Nanosponges: An Emerging Trend in Novel Drug Delivery System.

Roshan Ghorpade, Pramod Kumar Shirote, Nikhil Dhumal, Prasad Galande

Abstract- A targeted drug delivery system has been created as a result of recent advances in nanotechnology. Small sponges called "Nanosponges" have cavities filled with drug molecules and have an average diameter of less than 1 m. Nanosponges have a high porosity, a unique capacity to capture active molecules and the unique benefit of continual delivery. They are easy to make or physiologically safe. When enzymes, protein molecules, vaccines, and antibodies are given out and released. Nanosponges can also be utilised as a carrier for biocatalysts. The preparation process, characterisation, and parameters impacting nanosponges are highlighted in this review.

Keywords: Nanosponges, porous, continuous release, biocatalysts.

I. INTRODUCTION

The engineering and scientific study of nanotechnology involves controlling shape and size at the nanoscale in order to create, characterise, generate, and use systems, electronics, and structures [1]. A number of pharmaceutical drug delivery challenges are being addressed through nanotechnology. Researchers have been aware of the potential advantages of nanotechnology in improving medicine delivery and drug targeting for more than 20 years. Patients may greatly profit from improved delivery systems that lessen toxicity and boost efficacy, and it may also enlarge the pharmaceutical and drug delivery industries' marketplaces [2]. Nanosponges are an exciting medication delivery technology. Nanoparticles with porous features are referred to as "nanosponges." [3] It is a type of material from the present day and is made up of minuscule particles with a hollow that is only a few nanometers wide. They contains tiny particles with a hollow that is only a few nanometers wide. These tiny particles are able to contain both hydrophilic and lipophilic medicaion substances [4], it makes pharmacological drugs or weakly water-soluble chemicals more stable. Small sponges known as "nanosponges" have an average diameter of less than 1 m and are roughly the size of a virus. Tiny sponges are mixed into a precise dosage form, which circulates throughout the body until it reaches the target region. When they arrive, the sponges cling to their surface and begin to deliver the medication in a predictable and controlled way [5]. The use of nanosponges employed as a tool for therapeutic purposes to enhance lipophilic water solubility, preserve degradable compounds, and construct pathways for the transmission of medications for other routes of administration aside from oral. Before the twenty-first century, the only available form of the nanosponge medication delivery technology was as a topical application. oral and intravenous (IV) administration of nanosponges is now possible [6].

II. Characteristics of Nanosponges [7,8,9],

a) A variety of diameters (1 m or less) and surfaces with adjustable polarity are available in nanosponges.
b) They are porous substances with high aqueous solubility that are primarily employed to encapsulate poorly soluble medicines.
c) They can be replicated using simple thermal desorption, solvent extraction, microwaves, and ultrasounds.
d) Nanosponges can carry both lipophilic and hydrophilic medicines.

Figure number 1: Polymer Based nanosponges
They guard the medication against thermodynamic deterioration.

Nanosponges are materials that can tolerate pH levels of 1 to 11, as well as temperatures as high as 130°C.

Nanosponges are harmless and environmentally friendly, non-allergic, non-irritating. They are also non-mutagenic and non-allergic.

In the case of dosage therapy, Drug profiles might be rapid, medium, or slow.

By generating complexes of inclusion and exclusion, nanosponges can encapsulate a variety of compounds.

Nanosponges can connect more effectively to the target region because of chemical linkers. The capture, transportation, and controlled release of a number of compounds are made possible by their three-dimensional design.

Advantages of nanosponges:\[10,11,12]\:

- Medication delivery at a given location.
- They make medications more soluble.
- Fewer negative side effects (due to less medication interaction with nutritious cells).
- They improve the drug’s efficiency.
- They work with the great majority of vehicles and substances.
- These can be economical and free-flowing.
- This technology offers minimal adverse effects and the ability to entrap a wide range of substances.
- Stability, elegance, and formulation flexibility have all been improved.
- Since bacteria cannot pass through their 0.25 mm average pore size, these are self-sterilising.
- A nanosponge provides longer release and continued action for up to 12 hrs.
- It reduces anxiety and increases tolerance, which improves patient compliance.
- It optimises material processing by allowing the introduction of immiscible liquids, which can be transformed into powders.

Disadvantages of Nanosponges:\[13,14]\:

- It is based on the drug molecules’ loading capabilities.
- It does not include any huge molecules, just tiny molecules.
- Nanosponges can be either paracrystalline or crystalline.

Types of nanosponges:\[15,16]\:

- Cyclodextrin based nanosponges
- Titanium based nanosponges
- Silicon nanosponges partial
- Crosslinked polystrene nanosponges
- Carbamate nanosponges based on cyclodextrin
- Polyamidoamine nanosponges
- Ester nanosponges based on cyclodextrin
- Modified Nanosponges

Figure Number 1: Types of nanosponges

Composition of Nanosponges:\[17,18,19]\:

1. Polymer
2. Cross-linking compound
3. Drug compound
Table Number 1: Chemicals for preparation of nanosponges

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Components</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Polymer</td>
<td>Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins Ethyl Cellulose, Polymethylmethacrylate</td>
</tr>
<tr>
<td>2</td>
<td>Copolymer</td>
<td>Ethyl Cellulose, Poly (valerolactone-allylvalerolactone oxepanedione), Poly vinyl alcohol.</td>
</tr>
<tr>
<td>3</td>
<td>Crosslinker</td>
<td>Diarylcarbonates, Diisocyanates, Epichloridine, Carbonyl diimidazoles, Carboxylic acid dianhydrides.</td>
</tr>
</tbody>
</table>

1) Polymer:
The type of polymer used can influence how successfully Nanosponges develop and function. The medicine to be encapsulated and the required release determine the polymer to be used. The chosen polymer should have the ability to bind to particular ligands. The substitutable functional and active groups determine whether a polymer can be cross-linked. The polymer should possess the ability to bind with the particular ligands in order to facilitate targeted medication release.

2) Cross-linking compound:
Depending on the polymer's structure and the medicine that needs to be developed, a crosslinking agent might be chosen.

3) Drug Substance:
The following features of drug compounds should be present in nanosponges:
- Molecules with a weight between one hundred and four hundred Daltons in size.
- The molecule of a medication contains a maximum of five condensed rings.
- The solubility is below ten mg per millilitre in water.
- The material has a melting point that is lower than 2500 °C.

VII. Methods for synthesising nanosponges\textsuperscript{[20,21]}:

Figure number 2: Method of preparation

1. Emulsion-based solvent diffusion\textsuperscript{[22]}:
Various quantities of ethyl cellulose (EC) and PVA can be used to produce nanosponges. the dispersing phase gently added to 100 ml of an aqueous continuous phase containing a specified quantity of polyvinyl alcohol. For two hours, At 1000 rpm, the reaction
mixture was stirred. The generated nanosponges were recovered by filtering then dried for 24 hours at $40^\circ\text{C}$ in the oven. To make sure that any remaining solvents had been eliminated, the vacuum desiccators were used to store the dried nanosponges.

**Figure number 3: emulsion based solvent diffusion**

2. **Solvent method** [23]:
   This approach involved combining the polymer with an appropriate solvent, particularly a solvent that is polar and aprotic, such as dimethylformamide or dimethyl-sulfoxide. The crosslinker was added in excess to this combination, preferably with a 4 to 16 molar crosslinker/polymer ratio. At temperatures ranging from 10 $^\circ\text{C}$ to the solvent's reflux temperature, the reaction was performed for one to forty-eight hours. Dimethyl carbonate and carbonyl diimidazole are preferred crosslinkers among carbonyl compounds. The combination was allowed to cool to room temperature when the reaction was complete. The result was then mixed with a sizable volume of bidistilled water, which was then filtered under vacuum to recover the product, which was then ethanol-based prolonged Soxhlet extraction is a further purification method. The product was vacuum-dried before being mechanically milled to create a uniform powder.

3. **Ultra-sound assisted synthesis** [24,25]:
   By combining polymers and cross-linking substances without the need for a solvent and using sonication, nanosponges can be created. The produced nanosponges will be uniformly sized, spherical, and less than 5 microns in size. The crosslinker in this approach is di-phenyl carbonate (or pyromelitic anhydride). Here, combine the crosslinker and polymer in a flask. Heat the container ultrasonography it for 5 hours at 90 $^\circ\text{C}$ in a water-filled ultrasound bath. To get rid of any impurities or unreacted polymers, the solid was then crushed in a mortar and pestle before being extracted using the soxhlet technique and ethanol. Nanosponges were washed and then located at a temperature of 250 $^\circ\text{C}$.

4. **Quasi-emulsion based solvent diffusion** [26]:
   Additionally, the Nanosponges can be created via a solvent diffusion approach based on a quasi-emulsion at various polymer concentrations. An appropriate solvent was used to dissolve eudragit RL100 in order to prepare the inner phase. Once the medicine has been added, the solution can be ultrasonically heated to 350 $^\circ\text{C}$ to dissolve it. The water-based PVA solution (outer phase) received the addition of the inner phase. After stirring for 60 minutes, the mixture is filtered to remove the nanoparticles. The nanosponges are dried for 12 hours at 40 $^\circ\text{C}$ in air-heat oven.

**VIII. Factors affecting in formulation of nanosponges:**
There are several factors which affect on the formulation of nanosponges which are given below

1. **Polymer type** [27]:
   Nanosponges are created and act differently depending on the polymer used. The nanosponge's space should be large enough to allow the complexation of a drug molecule of a specific size.

2. **Type of drug** [28]:
   The following is a list of specific characteristics of medicinal compounds that will complex with nanosponges.
   - Molecules with a weight between one hundred and four hundred Daltons in size.
   - The molecule of a medication contains a maximum of five condensed rings.
• The solubility is below ten mg per millilitre in water.
• The material has a melting point that is lower than 2500 °C.

3. Temperature [29]:
Drug-nanosponge interactions may be impacted by temperature fluctuations. In general, if the forces of drug/nanosponge contact, such as van der Waal interactions, are diminished, it may result in an increase in temperature causing the drug/nanosponge complex's apparent stability constant to drop.

4. Substitution level [30]:
The complexity of the nanosponges can be seriously affected by the quantity, position, and form of the parent molecule's substituents.

IX. Characterization of nanosponges [31,32]:

![Characterization of nanosponges](image)

1. Particle shape and Polydispersity:
A 90 Plus particle sizer outfitted with MAS OPTION particle sizing software can be used to detect particle size using dynamic illumination scattering. This makes it possible to determine the average diameter and polydispersity index. Instruments for dynamic light scattering can also be used to measure the polydispersity index (PDI) [31]. A measure of variance or dispersion within the particle size distribution is the PDI. Lower PDI values are associated with monodisperse samples, while higher PDI values are associated with polydisperse samples, which have a larger range of particle sizes.

<table>
<thead>
<tr>
<th>Sr no.</th>
<th>Dispersion medium</th>
<th>Polydispersity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>one-dimensional standard</td>
<td>0-0.05</td>
</tr>
<tr>
<td>2</td>
<td>practically monodisperse</td>
<td>0.05-0.08</td>
</tr>
<tr>
<td>3</td>
<td>mid-range polydisperse</td>
<td>0.08-0.7</td>
</tr>
<tr>
<td>4</td>
<td>extremely dispersed</td>
<td>&gt;0.7</td>
</tr>
</tbody>
</table>

2. Microscopic study [33]:
both SEM and transmission used to investigate the substance's shape and surface topography (the substance/nanosponge complex) can be examined using electron microscopy. The creation of the composition complexes is indicated by the different crystallisation conditions of final product and the raw ingredients as seen under the TME and SEM.

3. Solubility study [34]:
Inclusion complexes can be used to evaluate the drug's solubility and bioavailability. This approach is the most commonly employed to examine the inclusion complexes of nanosponges. Phase solubility plots provide information on the degree of completion. To estimate the pH of the medication, drug solubility studies are conducted, map out how the drug is soluble, and assess the variables influencing drug solubility.
4. **Zeta potential determination** \(^{[35]}\): 
The difference between two fluid layers' potentials is known as the zeta potential (the dispersion medium and the immobility layer) that are imprisoned with scattered particles. The primary indicator of a colloidal dispersion's stability is its zeta potential. An extra electrode can be added to a zeta sizer or particle size analyzer to measure the zeta potential. A colloidal dispersion is more stable the higher its zeta potential value.

5. **Loading efficiency** \(^{[36]}\): 
The effectiveness of nanosponges for loading pharmaceuticals can be evaluated through the quantitative estimation of such drugs using UV spectrophotometers or HPL-chromatography technology.

One can use the following equation to determine the loading efficiency (%) of nanosponges:

\[
\text{Loading efficiency} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical mass}} \times 100
\]

6. **Drug release kinetics** \(^{[37]}\): 
To better understand how drugs are released from nanosponges, release data was analysed using models for Higuchi, the first order, a zero-order, Korsmeyer-Peppas, Kopcha, Hixon Crowell, and Makoid-Banakar. Utilising the software prism graph paper, the information may be studied. The computer programme determines the functions that are nonlinear parameters based on which experimental results and the non-linear function fit together most closely.

X. **Nanosponges Example**

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Drug</th>
<th>Nanosponges polymer</th>
<th>Activity / Indication</th>
<th>Study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antisense oligonucleotides</td>
<td>Poly L-lysine Sodium alginate</td>
<td>viral infection, cancer treatment, and pathological conditions</td>
<td>study on bioavailability</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>Tamoxifen</td>
<td>β-cyclodextrin</td>
<td>Mammary cancer</td>
<td>Cytotoxicity</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>Resveratrol</td>
<td>β-Cyclodextrin</td>
<td>Inflammatory conditions, Ex-vivo Study of Cytotoxicity and Drug Accumulation in Rabbit Buccal Mucosa</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Econazole nitrate</td>
<td>Polyvinyl alcohol Ethyl cellulose</td>
<td>Antifungal irritation research</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>Paclitaxel</td>
<td>β-Cyclodextrin</td>
<td>Cancer</td>
<td>Cytotoxicity, Bioavailability</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>Terbinafine hydrochloride</td>
<td>Polyvinyl alcohol</td>
<td>Antifungal Drug release study</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>Flurbiprofen</td>
<td>β-Cyclodextrin</td>
<td>Rheumatoid arthritis In- Vivo study, In- Vitro study</td>
<td></td>
<td>44</td>
</tr>
</tbody>
</table>

XI. **Marketed Preparation of Nanosponges** \(^{[45,46]}\):

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Drug</th>
<th>Marketed name</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Iodine</td>
<td>Mena-gargle</td>
<td>Topical</td>
</tr>
<tr>
<td>2</td>
<td>Piroxicam</td>
<td>Brexin</td>
<td>Oral</td>
</tr>
<tr>
<td>3</td>
<td>Tamoxifen</td>
<td>-</td>
<td>Oral</td>
</tr>
<tr>
<td>4</td>
<td>Dexamethasone</td>
<td>Glymesason</td>
<td>Dermal</td>
</tr>
<tr>
<td>5</td>
<td>Alprostadil</td>
<td>Prostavasin</td>
<td>1.V</td>
</tr>
</tbody>
</table>

XII. **Example of Nanosponges for the treatment of diabetes mellitus**: 

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Drug</th>
<th>Polymer</th>
<th>BCS Class</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug Name</td>
<td>Polymer/Ingredient</td>
<td>BCS Class</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>--------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1</td>
<td>Netaginide</td>
<td>Ethyl cellulose Polyvinyl alcohol</td>
<td>BCS class - 2</td>
<td>They increase netaginide's solubility in water, cut down on dosage requirements, and boost patient compliance.</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>Gliclazide</td>
<td>Polyvinyl alcohol Triethyl citrate</td>
<td>BCS class - 2</td>
<td>The use of gliclazide nanosponges improves the drug's solubility and dissolving rate.</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>Glibenclamide</td>
<td>Ethyl cellulose</td>
<td>BCS class - 2</td>
<td>a drug's release from nanosponges decreased with increasing polymer concentration.</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>Tolbutamide</td>
<td>β-Cyclodextrin</td>
<td>BCS class - 2</td>
<td>Nanosponges increases solubility and show continuous drug release.</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>α - Magnostin</td>
<td>Polymethylmethacrylate</td>
<td></td>
<td>MGN-nanosponges they are effective in the treatment of diabetes because they extend the antidiabetic reaction in plasma.</td>
<td>51</td>
</tr>
</tbody>
</table>

XIII. Conclusion:
The delivery of drugs by nanosponges is a unique method. They can incorporate either hydrophobic or a lipophilic medications. They can administer medications to the target area in a regulated and reliable technique via topical, oral, or parenteral routes. the nanosponges enhance the solubility of poorly soluble medicines, particularly those classified as BCS II medications. The advantage of this system is they offer specific site targeting, reduce the side effect, improve stability, better patient compliances and improve formulation flexibility.

REFERENCES:
17. Tarun Kumar Satpathy * 1, Neelesh Chaubey 1, B. Usha Sri 2 and Venkata R. Naidu 3 College of Pharmacy 1, Sri Satya Sai University of Technology and Medical Sciences, Sehore - 466001, Madhya Pradesh, India NANOSPONGES – NOVEL EMERGING DRUG DELIVERY SYSTEM published 01 July 2020


43. Singh S, Monika K. Nanosponges as Emerging Carriers for Drug Delivery. Systematic Reviews in Pharmacy. 2022 Jan 1;13(1).


46. Dabhi FA, Shah VD, Pandya BD. A REVIEW ON NANOSPONGES: AN ASCENDANCE OF POTENTIAL NANOCARRIER FOR EMERGING DRUG DELIVERY.


