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Review Article

A COMPREHENSIVE REVIEW ON NANOSPONGES

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ABSTRACT

Nanosponges are an innovative class of advanced drug delivery systems showing versatile benefits. Distinguished by high surface area, tunable polarity and nanometer-sized cavities, nanosponges facilitate sustained and targeted drug delivery while minimizing toxicity. They also enable drug administration by multiple routes, such as oral, topical, parenteral and inhalation. Cyclodextrin-based nanosponges, in particular, demonstrate significant advantage for drugs with poor solubility, yielding improved therapeutic outcomes. Applications of nanosponges in cancer therapy, autoimmune treatment, antimicrobials, enzyme stabilization and protein delivery frequently surpass traditional drug delivery systems. Various synthesis techniques, including solvent evaporation and ultrasound-assisted methods and characterization methods are presented in this review article. The stability and performance of the nanosponges can be improved by proper choice of the polymer and crosslinker during the preparation. Drug molecules with molecular weight ranging from 100-400 Daltons with less than five condensed rings are capable of easy entrapment in the cavities of nanosponges. Ongoing research and technological advances continue to establish nanosponges as a transformative solution in precision medicine and novel drug delivery systems.

Keywords: Nanosponges, Cyclodextrins, Applications, Preparation methods, Factors, Characterization.

INTRODUCTION

Nanosponges constitute an advanced platform in nanotechnology-driven drug delivery. They are built as hyper-crosslinked polymeric structures with a porous, sponge-like framework, typically 100-200 nm in size. Their design enables encapsulation of both hydrophilic and lipophilic drugs, which significantly improves bioavailability, stability, and solubility while protecting therapeutic agents from degradation in the body (Garg *et al*., 2023; Tejashri *et al*., 2013). The 3D porous architecture supports controlled and sustained drug release, minimizing side effects and enhancing patient adherence by delivering medications over extended periods. Nanosponges can also be engineered to respond to specific environmental triggers like pH, temperature, or enzyme activity enabling targeted release at disease sites (Ravi Silpa *et al*., 2019). Unique properties including high drug-loading capacity, modularity in size and surface function and non-toxic nature set nanosponges apart from conventional carriers such as liposomes and micelles (Meshram *et al*., 2024; Srivastava *et al*., 2024). Beyond their role as drug carriers, nanosponges have found diverse applications in biomedical and environmental fields. They can serve as carriers for enzymes, proteins, vaccines, and antibodies, providing controlled and protected delivery for therapeutic and diagnostic uses. Nanosponges exhibit potential as chemical sensors for environmental pollutants like hydrogen gas and volatile organic compounds due to their sensitive, interconnected nanostructures (Lakshmi *et al.,* 2020). Additionally, they have been explored for oxygen delivery systems where controlled oxygen release is critical for treating conditions like hypoxia. In dermatology, they enable precise delivery of topical agents and improve the solubility and stability of cosmetic ingredients (Iravani *et al.,* 2022; Singh *et al.,* 2022). Some nanosponge-based drug formulations are already commercially available or in clinical trials, highlighting their translational potential (Subramanian *et al.,* 2012; Tiwari *et al.,* 2022). Para-crystalline nanosponges, known for their porous nature and

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non-toxicity, maintain thermal stability up to 300°C, making them highly suitable for drug loading applications. These nanosponges also exhibit remarkable stability across a wide pH range (1 to 11), ensuring consistent performance in various physiological environments. Furthermore, nanosponges have the capacity to form both inclusion and non-inclusion complexes with a variety of drugs, broadening their versatility in pharmaceutical formulations. Additionally, by incorporating magnetic particles into the reaction mixture during synthesis, nanosponges can be endowed with magnetic properties. These distinct physicochemical features underscore nanosponges adaptability and promise in drug delivery and beyond (Tejashri *et al.,* 2013).

Nanosponges show many advantages (Vishwakarma *et al.,* 2014; Indira*et al.,* 2012). They remain stable within a wide pH range (1-11). Nanosponges are non-irritating, non-toxic, non-allergenic, and fully biodegradable. They are compatible with most excipients and vehicles. Drug encapsulation can be carried out either inside the nanosponge (with adjuvants) or outside. The size of nanosponges can be adjusted by modifying the ratio of crosslinker to polymer. There are some disadvantages associated with nanosponges (Salunkhe *et al.,* 2018). Their performance depends mainly on their drug-loading capacity. They are more suitable for small molecules rather than large biomolecules. There may be risks of dose dumping. In some cases, drug release may be delayed more than desired. The difference in size and porosity is the small distinction that separates nanoparticles from nanosponges. Nanoparticles have nanometer-sized pores, whereas nanosponges have pores that vary in size but are typically smaller than 5 µm. Nanosponges have been alluded as nanoporous nanoparticles or microparticles on various occasions. Nanosponges have a structure with several domains because they include both hydrophobic and hydrophilic groups. Different types of nanosponges (Pyrak *et al.,* 2024) are given as flowchart in figure 1.

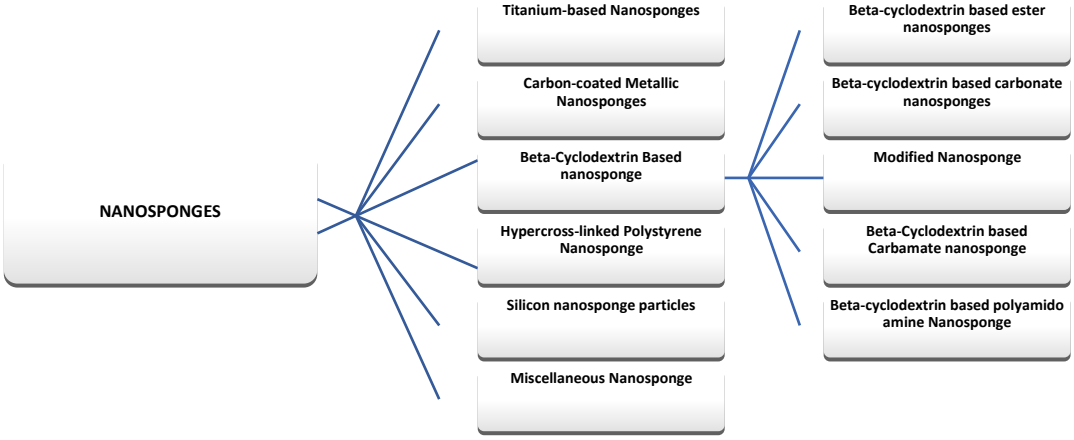

Figure 1. Different types of nanosponges.

APPLICATIONS OF NANOSPONGES

Drugs may dissolve faster using nanosponge, which may also increase their solubility and stability, cover undesirable smells, and convert liquids to solids. It has been discovered that cyclodextrin-based nanosponges carry medications to the desired site more efficiently than direct injection. They can be administered parenterally in sterile water, saline, or other aqueous solutions. For topical administration, they might be mixed to create a topical hydrogel (Mandan *et al.,* 2018)

Cancer treatment

Because of their poor solubility, anticancer drugs are among the most challenging to develop in the pharmaceutical industry today. One study discovered that the combination of nanosponge and injection is three times more effective in preventing tumor development than straight injection. Following the complex procedure of loading medicine into the nanosponge, a specific peptide is securely bound to the top layer of radiation-induced cells on the cancer receptor. When the nanosponges come into touch with cancer cells, they stick to their surfaces and begin releasing therapeutic compounds. One advantage of targeted drug administration is that it may produce a more favorable pharmacological impact at the same dose with fewer adverse effects (Linisha *et al.,* 2025).

Delivery of proteins and enzymes

β-Cyclodextrin based nanosponges were tested for their ability to encapsulate bovine serum albumin. Because the protein solution containing bovine serum albumin is unstable, it is lyophilized. When proteins are lyophilized from their original structures, they may become denatured. When proteins like bovine serum albumin (BSA) are dispersed by cyclodextrin-based technology, nanosponges may increase their stability. Nanosponges have also been used to immobilize enzymes, encapsulate proteins, regulate distribution, and stabilize them.

Fungal infection treatment

Fungal skin diseases are among the most dangerous illnesses in the world. Topical treatment is a viable therapeutic choice for skin ailments because it offers several advantages over systemic adverse effects, including the ability to modify medications to reach the sick location directly. Class II biopharmaceuticals, such as Itraconazole, are antifungal medicines with low bioavailability and a slow breakdown time. It has been discovered that itraconazole nanosponges improve bioavailability and solubility. When itraconazole is added to these nanosponges and cyclodextrin acts as a carbon cross, its solubility may improve (Güngör *et al.,* 2013).

Treatment from poisons

Nanosponges have the potential to remove toxic compounds from our bloodstream by absorbing toxins. The nanosponge mimics a red blood cell in the bloodstream, tricking toxins into attacking it and then absorbing them. Each nanosponge can absorb a certain number of toxic molecules depending on the poison (Hu*et al.,* 2013).

Enhancement of drug solubility

Poor solubility is one of the most important issues to address when designing and developing drug delivery systems. Medication solubility issues can undermine the efficacy of a formulation. Nanosponge contains molecules in its center, increasing the formulation's solubility. Currently, a cyclodextrin nanosponge is employed to improve solubility (Nabeela *et al.,* 2018; Jain *et al.,* 2020).

Delivery system for oxygen

Oxygen delivery system through the usage of CD, an oxygen delivery system was created and formulated as NSs. For this, NSs made up of alpha, β, and γ-CD are combined in aqua, soaked in oxygen, and then examined in vitro (Cavalli *et al.,* 2010). The β-CD NS/hydrogel combo device allows for oxygen infusion through a silicone layer. Research has shown that NS has the ability to release oxygen in a regulated manner throughout time. The oxygen-deficient cell mass found in several oxygen-deficient illnesses can be adhered to by oxygen-encapsulated NSs.

Anti-viral application

Nanosponge can be employed in both pulmonary and nasal delivery systems. It employs nanocarriers to transport antiviral medications based on small interfering ribonucleic acid (siRNA) to the nose or lungs, allowing it to treat viruses that cause respiratory tract conditions including rhinoviruses and influenza viruses. Zidovudine and saquinavir served as nanocarriers (Challa *et al.,* 2005).

MATERIALS AND METHODS

Different excipents used in the formulation of nanosponges are mentioned below in the Table 1 (Waghmare *et al.,* 2017). The selection of polymer can have an effect on the structure as well as the appearance of Nano sponges. The cavity size should be suitable for consolidating the specific drug particle. The polymer used is determined by the delivery method and drug to be encapsulated. Researchers determined the type of polymer used should be capable of adhering explicit legends. The crosslinking expert determination can be made based on the structure of the polymer and the drug to be focused. Drug particle comprises of under-five consolidated rings solubility in water is under 10 mg/ml.

Table 1. Excipients used in the formulation of nanosponge.

Crosslinker	Polymer	Polar solvents	Co polymer
Dichloromethane	Hydroxy propyl β-cyclodextrin	Dimethylacetamide	Poly (Valerolactone allyl Valerolactone)
Pyromellitic anhydride	Poly-Valerolactone	Dimethylformamide	Poly (Valerolactone allyl Valerolactone oxypanedione)
Diisocyanates	Methylβ-Cyclodextrin	Ethanol	Ethyl cellulose
Carbonyl diimidazole	Poly-Valerolactone		Polyvinyl alcohol
Glutaraldehyde	Acrylic Polymer		
Carboxylic acid dianhydrides	Eudragit RS100		
Diarylcarbonates	Hyper Crosslinked Polystyrene Cyclodextrin (alkoxy carbonyl cyclodextrins)		

MATERIALS AND METHODS

Emulsion solvent method

In the emulsion solvent diffusion method for nanosponge synthesis, different proportions of ethyl cellulose and polyvinyl alcohol (PVA) are used to control the characteristics of the final product. The process involves creating two phases: a dispersed phase, consisting of ethyl cellulose and the chosen drug dissolved in 20 ml of

dichloromethane, and a continuous aqueous phase containing PVA in 150 ml of distilled water. These phases are combined, and the resulting mixture is stirred at 1000 rpm for approximately two hours to ensure even distribution and efficient nanosponge formation. The nanosponges are then separated from the mixture via filtration. Once collected, the product undergoes drying in an oven, typically at 40°C for 24 hours, which removes residual solvents and stabilizes the nanosponge structure (Kandekar *et al.,* 2023). This method allows fine-tuning of nanosponge size, porosity, and drug-loading capacity by varying the ratios of ethyl cellulose and PVA, making it an effective technique for creating nanocarriers with properties adapted to specific pharmaceutical applications. The detailed technique of emulsion solvent method is given below in figure 2.

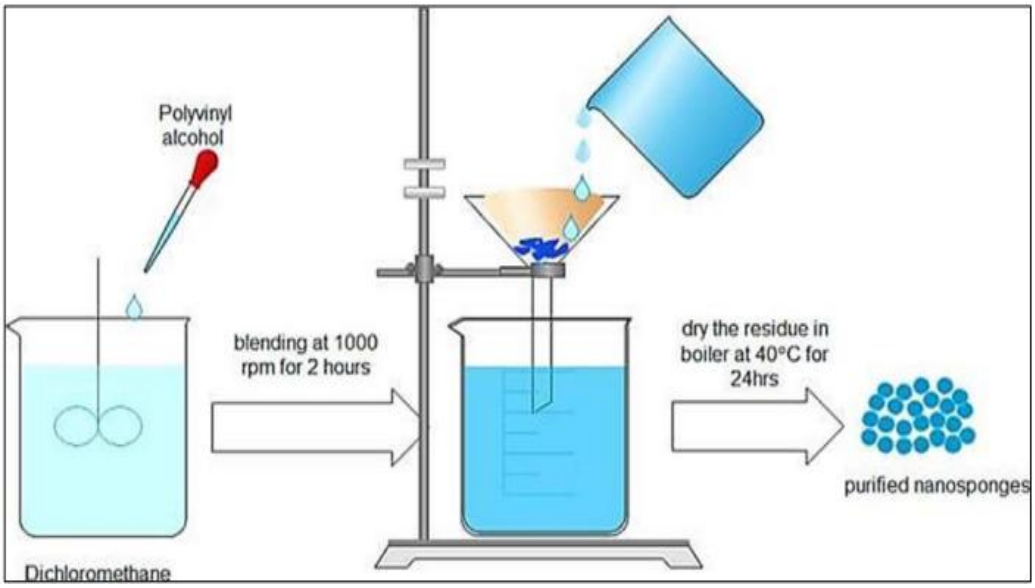

Figure 2. Emulsion solvent method.

Solvent evaporation method

In the polar aprotic solvent method for nanosponge synthesis, the polymer is first dissolved in a suitable solvent such as dimethyl formamide (DMF) or dimethyl sulfoxide (DMSO), which are particularly effective because they don't interfere with the crosslinking reaction. The polymer solution is then added to a large excess of crosslinker, ideally using a crosslinker-to-polymer molar ratio anywhere from 4:1 to 16:1, depending on the desired nanosponge properties. The mixture is allowed to react at temperatures ranging from as low as 10°C up to the solvent's reflux temperature, with reaction times typically spanning 1 to 48 hours. Once the reaction is complete, the solution is cooled to room temperature and poured into a large volume of bi-distilled water, which causes the nanosponge product to precipitate out. The precipitated nanosponges are then collected through vacuum filtration and purified by prolonged Soxhlet extraction using ethanol to remove excess crosslinker and residual solvents. The final step involves vacuum drying, followed by grinding with a mechanical mill to achieve a uniform, homogeneous powder suitable for further use in drug delivery formulations (Pedrazzo *et al.,* 2020). This method is appreciated for its adaptability and production yield but can sometimes result in larger particle sizes and less spherical nanosponge morphology. Solvent evaporation method was illustrated in the below figure 3.

Ultrasound assisted method

This method describes a solvent-free synthesis of nanosponges using polymer and crosslinker, where the two are mixed in a defined molar ratio and subjected to ultrasound sonication for 5 hours at 90°C. The ultrasound bath helps to maintain uniform reaction conditions and promotes thorough mixing, leading to the formation of spherical and uniform nanosponges. After the reaction, the mixture is cooled to room temperature, and the solidified product is roughly broken apart. To purify the nanosponges, the product undergoes thorough washing with water to remove any non-reacted polymer, followed by Soxhlet extraction with ethanol to further refine the material. The final product is dried and stored at 25°C, ensuring stable, high-quality nanosponges suitable for pharmaceutical applications. This approach yields nanosponges with consistent size and morphology due to the efficient energy transfer and mixing provided by sonication, while avoiding the complications of residual solvent contamination (Farsana *et al.,* 2021; Subramanian *et al.,* 2012).

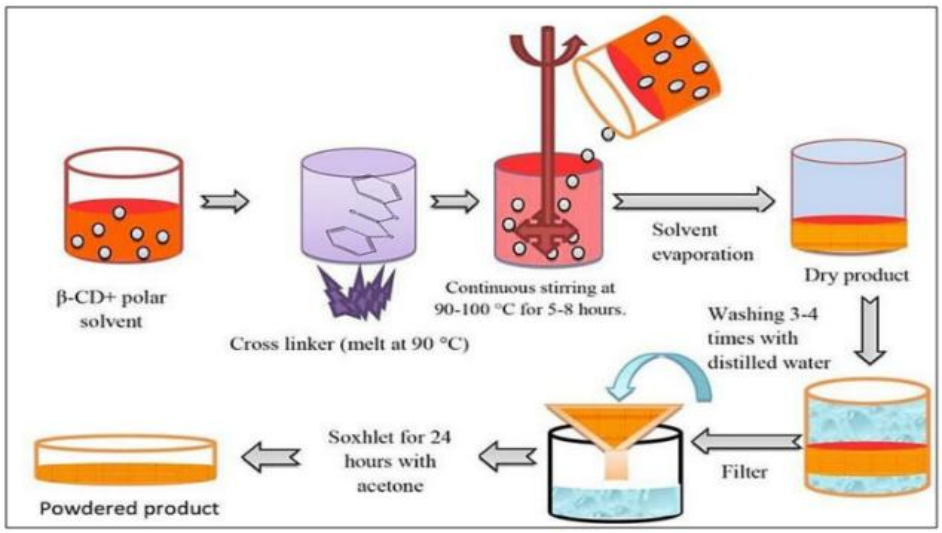

Figure 3. Solvent evaporation method. Adapted from (Chandur *et al.,* 2021).

Melt method

The melt procedure for preparing nanosponges begins by melting both β-cyclodextrins (β-CDs) and the crosslinker. Once both components have liquefied, additional finely blended ingredients are added to a 250 mL jar that is maintained at 100°C. The reaction is then allowed to proceed for 5 hours under stirring with a magnetic mixer, ensuring thorough and uniform mixing. After completion, the reaction mixture is left to cool, and the resultant solid product is broken down mechanically. The final purification step involves washing the product with suitable solvents to efficiently remove any by-products and unreacted materials, yielding purified nanosponges with the desired characteristics (Gandhi *et al.,* 2025).

Bubble electrospinning

A conventional electrospinning setup generally consists of a syringe loaded with polymer solution, a syringe pump to control flow, a high-voltage power supply, and a grounded collector to gather the nanofibers. However, a common limitation of this method is the relatively low production volume of nanofibers. Bubble electrospinning is an alternative technique that can use polymers such as polyvinyl alcohol (PVA). In this technique, a 10% PVA solution is prepared by dissolving the polymer in distilled water and heating it at 80-90°C for about 2 hours to form a homogeneous one-phase mixture. After heating, the polymer solution is allowed to cool down at room temperature before being used to produce nanoporous fibers. This approach improves the scalability of nanofiber production while maintaining the desirable fibre morphology for various applications (Yang *et al.,* 2009).

Quasi emulsion solvent method

Nanosponges are formulated with varying amounts of polymer, where the inner layer is created using Eudragit RS 100 before subjecting it to an appropriate dissolvable phase. The drug included in the formulation exhibits instability and degrades at 35°C when subjected to ultrasonication. Polyvinyl alcohol (PVA) is incorporated in the outer phase, serving as an emulsifier to stabilize the mixture. The formulation is then mixed at room temperature at a stirring speed of 1000 to 2000 rpm for 3 hours to ensure proper emulsification and uniformity. After thorough mixing, the product is dried in an air-warmed oven at 40°C for 12 hours to remove residual moisture, resulting in stable, well-formed nanosponges with optimized drug encapsulation and controlled releasecharacteristics (Bhowmik *et al.,* 2018).

MECHANISM OF DRUG RELEASE

Nanosponges encapsulate the active ingredient within their open porous structure without a continuous membrane, allowing the drug to freely diffuse into the surrounding vehicle until saturation equilibrium is achieved. When the nanosponge formulation is applied to the skin, the vehicle begins to absorb or evaporate, disrupting this equilibrium. Consequently, the active ingredient continuously diffuses from the nanosponges into the vehicle and subsequently into the skin. This mechanism enables sustained release of the drug onto and into the skin for an extended duration as nanosponges remain adhered to the stratum corneum (Bhowmik *et al.,* 2018; Girigoswami *et al.,* 2022).

Factors influencing nanosponge formation

The nature of the polymer used in the preparation of nano sponges can have an impact on their development as well as the pre-plan. The depression of a nano sponge should be large enough to catch a medicine (Sabzi *et al.,* 2018).

Drug

To be incredible with nano sponges, the drug atoms should have some specific properties, as listed below. Temperature changes can affect the complexation of medicines or nano

sponges. Expanding the temperature often reduces the disorientation, which might be due to a decrease in communication powers, such as hydrophobic and Vander Waal powers of medication/nano sponges.

Complexation Temperature

The durability of a complex is affected by temperature fluctuations. Durable kinetics and heat rises are inversely connected. As temperature rises, the magnitude of real strength decreases due to a reduction in medication/nano sponge forces. Maintaining temperature is crucial for the manufacture of nanosponges (Aldawsari *et al.,* 2023).

Degree of Substitution

The compound capacity of nano sponges is influenced by the number, kind, and posture of the replacement on the polymer substance. The type of replacement is required because CD derivatives are available in a variety of functional areas (Lala *et al.,* 2011).

CHARACTERIZATION STUDIES

The nanosponge can be characterized by using the following methods.

Thermo-analytical methods

Thermo-analytical investigation determines if the drug or material changes before the nanosponge is thermally destroyed. Drugs may be inactivated into substances by processes such as melting, evaporation, breakdown, oxidation, and polymorphic conversion. The temperature chart acquired by DTA and DSC can show expansion, displacement of water, the emergence of additional peaks, or the disappearance of some peaks. Weight loss changes can also be utilized for illustrating the establishment of inclusion complexes (Swaminathan *et al.,* 2010).

Microscopic studies

Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) are used to look into the microscopic properties of nanosponges. Even if the raw material crystallization state appears to change, variations in the raw material and product states as observed through an electron microscope indicate the formation of inclusion complexes (Mahmoudian *et al.,* 2018; Panda *et al.,* 2015).

Particle size determination

The size of the nanoparticles is a crucial factor to consider while optimizing the nanosponge. A drug's particle size may have an impact on both its release and solubility. Particle size can be determined using a Zeta sizer or a laser light diffractometer. Plotting the total percentage of drug release from nanosponges of varied particle sizes over time can be used to investigate how particle size influences drug release. Nanoparticles ranging in size from 10 to 25 nm are more suited for topical medicine administration since larger particles may feel gritty (Nandish Kumar *et al.,* 2022).

Thin layer chromatography

In Thin Layer Chromatography (TLC), the Rf value of the drug molecule was drastically lowered, allowing the complex formation between the drug and the nanosponge to be detected. The inclusion and complexation of host and guest molecules are governed by a reversible process. As a result, only spots of the guest and host molecules are shown on the TLC plate, indicating that the complex may entirely split into guest and host molecules during chromatography.

Zeta potential

The zeta potential is the potential difference between the fluid's immobilized and dispersion medium layers, both of which are surrounded by dispersed particles. The zeta potential is the fundamental parameter for assessing the stability of colloidal dispersion. The zeta potential can be measured by adding an additional electrode to the particle size equipment or zeta sizer. The higher the zeta potential value of a colloidal dispersion, the higher its stability (Maravajhala *et al.,* 2012).

Infrared spectroscopy

Infrared spectroscopy (IR) is used to evaluate the interaction of therapeutic drugs with nanosponges. The use of IR is limited to drugs containing bands or features such as sulfonyl or carbonyl groups. Information regarding hydrogen in different functional groups is included in infrared investigations. As a result, the absorption band becomes stronger and moves to lower frequencies. The stretching vibrations of the group involved in the formation of hydrogen bonds lead the bands to broaden.

X-ray diffractometry

X-ray powder diffractometry data identify solid-state complexes. In the event that the drug is a solid, the diffraction pattern should be compared to the mechanical combination of the dry material and the hypothetical complex, which alters the pattern. A physical mixture's diffraction pattern results from the interaction of two constituents. They produce diverse mixture peaks and are useful in determining complex formation and chemical breakdown. It may also be used to determine the inclusion structure and its interactions. The interactions between host and foreign molecules may be accurately defined, allowing for the establishment of an exact connection (Tamkhane *et al.,* 2014).

Solubility studies

The phase solubility method is the most frequently utilized methodology for studying inclusion complexation because it examines how nanosponges alter pharmaceutical solubility. The phase solubility diagram reflects the level of complexity. Higuchi and Connors model has described the phase solubility method used to study inclusion complexation, in which effect of a nanosponges can be examined.

Porosity

This parameter measures the proportion of the total volume that is occupied by pores or voids within the material, providing insight into the porosity and structural properties of nanosponges (Simranjot *et al.,* 2019).

This equation calculates the percentage yield by comparing the actual mass of nanosponges obtained after production to the total initial mass of raw materials used (Kiliçarslan *et al.,* 2003).

$$\text{Production yield} = \frac{\text{Practical mass of nanosponges}}{\text{Theoretical mass of nanosponges}} \times 100$$

***In-vitro* release studies**

A dissolution apparatus with a modified basket constructed of stainless-steel revolving at 150 rpm may be used to measure drug release from nanosponge. To guarantee sink conditions, the dissolving medium is chosen based on the solubility of the actives. A sample from the dissolving media can be analyzed using an appropriate analytical method. In most circumstances, depending on the formulation, a Franz diffusion cell can be employed.

CONCLUSION

Nanosponges are making waves in medicine as smart, tiny carriers that can hold and release medications in a much more controlled and precise way. Their network of pores lets them trap all kinds of drugs, and deliver them right where they are needed. Nanosponges are already being put to use in areas such as cancer treatment, fighting infections, delivering proteins and even clearing toxins from the body, making them an exciting new tool in the pharmacy toolkit. At the same time, like any new technology, nanosponges face some challenges. They do their best work with smaller drug molecules. Researchers are fine tuning these novel carriers to get the highest benefit. Nanosponges have the potential to transform how medicines are delivered, offering patients safer, more effective treatments that are tailored to their needs.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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