# A REVIEW ARTICLE ON NANOSPONGES DRUG DELIVERY SYSTEM

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**Abstract**

Numerous dosage forms were created as a result of the development of nanotechnology. Due to a number of significant issues, effective targeted drug delivery systems have long been a pipe dream. As a workable solution, discrete functionalized particles known as "Nanosponge" have been created.

These issues might be resolved by the creation of novel colloidal carriers known as nanosponges. A new and developing technology called nanosponge allows for exact control over the release rates of topical medication delivery. One important step in solving these issues is the development of nanosponges. Nanosponges are microscopic sponges that are roughly the size of viruses and can contain a wide range of medications.

These microscopic sponges can move throughout the body until they reach the precise target location, adhere to the surface, and start to release the medication in a regulated and predictable way. For a given dosage, the drug will be more effective since it can be released at the precise target place rather than circulating throughout the body. The aqueous solubility of these sponges is another crucial feature that makes it possible to employ these systems efficiently for medications with low solubility.

## Introduction

Nanosponges are nanosized drug carriers with a three-dimensional structure created by crosslinking polymers. They have the advantage of being able to hold a wide range of drugs of various sizes. [1] Nanosponges come in a variety of shapes and sizes. They are distinguished by the research method used, the type of polymer used, and the type of drug they may contain. are superior to other delivery systems because they can provide a controlled drug release pattern with targeted drug delivery. [2]The period of action, as well as the drug's residence time, may be regulated. Since it is made of biodegradable materials, it has a low toxicity and is safe to use. The efficiency of drug encapsulation is determined by the size of the drug molecule and the amount of void space available.[i] Cancer, enzyme and biocatalyst carrier, oxygen delivery, solubility enhancement, enzyme immobilization, and poison absorbent are some of the applications for nanosponges. The method of preparation, characterization, factors affecting nanosponge development, drug loading and release mechanism, recent developments in this area, and patents filed in the area of nanosponges are all highlighted in this study

- The nanosponges are nanostructures that can carry small drug molecules.
- These can be administered by multiple routes and have a variety of applications.
- Variety of drugs with hydrophilic and hydrophobic characteristics can be administered for the treatment of many diseases.
- They are porous in nature, crosslinked by the use of multiple polymer

Their internal portion is porous in nature and has voids, which has the capacity to hold drug molecules.

**Types of Nanosponges**

There are many types of NS that are available and can be designed and formulated depending on the polymer added, its concentration, and the method of preparation used accordingly. The most common types of NS which are prepared and have been diversely used are beta CD-based NS. The formulation aspect for beta-CD NS is a relatively simple process and there are relatively multiple modifications that are possible.

Types of Nanosponges

1. Titanium based Nanospondes
2. Carbon coated metallic Nonosponges
3. Beta Cyclodextrin Based Nanosponges
4. Hypercross linked Polystyrene Nanosponges
5. Silicon Nanosponges Particles
6. Modified Nanosponges
7. Miscellaneous Nanosponges

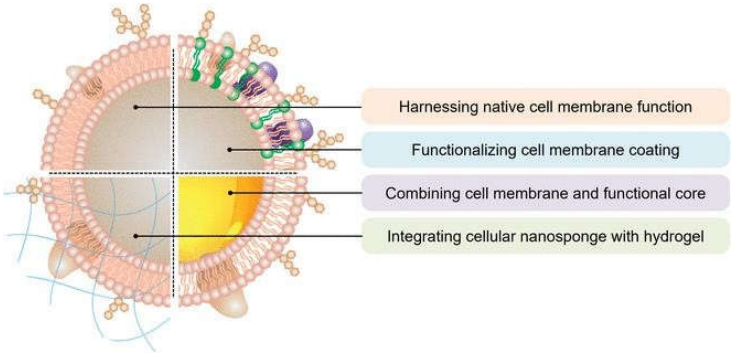


**Fig. 1**. A schematic showing the major design strategies for cellular nanosponges as medical countermeasures. These designs include harnessing native cell membrane functions for biological neutralization, functionalizing cell membrane coatings to enhance neutralization capabilities, combining cell membranes and functional cores for multimodal neutralization, and integrating cellular nanosponges with hydrogels for localized

application

**Features of Nanosponges**

This kind of encapsulating nanoparticle can contain the medication molecule at its center. The crosslinker's functional groups and concentration have an impact on the NSs' porosity and provide adjustable polarity. As a result of the crosslinker's assistance in creating cavities in the framework, the drug release pattern can be modulated. NSs are stable and nonlethal up to temperatures as high as about 300 °C.[3]

NSs medicines are available in oral, parenteral, topical, and inhalational forms. For the creation of oral formulations, excipients such as lubricants, diluents, anticaking agents, and NSs are distributed collectively in the form of a matrix. When creating a topical formulation with NSs, the NSs are combined with topical hydrogel; when creating a parenteral formulation, they are combined with sterile water, salt, or an aqueous solution. [4]

As the NSs have the ability to stick to surfaces, they can aid in predictable and regulated medication release. Because the medication release pattern lasts for 12 hours, it provides an opportunity to incorporate an insoluble liquid that enhances material processing and can be powdered subsequently. Due to their high aqueous solubility, they can be used to give medications that are not very soluble in water. They are equally capable of carrying medications that prefer water or oil. They are very stable, beautiful, and have less adverse effects. Their formulation flexibility is enhanced.

They are not the source of allergies, cancer, or any other disease. Their nature might be either crystalline or paracrystalline. They produce transparent, milky-colored colloidal combinations in water, and they also have the added benefit of being easily redeveloped using solvent extraction, microwaves, and thermal desorption. By combining ferrite and magnetic agents with the medication during preparation, an external magnetic arena can be used to precisely release the medication. [5]

**Advantages of Nanosponges**

NSs aid in masking the disagreeable taste of medications, particularly those that must be taken orally or by buccal route. Because the different chemicals are encapsulated within the NSs during formulation, the adverse effects of those compounds can be minimized. They offer a decent level of formulation stability. Their pore size of 0.25 micrometers prevents

bacteria from penetrating, which contributes to their self-sterilizing properties. Patient compliance has improved as a result of a reduction in the frequency of medication delivery. They can be quickly commercialized because the process of scaling them up is simple. The NSs can encapsulate pharmacological moieties that are lipophilic or hydrophilic. [6]

Crosslinkers are used in the formulation of NSs, which allows for targeted medication delivery to the intended target. They are readily regenerable by techniques including cleaning, fracturing with mildly inert gasses, employing environmentally friendly solutions, gradually raising the temperature, or varying the pH or ionic content. Because crosslinkers and other components are employed in the formulation of NSs, the encapsulated drug is shielded from first pass metabolism.[7]

**Disadvantages of Nanosponges**

Small medicinal molecules can be incorporated by the NSs. The degree of crosslinking influences the amount of drug loading capacity because it establishes the amount of empty space in the NSs that can be used for drug loading. The early disintegration of the crosslinker may result in dose dumping.

**Table 1 Components used in preparation of Nanosponges**

| Polymer | Copolymer | Crosslinker | Polar Solvents |
|---|---|---|---|
| • HyperCrosslinked PolystyreneCyclodextrin (alkoxy carbonyl cyclodextrins) | • Poly(Valerolactone allyl Valerolactone • Poly(Valerolactone allyl Valerolactone oxypanedione) | • Carbonyl diimidazole • Carboxylic acid dianhydrides | Ethanol Dimethylacetamide |
| • Methylβ-Cyclodextrin | • Ethyl cellulose | • Diarylcarbonates | Dimethylformamide |
| • Hydroxy propyl β-cyclodextrin | • Polyvinyl alcohol | • Dichloromethane | |
| • Poly-Valerolactone | | • Diisocyanates | |
| • Eudragit RS100 | | • Glutaraldehyde | |
| • Acrylic Polymer | | • Pyromellitic anhydride • 2,2bis(acrylamide) Acetic Acid | |

**Method of Nanosponges**

**1. Solvent Method**

Appropriate solvents were employed in the procedure, such as polar aprotic solvents like dimethylformamide and dimethyl sulfoxide**.** Polymer was added and well mixed with this. It is best to employ an 8:2 crosslinker/polymer ratio when adding the aforementioned mixture. Following the foregoing mixing, the combination was allowed to react for 48 hours at temperatures between 10 °C and the solvent's reflux temperature. After the reaction was finished, the solution was cooled to room temperature.[8]

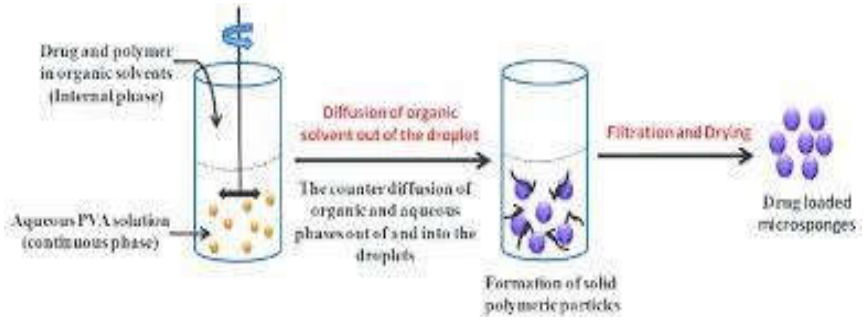


**Fig 2.** Solvent Method of Nanosponges

## 2. Ultrasound-assisted method

The polymer ultrasonics junction is used in the ultrasound-assisted synthesis process. Polymer crosslinking results from ultrasonic vibrations, and crosslinking can be obtained without the use of any solvent. The polymer and crosslinker were mixed at a suitable molar ratio in a flask. The flask was placed in an ultrasonication bath for five hours at a temperature of ninety-three degrees Celsius. After sonication, the temperature of the collected mixture was lowered. The result was then roughly separated and cleaned with an excessive amount of water to remove unreacted chemicals and polymer. Using Soxhlet extraction and ethyl alcohol, the cleaned solid was purified. The obtained filtered nanoscale particles were vacuum-dried and appropriately treated until additional drug loading.[9]

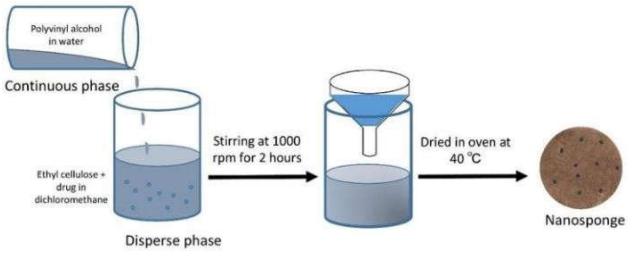


**Fig 3**. Ultrasound Assisted Method

## 3. Melt method

During the melting process, the polymer and the crosslinker are fused together. Every component was homogenized finely. NSs were gathered by regularly washing the purchased item with an appropriate liquid. After the product has been cleaned, the waste polymer and unreacted reagents are extracted, and the product is divided into NSs. These blank NSs were additionally subjected to the encapsulation of drugs.[10]

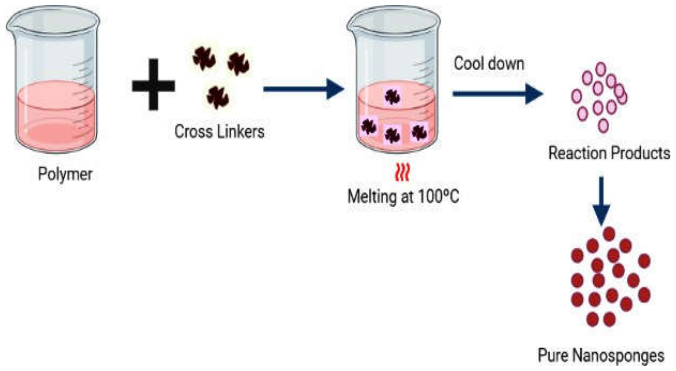


**Fig 4.** Melt Method of Nanosponges

### 4. Bubble electrospinning

The main components of a traditional and standard electrospinning arrangement are a grounded collector, a high-voltage power source, a syringe, and a syringe pump, as described in numerous literatures. However, a significant constraint limiting their potential uses is the quantity of nanofibers produced. Additionally, polyvinyl alcohol can be utilized as a polymer in bubble electrospinning. A one-phase mixture was obtained by moving the 10% polymer solution at 80–90°C for two hours after adding distilled water to it. After allowing the polymer solution to reach room temperature, it was utilized to create nanoporous fibers.[11]

### 5. Synthesis by the use of microwave radiation

This straightforward method of synthesizing CD NSs by microwave irradiation drastically cuts down on reaction time. The levels of crystallinity in these NSs are higher. When NSs are synthesized using microwave radiation instead of more conventional heating techniques, the reaction time is halved and consistent crystallinity and a homogeneous particle size distribution are created. Singireddy together with others. The research's findings revealed that the model drug's drug-holding capacity had increased thanks to NSs made using microwave-assisted synthesis. The high resolution-transmission electron microscopy (HRTEM) results demonstrated that the nanostructures (NSs) produced using microwave synthesis had a limited size distribution and a high degree of compaxtibility. Under microwave-assisted heating conditions, all reactions showed a significant reduction in reaction time and an improvement in the reaction products. The advantage of employing microwave irradiation for synthesis is that it provides accurate energy delivery by delivering straight energy to the targeted molecules. Since the energy is not wasted heating the liquid next to the molecules of the reactant or the container walls, the entire effect is seen as the reaction moves closer to completion. Zainuddin et al. synthesized β-CD in a

paracrystalline form using a microwave synthesizer and crosslinked it with diphenyl carbonate (DPC).[12]

## 6. Preparation of NSs from hypercrosslinked β-cyclodextrin

Derived from β-cyclodextrins, their role as carriers for drug delivery is realized as nanosporous materials. Due to their three-dimensional structures, which resemble a typically circular assembly akin to a protein with slots and openings in the core, they are formed. For example, di-isocyanates, diaryl carbonates, carbonyl by factors such as porosity and surface charge thickness corresponding to various atoms. Nanosponges are formulated based on the crosslinker used within a neutral or acidic environment. They consist of solid particles and have a modified crystalline structure. The efficacy of nanosponges is showcased through the solubility and stability of diverse structures . These materials are employed to enhance the solubility of drugs with poor water solubility.[13]

## 7. Emulsion solvent diffusion method

This technique operates in two steps to manipulate the proportions of natural and aqueous phases ethyl cellulose and polyvinyl alcohol. In dichloromethane 20 ml with a clear amount of polyvinyl alcohol added to 150 ml of a continuous process fluid, the dispersed phase with ethyl cellulose and moiety undergoes dissolution. The mixture is then stirred at 1000 rpm for 2 hours. The desired nanosponges were extracted via filtration and dried in an oven at 40 °C for 24 hours. The dried nanosponges were stored in desiccators, ensuring the removal of residual solvents . Ilyas et al. prepared sodium naproxen nanosponges using the solvent diffusion technique, achieving a diffusion rate close to 89% in certain formulations, with a drug loading efficiency nearing 98%. They also assessed viscosity, particle size, zeta potential, and stability studies. Fourier Transform Infrared Spectroscopy FTIR results indicated no interaction between the drug and the excipients. The findings suggested high drug loading efficiency and an exceptional drug release profile.[14]

## 8. Quasi emulsion solvent method

Nanosponges were prepared in various quantities using the polymer. With Eudragit RS 100, the inner phase is established and introduced into a suitable solvent phase. The drug utilized exhibited a reaction and dissolved at 35 °C during ultrasonication . As an emulsifying agent, this internal process employed the external phase containing polyvinyl alcohol. At room temperature, the blend is mixed at 1000–2000 rpm for 3 hours and dried

for 12 hours in an air-heated oven at 40 °C .

**Ability to load drugs in Nanosponges**

The nanosponges are suspended in water and sonicated to prevent aggregation. A centrifugation process is then performed on the dispersion to produce a colloidal solution, which, upon freeze-drying, separates into supernatant and dried nanosponges. In the following step, an excess amount of drug is dispersed and continuously stirred for a designated time, promoting complexation and supporting the formation of nanosponges in an aqueous suspension. After complexation, the un-complexed drug is isolated by repeating the centrifugation process . Ultimately, either a solvent evaporation method or freeze-drying technique is utilized to yield the Nanosponges .[15]

| Class of drug | Drug |
|---|---|
| Antianxiety drugs | Lorazepam |
| Antiarrhythmic agents | Amiodarone hydrochloride |
| Antibiotics | Azithromycin, ciprofloxacin, erythromycin, ofloxacin, sulfamethoxazole, trimethoprim, Cephalexin |
| Anticoagulants | Warfarin |
| Anticonvulsants | Carbamezapine, clonazepam, felbamate, primidone |
| Antidiabetic and antihyperlipidemic drugs | Atorvastatin, fenofibrate, glibenclamide, Glipizide, nateglinide |
| Antiepileptic | Phenytoin |
| Antifungal | Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole, Voriconazole |
| Antihistamines | Terfenadine |
| Antihypertensives | Felodipine, nicardipine, nifedipine, telmisartan |
| Antineoplastic agents | Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Paclitaxel, Raloxifene, Tamoxifen |
| Antiretrovirals | Indinavir, Nelfinavir, Ritonavir, Saquinavir |

| | |
|---|---|
| Anthelmintics | Albendazole, Mebendazole, Praziquantel |
| Cardiac drugs | Carvedilol, Digoxin, Talinolol |
| Immunosuppressants | Cyclosporine, Sirolimus, Tacrolimus |

**Mechanism of drug release from Nanosponges**

NSs have many apertures at their center, allowing drug molecules to pass through until the liquid reaches saturation. When the encapsulated moiety is applied to the skin or taken internally, it moves freely into the vehicle and is absorbed by the skin . This reduces the concentration of the drug in the vehicle, disrupting the balance. The procedure continues until the entire medicine has been absorbed by the body. The approach outlined above helps select automobiles appropriate for NS preparation. [16]

**Recent advancements in Nanosponges**

Numerous enhancements and progressions in the NSs drug delivery system have been observed in recent years. The variety of drugs incorporated into these systems has also grown, along with the techniques used for their preparation. Additionally, the entrapment efficiency and the types of polymers utilized as components have expanded

**Factors Influncing Nanosponges**

- **Type of Polymer**

  The type of polymer employed can affect both the development and functionality of nanosponges. To facilitate complexation, the nanosponge's cavity size must be appropriate for housing a drug molecule of a specific size.

- **Type of Drugs**

  Drug compounds intended for complexation with nanosponges must possess specific attributes outlined below. [17]

  - The molecular weight of the drug should range from 100 to 400 Daltons.
  - The drug molecule must contain fewer than five condensed rings.
  - Water solubility should be below 10 mg/ml.
  - The melting point of the compound should be less than 250°C.

- **Temperature**

  Variations in temperature can influence the complexation of Drug/Nanosponge. Typically, a rise in temperature leads to a reduction in the magnitude of the

apparent stability constant of the Drug/Nanosponge complex, which may be attributed to a potential decrease in the interaction forces between the drug and the nanosponge, such as van der Waals forces and hydrophobic interactions, as temperature increases.

- **Method of Preparation**

  The approach used to load the drug into the nanosponge can influence the complexation between the drug and the nanosponge. Nevertheless, the efficacy of a method is contingent upon the characteristics of both the drug and polymer; in many instances, freeze-drying has proven to be the most effective for drug complexation.

- **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.

**Application of Nanosponges**

- **Nanosponges for drug delivery**

  Nanosponges can effectively transport water-insoluble medications (class-II pharmaceuticals according to the Biopharmaceutical Classification System) due to their nanoporous shape. These complexes can be used to cover up bad tastes, turn liquids into solids, and speed up the rate at which medications dissolve, become more soluble, and remain stable. According to reports, β-Cyclodextrin- based nanosponges can carry drugs to the target region three to five times more efficiently than direct injection. By loading into the nanosponges, drugs that are very important for formulation in terms of their solubility can be effectively supplied.

  The solid-natured nanosponges can be prepared as topical, parenteral, oral, or inhaled dose forms. The complexes can be distributed in a matrix of excipients, diluents, lubricants, and anticaking agents appropriate for the manufacturing of capsules or tablets for oral administration. The complex can be easily transported in sterile water, saline, or other aqueous solutions for parenteral delivery. They can be successfully added to topical hydrogel for topical delivery. [18]

- **Nanosponges as a carrier for biocatalysts**

  Nanosponges serve as delivery systems for enzymes, proteins, vaccines, and

antibodies. Numerous industrial chemical transformation processes have operational drawbacks, such as low yields from non- specific reactions, the frequent requirement to run at high temperatures and pressures necessitating the use of significant amounts of energy, and the downstream process requiring extremely large amounts of cooling water.

Enzymes can be used as biocatalysts to eliminate or drastically minimize all of these disadvantages. These enzymes are very selective, react quickly, and function in mild reaction conditions. Because they lower energy usage and pollution creation, they have a positive environmental impact.

The stability, economy, and specificity of enzymes have all improved due to advancements in genetic engineering, and the variety of industrial uses for them keeps growing.

- **Cancer Therapy**

Nanosponges that can be employed to transport anticancer drugs to tumors. They assert that the technique reduces tumor growth three to five times more effectively than administering the medications directly. The drug-loaded small nanosponges reveal a targeting peptide that attaches to the tumor's radiation-induced cell surface receptors. The sponges adhere to the surface of tumor cells when they come into contact with them, which causes them to release their cargo. Reduced adverse effects and more effective treatment at the same dose are two advantages of targeted drug delivery. To date, paclitaxel has been used as the sponge load in studies conducted on animals. Due to its severe side effects, lactone ring instability, and poor aqueous solubility, camptothecin, a plant alkaloid and strong

anticancer agent, has limited therapeutic utility. One new class of cross-linked cyclodextrin derivatives is cyclodextrin-based nanosponges. They have been utilized to protect the labile groups, regulate the release, and make poorly soluble actives more soluble. The purpose of this study was to create camptothecin compounds using nanosponges based on β-cyclodextrin.[19]

- **Topical agents**

A novel technique for the regulated release of topical medicines with delayed drug release and drug form retention on skin is the nanosponge delivery system. The

active components in conventional dermatological and personal care products are usually present in quite high concentrations but have a brief duration of effect. A cycle of short-term overmedication and long-term undermedication could result from this. When active substances permeate the skin, they may cause rashes or more severe side effects. This technique, on the other hand, permits a steady and uniform rate of release, minimizing discomfort while preserving effectiveness. A designed product can contain a wide range of ingredients, including gel, lotion, cream, ointment, liquid, or powder.[20]

- **Solubility enhancement**

  In addition to offering a regulated release profile, nanosponges have been utilized to increase the solubility and rate of dissolution of poorly soluble medications. It may not be universally applicable to all molecules, though, as molecular size and conformation are important factors affecting inclusion complexation within nanosponges. Cefpodoxime proxetil (CP) nanosponges have been created to increase the drug's rate of dissolution. Itraconazole nanosponges based on crosslinked β-cyclodextrins have been reported to improve the solubility of poorly soluble medications. It was discovered that using a ternary solid dispersion system increased itraconazole's solubility by more than 50 times. The solubilization efficiency of nanosponges was improved by using copolyvidonum in conjunction with them.

**Characterization of Nanosponges**

- **Loading efficiency**

  To determine the loading effectiveness of nanosponge complexes, they must be dissolved in an appropriate solvent, broken up by sonication, diluted appropriately, and then subjected to UV spectrophotometer and HPLC analysis.

- **Microscopy studies**

  Drugs, nanosponges, and the result (drug/nanosponge complex) can all be studied microscopically using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Even though there is a noticeable difference between the raw material's and the co-precipitated product's

crystallization states, the difference between the two materials' crystallization states as

observed under an electron microscope suggests the creation of inclusion complexes.

- **Particle size and polydispersity**

  Using a 90 Plus particle sizer fitted with MAS OPTION particle sizing software, the particle size can be ascertained via dynamic light scattering. This allows for the calculation of the mean diameter and polydispersity index.

  Instruments for dynamic light scattering can also be used to measure the polydispersity index (PDI). The particle size distribution's width, spread, or variation is measured by the PDI.

  A greater PDI value denotes a polydisperse sample with a larger particle size distribution, while monodisperse samples have a lower PDI value.[20]

- **Zeta Potential**

  Zeta potential is a surface charge measurement that can be made with an extra electrode in the particle size apparatus.

- **Fourier Transform Infrared (FTIR) Analysis**

  To confirm that there might be a chemical bond interaction between the medication and the polymer, Fourier transform infrared analysis was performed. The samples were scanned using a carbon black reference and in the 400–4000 cm-1 range. Clean, dry helium gas was carefully used to purge the detector in order to raise the signal level and lower moisture.[21]

- **Thin layer chromatography**

  The Rf value of a medication molecule significantly decreases in Thin Layer Chromatography, which aids in determining the complex formation between the drug and Nanosponge. The process of inclusion complexation between host and guest molecules is reversible. As a result, during the chromatographic process, the complex may fully split into guest and host molecules, leaving just the spots of the guest and host molecules visible on the TLC plate.

- **Infra-Red spectroscopy**

  The interaction between the drug molecules and the nanosponge in the solid state is estimated using infrared spectroscopy. Bands that could be attributed to the included portion of the guest molecules are readily obscured by the bands of the nanosponge spectrum, and these bands frequently only slightly alter upon complex formation if the fraction of the guest molecules encapsulated in the complex is less

than 25%. The method is less illuminating than alternative approaches and is often not appropriate for detecting inclusion complexes.

Only medications with certain distinctive bands, like carbonyl or sulfonyl groups, can be used with infrared spectroscopy. Information about the role of hydrogen in different functional groups can be found through infrared spectral analyses. Due to the stretching vibration of the group involved in the creation of the hydrogen bonds, this typically causes the absorbance bands to move to a lower frequency, increase in intensity, and broaden the band. The stretching vibration band is most significantly shifted by the hydrogen bond at the hydroxyl group.

- **Thermo Analytical Method**

  Thermo-analytical techniques measure whether the drug material changes in any way prior to the nanosponge's thermal degradation. The drug substance may undergo polymorphic transition, oxidation, breakdown, melting, or evaporation. The complex development is shown by the change in the drug's composition. It is possible to watch for broadening, shifting, the introduction of new peaks, or the removal of specific peaks in the thermogram produced by DTA and DSC. Additionally, variations in weight loss may offer proof that inclusion complexes are forming.

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