of nanosponges particles have an open structure; the active constituent is free to move in and out of the particles into the vehicle until the equilibrium is reached when the vehicle becomes saturated. When the product is applied to the skin, the active constituent already present in the vehicle becomes unsaturated, disrupting the balance. This will initiate the flow of active substance from the nanosponge's particle into the vehicle, which will then be applied to the skin until the vehicle has dried or been absorbed. The sponge particle matter that remains on the skin surface (Stratum Corneum) will continue to distribute the active ingredient to the skin even after the vehicle has dried. As a result, the action of the release is prolonged. Even after that, nanosponges particles maintained on the stratum corneum's surface will progressively release active substance to the skin, resulting in a protracted release(Bilal J. et al. 2021).

## COMPOSITION OF NANOSPONGES

### I. Polymer:

Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Alkyloxycarbonyl Cyclodextrins, Methyl β-Cyclodextrin, Hydroxy Propyl β-Cyclodextrins(Jilsha and Viswanad 2013).

### II. Cross linking agent

The crosslinking agent selection can be carried out depending upon the structure of polymer and the drug which is to be formulated. The different examples include Diphenyl Carbonate, Diarylcarbonates, Epichloridine,Glutarldehyde, Carboxylic acid dianhydride, Acetic acid and Dichloromethane(Jain et al. 2019).

### III. Drug substance

- Molecular weight between 100 and 400 Daltons.
- Drug molecule consists of less than five condensed rings.
- Solubility in water is less than 10 mg/ml.
- Melting point of substance is below 250 °C(Ravi, Krishnakumar, and Nair 2019).

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## PREPARATION METHODS OF NANOSPONGES

### 1) Melt method

In melt method, cyclodextrin reacts with a suitable crosslinker such as dimethyl carbonate, diphenyl carbonate, isocyanates, diaryl carbonates, carbonyldiimidazole (C7H6N40), carboxylic acid anhydrides, and 2, 2-bis (acrylamide) acetic acid. All of the ingredients are carefully integrated and placed in a 250 mL flask heated to 100°C for 5 hours with a magnetic stirrer. The mixture is allowed to cool before the resulting product is broken down and rinsed with a suitable solvent to remove any unreacted excipients. New 3

### 2)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(Jain et al. 2019).

### 3) Emulsion Solvent Diffusion Method

Cyclodextrin is pre-empted by cross-linker reactions. Sponges can be managed for attaching different molecules to the surface load density, porosity and pore size. Depending on the agent used for cross-linking, Nano sponges can be produced in acidic or natural shapes. They are solid nanoparticles can be prepared using an ultrasound-assisted method in crystalline, spherical shape(Salunke et al. 2019).

### 4) Solvent Method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 10oC. Then allow this solution to cool at room temperature. Add this to excess quantity of bidistilled water and filter the product. Then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder(Rajkondawar and Patil 2020).

### 5) Ultrasound-assisted synthesis

In this method, NSs were obtained by reacting polymers with the cross-linkers in the absence of solvent and under the sonication. The NSs obtained using this method will be spherical and uniform in the size. The polymer was mixed and the cross-linker in a particular molar ratio in the flask. The flask was placed in an ultrasound bath which was filled with water and heated it to 90°C. This mixture was sonicated for 5 h. Then, the mixture was cooled, and the product was broken roughly. The product was washed with water to remove the nonreacted polymer and it was subsequently purified by prolonged Soxhlet extraction with the ethanol. The obtained product was dried under the vacuum and was stored at 25°C until further use(Pawar, Naik, and Jadhav 2016).

### 6)Loading of drug into nanosponges

Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying. Prepare the aqueous suspension of Nanosponge and disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying(Pawar, Naik, and Jadhav 2016).

Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex(Salunke et al. 2019).

## FACTORS INFLUENCE NANO SPONGE FORMATION

### Type of polymer

The formation as well as the performance of nanosponge depend upon the selection of suitable polymer. The cavity or pore size of the nanosponge should be able to accommodate the drug molecule of suitable size(Jain et al. 2019).

### Type of drug

Certain properties of drug compounds that will be complexed with nanosponges are listed below.

a) The molecular weight must be between 100 to 400 Daltons
b) The drug molecule structure should contain not more than five condensed rings.
c) The solubility in water should be less than 10 mg/ml
d) The melting point should be less than 250 °C(Subramanian et al. 2012).

### Temperature

Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge

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complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature(Muni Raja Lakshmi, Suma Shree, and Lakshmi Priya 2021).

### Method of preparation

The loading of drug into the nanosponge formulation can affect the complexation. The nature of the drug and polymer can affect the complexation. In many cases freeze drying was found to be more effective method for the drug complexation(S Shivani 2019).

### Degree of substitution

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule(Bilal J. et al. 2021).

### Evaluation of nanosponges:

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods:

### THERMO-ANALYTICAL METHODS

Thermo-analytical methods determine whether the drug substance undergoes some change 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 thermogram obtained by DTA and DSC 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(Subramanian et al. 2012).

### 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 nanosponges on the solubility of drug. Phase solubility diagrams indicate the degree of complexation .In this method the drug was added to an Erlenmeyer flask containing an aqueous solution of various percentages of nanosponges. The Erlenmeyer flask was stirred on a mechanical shaker at room temperature. When a steady state was reached, the suspension was filtered by centrifugation using a 3 000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 U.S.A). The solution obtained was analyzed to determine the drug concentration by high performance liquid chromatography(Ravi, Krishnakumar, and Nair 2019).

### MICROSCOPY STUDIES

Scanning electron microscopy and transmission electron microscopy can be used to study the morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product observed under electron microscope indicates the formation of the inclusion complexes(Muni Raja Lakshmi, Suma Shree, and Lakshmi Priya 2021).

### Infra-Red spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state. Nanosponge bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges. The technique is not generally suitable to detect the inclusion complexes and is less clarifying than other methods. The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infrared spectral studies give information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band(Philip et al. 2014).

### Thin layer chromatography

in thin layer chromatography, the $R_f$ values of a drug molecule diminish to considerable extent and this helps in identifying the complex formation between the drug and nanosponge(Shringirishi et al. 2014).

### Loading efficiency

The loading efficiency of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer and high-performance liquid chromatography methods. The loading efficiency (%) of nanosponges can be calculated according to the following equation(Jilsha and Viswanad 2013).

### Particle size and polydispersity

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software.

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From this the mean diameter and polydispersity index can be determined(Muni Raja Lakshmi, Suma Shree, and Lakshmi Priya 2021).

### Resiliency

Sponge resiliency (viscoelastic characteristics) can be altered to generate softer or firmer beadlets depending on the final formulation's requirements. The rate of release is slowed by increased crosslinking. As a result, the resiliency of sponges will be investigated and optimized in accordance with the requirements, taking into account release as a function of cross-linking with time(Salunke et al. 2019).

### Zeta potential

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment(laila abdulhussein alwan 2021).

### Application of nanosponge

Due to their biocompatibility and versatility, nanosponges have many applications in the pharmaceutical field. They can be used as excipients in preparing tablets, capsules, pellets, granules, suspensions, solid dispersions or topical dosage forms. They can encapsulate variety of drugs. Nanosponges can act as multifunctional carriers for enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical and chemical stability of product(Shringirishi et al. 2014). Following are the application.

### Nano sponges for Drug delivery:

Nano sponges can ideally carry water-insoluble drugs and/or agents (BCS ClassII drugs) because of their Nano porous structure. These complexes can be employed to enhance substance degradation, solubility and stability(Shrestha and Bhattacharya 2020).

### Solubility enhancement

The low water solubility of many drugs is one of the most significant barriers to their development. About 40% of new drugs are water insoluble, which makes them difficult to use in clinical trials. The formulation of medications that are poorly water soluble is a tough problem to solve. Nanosponges can help compounds that have a low water solubility enhance their wetting and solubility. The medications can be molecularly disseminated within the nanosponge structure before being released as molecules, eliminating the need for dissolution. As a result, the drug's perceived solubility can be boosted. Many formulation and bioavailability issues can be overcome by increasing a substance's solubility and dissolving rate, and nanosponges can significantly improve drug solubility(Jain et al. 2019).

### To provide stability

Nanosponges have the ability to selectively trap a few families of protein molecules from the blood, allowing them to be protected from enzymatic breakdown(Tejashri, Amrita, and Darshana 2013).

### Sustained delivery system

A modified-release product's design is often designed to help improve the treatment regimen by delivering the drug slowly and continuously over the dose period. This allows for a reduction in the dose given, a change in the pharmacokinetic profile, and a reduction in side effects. Using appropriate polymers and crosslinking agents, drug release kinetics from nanosponges can be achieved with a sustained release profile over time. Following encapsulation, nanosponges can be utilized to retain and extend the release of volatile compounds such as essential oils(Shrestha and Bhattacharya 2020).

### Nanosponges for cancer therapy

Because of their limited solubility, anticancer drug distribution is one of the most challenging tasks in the pharmaceutical industry today. According to one article, the nanosponge complex is three times more efficient than direct injection in reducing tumour growth. The complex of the nanosponge loads a medicine and exposes a targeting peptide that binds strongly to the tumour receptor's radiation-induced cell top layer. When nanosponges come into contact with a tumour cell, they stick to its surface and begin to release medication molecules. Targeting drug delivery has the advantage of providing a more effective therapeutic impact at the same dose with fewer side effects(Bilal J. et al. 2021).

### Protection from light or degradation

Nanosponges can also be utilized as carriers to protect encapsulated molecules from degradation caused by light, chemicals, and enzymes. As a result, the molecule's stability and potency are improved(Shringirishi et al. 2014).

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**Drugs used as nanosponge drug delivery:**

**Table 1. Various drugs used in Nano sponge and major findings**(Shrestha and Bhattacharya 2020)**.**

| Sr. No. | Drug | Polymer and Crosslinker Used | Disease | Study | *In-Vitro/ In-Vivo* Models | Major Finding |
|---|---|---|---|---|---|---|
| 1. | Camptothecin | β-CD, Diphenyl carbonate | Cancer | Haemolytic activity | HT-29 Cell line | Prolonged-release profile & increased stability of the drug. |
| 2. | Paclitaxel | β-CD, Diphenyl carbonate | Cancer | Cytotoxicity study | MCF-7 Cell line | Better inhibition of cells proliferation |
| | | | | Bioavailability | Sprague Dawley rats | Increased bioavailability |
| 3. | Resveratrol | β-CD, Carbonyldiimidazole | Dermatitis, Gonorrhoea, Anti-oxidant | Cytotoxicity study | HCPC-I cell line | Better inhibition of cells proliferation |
| | | | | Permeation study | Pigskin (*ex-vivo*) | Better permeation through the skin due to an increase in solubility |
| 4. | Tamoxifen | β-CD, Carbonyldiimidazole | Anti-estrogen | Solubility | - | Enhanced solubility |
| | | | | Cytotoxicity study | MCF-7 cell line | Better inhibition of cells proliferation |
| 5. | Dexamethasone | β-CD, Diphenyl carbonate | Anti-tumour | In-vitro release | Dialysis membrane | Prolonged-release of drugs |
| 6. | Oxygen delivery | α, β, γ – CD, Carbonyldiimidazole | Hypoxic condition | Cytotoxicity study | Vero cells | No toxicity toward Vero cell |
| | | | | In-vitro release | Teflon vials (with & without US propagation) | Burst release initially, followed by slow, prolonged release. US enhanced the *in vitro* release |
| 7. | Erlotinib | β-CD, Pyromellitic dianhydride | Lung cancer | Cytotoxicity study | A549 cell (Human lung carcinoma cell) | Erlotinib nanosponge produced a higher inhibitory effect at a lower dose and for an extended period of time than that of plain Erlotinib |
| 8. | Telmisartan | β-CD, Diphenyl carbonate | Hypertension | Solubility | - | Enhanced solubility of the drug |
| 9. | Rilpivirine | β-CD, Diphenyl carbonate | Anti HIV | Bioavailability | Sprague Dawley rats | Enhanced bioavailability |

## CONCLUSIONS

Nano sponges may be developed as various dosage forms as parenteral, aerosol, topical, tablets and capsules because of their small dimensions and spherical form. The Nano sponge method for drug delivery is also an advantage in the area of a controlled system for the delivery of different drugs. These are three-dimensional fabrics formed by extensive interconnection between polymers into small Nano cavities, which include both hydrophilic and hydrophobic medicine. This integration complexity improves the water solubility of medicines with low water solubility. The use of biodegradable polymers allows for controlled and predictable release of the

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drug to preserve constant levels of drugs. Further development in delivery of Nano sponge drugs is the use of peptide linkers, typically for tumors, to precisely target a receptor. This minimizes mainly d negative effects.

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