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REVIEW ON NANOSPONGES:A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Targeted drug delivery systems are a promising method for delivering active moieties to specified locations. However, successful molecular targeting necessitates the use of a specific delivery method. Nanosponges have considerably enhanced medication delivery by overcoming issues such as toxicity, poor bioavailability, and erratic release. Nanosponges, which can hold both hydrophilic and hydrophobic medicines, occur in a variety of shapes and sizes and are constructed of a variety of polymers. They outperform alternative delivery systems due to their regulated release pattern and focused drug administration. The researchers created nanosponges with three-dimensional porous architectures, a restricted size distribution, and great entrapment efficiency. These tiny sponges may circulate throughout the body and adhere to specific places, allowing medications to be released in a regulated and predictable manner. Crosslinking cyclodextrine with carbonyl or dicarboxylate can be used to create nanosponges (Crosslinkers).

KEYWORD: Nanosponges, Bioavialability, targeted delivery, Hydrophilic and Hydrophobic drugs.

INTRODUCTION

Obtaining the desired therapeutic outcomes has long been a goal of tailored medication delivery systems. First designed for topical administration, the Nanosponge drug delivery system has evolved to be supplied via oral and intravenous routes in the twenty-first century.[1] Nanosponges are small mesh-like structures that have a size of less than 1µm. Their porous structure and small size allow them to effectively bind with poorly soluble drugs, enhancing the bioavailability and solubility of these drugs. Nanosponges can

accommodate a broad range of drugs, including both hydrophilic and lipophilic ones, making it easy to load them into the nanosponges.[2] Nanosponge cavities are narrow and can be filled with a variety of substances, increasing the stability of poorly water-soluble drugs or molecules.[3] Nanosponges are three-dimensional scaffolds or networks of degradable polyester. To make the nanosponges, these polyesters are combined with a crosslinker in a solution. The polyester used is usually biodegradable, which allows it to degrade gradually in the body. When the nanosponge scaffold inevitably degrades, the drug molecules it has loaded are released in a regulated manner.[4]

Advantages of Nanosponges

1. Enhancing the aqueous solubility of lipophilic drugs is a key goal.
2. To protect the molecules and to develop drug delivery systems for various administration routes.
3. They react with water and serve as a fluid conveyance to disguise disagreeable flavors.
4. The chemical linkers allow the NSs to bind just at the target spot.
5. Nanosponges complexes are stable throughout a wide pH range (i.e. 1- 11) and at 130 °C.[5-7]
6. Decrease the number of times you take your medication.[8]

Disadvantages

1. Nanosponges are made up of just small molecules.[9]
2. Just the loading capabilities of medicinal compounds are considered.[9]
3. Dose dumping may occur at times.[10]

METHODS OF PREPARATIONS

Table 1: Shows the polymers and crosslinkers employed in the fabrication of nanosponges.

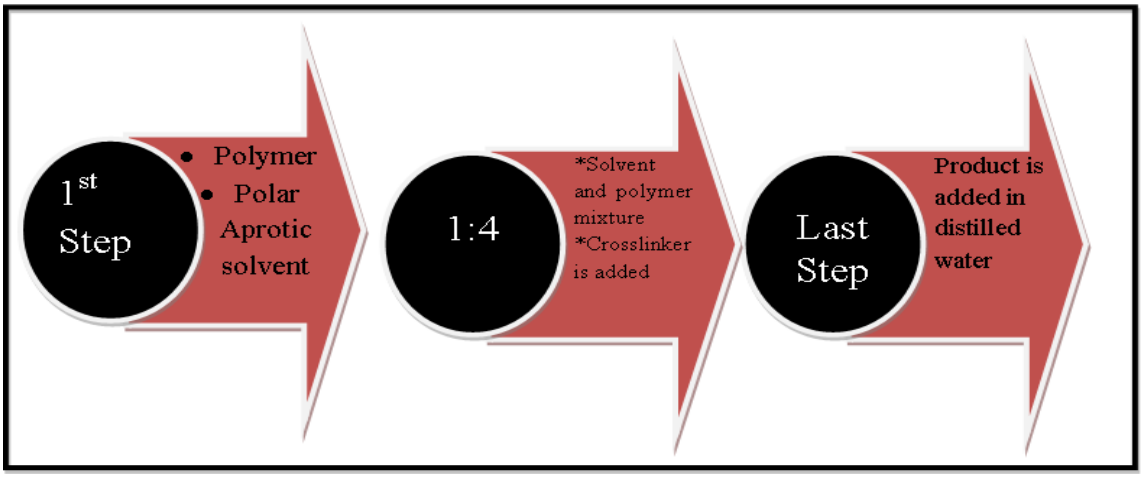
Polymers	Hyper cross linkage polystyrenes, Cyclodextrins (alkyl β-cyclodextrins, alkoxy carbonyl cyclodextrins, hydroxy propyl betadex), and some di block polymers like ethyl cellulose, polyvinyl chloride, etc.
Crosslinkers	Diphenyl carbonate, carbonyl di imidazole, pyromellitic di-anhydride, glutaraldehyde, carboxylic acid di anhydrides, di-isocyanates, and epichloridine.[11]
Solvents	Dichloromethane, dimethyl sulfoxide, ethanol, methanol, chloroform, deionized water.,
Copolymers	Ethyl cellulose, polyvinyl alcohol [12]

NANOSPONGES PREPARATION METHODS

In general, four approaches are used in the practical preparation of nanosponges.

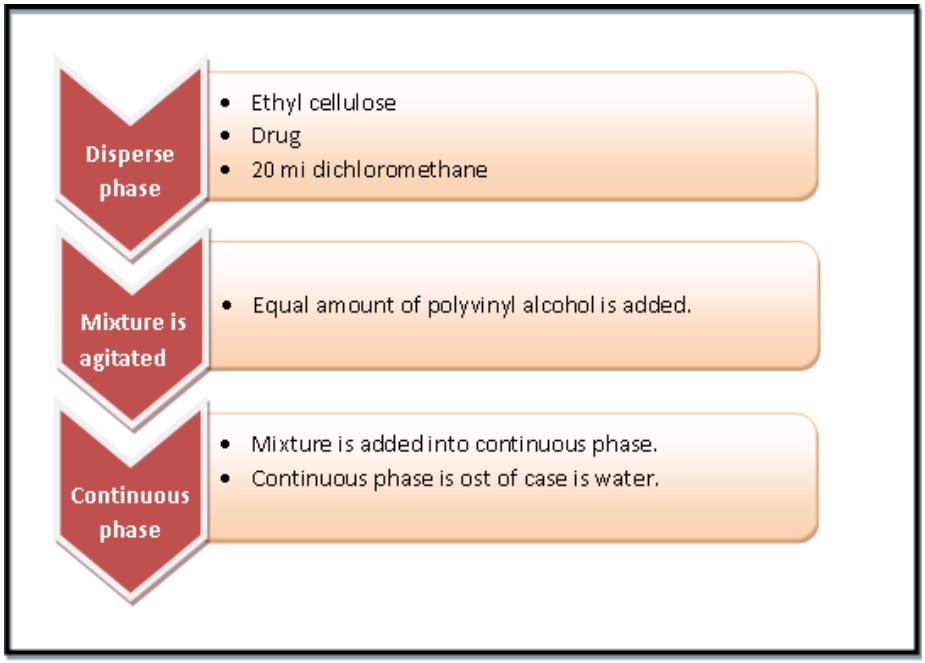
Solvent method

Nano sponges are created by combining polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) with the polymer. The mixture is then crosslinked at a 1:4 ratio with a crosslinker. The foregoing reaction should be carried out at a temperature of 10 C to reflux the temperature of the solvent for 1 to 48 hours. When the reaction is finished, the solution is cooled to room temperature and the result is added to bi-distilled water. The product is recovered by filtering it under vacuum and purifying it with ethanol via soxhlet extraction, followed by drying.[4]



Emulsion Solvent Diffusion Method

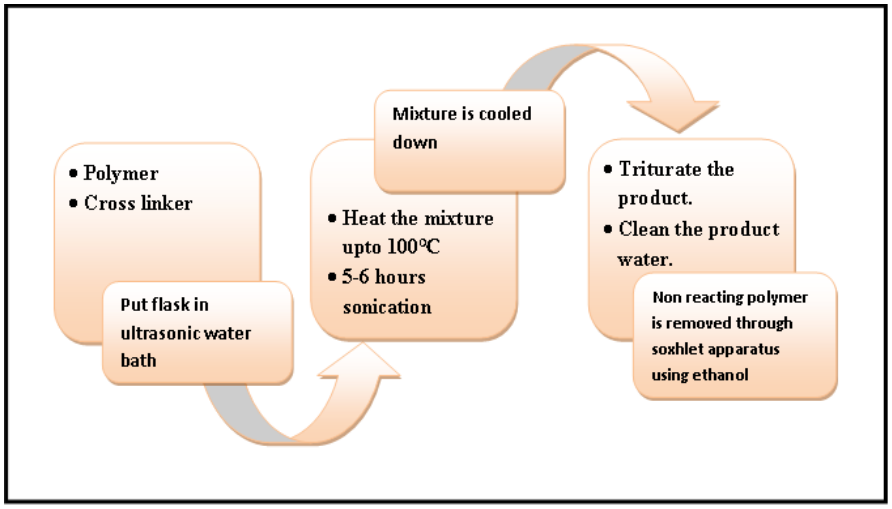
Two steps are used in this procedure. The first is the dispersed phase, while the second is the continuous phase. The dispersion phase contains ethyl cellulose and medication, followed by 20 mL dichloromethane. This combination is then added to 150 ml of continuous aqueous phase along with an equal amount of polyvinyl alcohol. After that, the mixture is magnetically stirred. The substance is then dried.[14]



Ultrasound-Assisted Synthesis

The third technique is ultrasound-assisted synthesis. The polymer and crosslinker are combined in a flask and reacted in an ultrasonic water bath without the addition of a solvent. The mixture is heated to 90°C before being sonicated for 5-6 hours.

At room temperature, the product is chilled. Water is used to remove excess polymer, and the Soxhlet apparatus is used to purify it.[15,16]



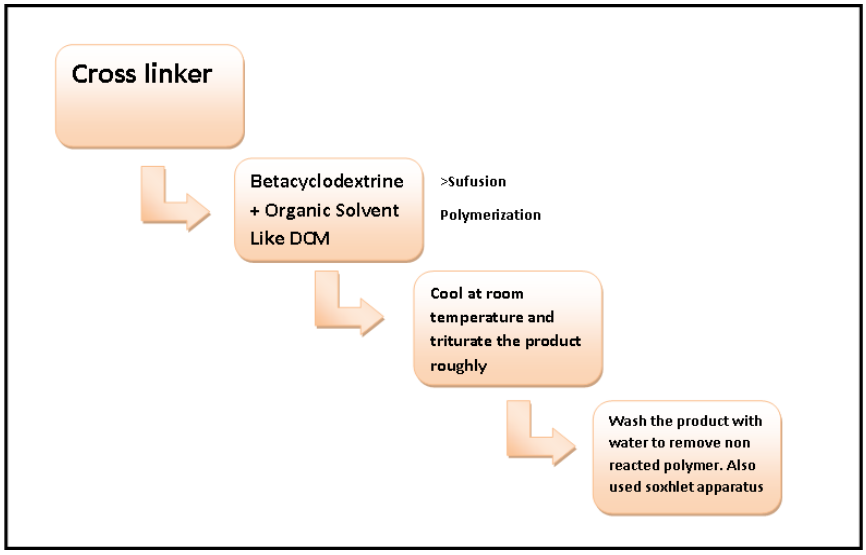
Nanosponge prepared from hyper crosslinked cyclodextrin

The melt method involves melting the crosslinker together with CDs, and homogenizing all the ingredients in a 250 ml flask heated at 100 °C. The reaction is then carried out for 5 hours

under magnetic stirring. After cooling, the obtained product is broken down and washed repeatedly with suitable solvents to eliminate any unreacted excipients and by products.

On the other hand, the solvent method does not require a melting step, and instead involves solubilizing the crosslinker in solvents like dimethylformamide or dimethylsulfoxide (DMF/DMSO). The polymer is typically mixed with a polar aprotic solvent and then added to an excess quantity of the crosslinker. The crosslinker/polymer molar ratio is varied to optimize the process, and the reaction is carried out at temperatures ranging from 10 °C to the solvent's reflux temperature, for 1 to 48 hours. Preferred crosslinkers for this reaction are diphenyl carbonate (DPC), dimethyl carbonate (DMC), or carbonyldiimidazole (CDI).

To obtain the product, the cooled solution is added to a large excess of bidistilled water, and the product is recovered by filtration under vacuum. The product is further purified by prolonged Soxhlet extraction.[17,18]



Loading of drug into nanosponges

To achieve a particle size of less than 500 nm, pre-treatment of nanosponges is necessary. This involves dissolving or suspending the nanosponges in water and vigorously sonication to prevent accumulation. After centrifugation, a colloidal fraction is produced, and the supernatant is collected and dried using a freeze dryer.

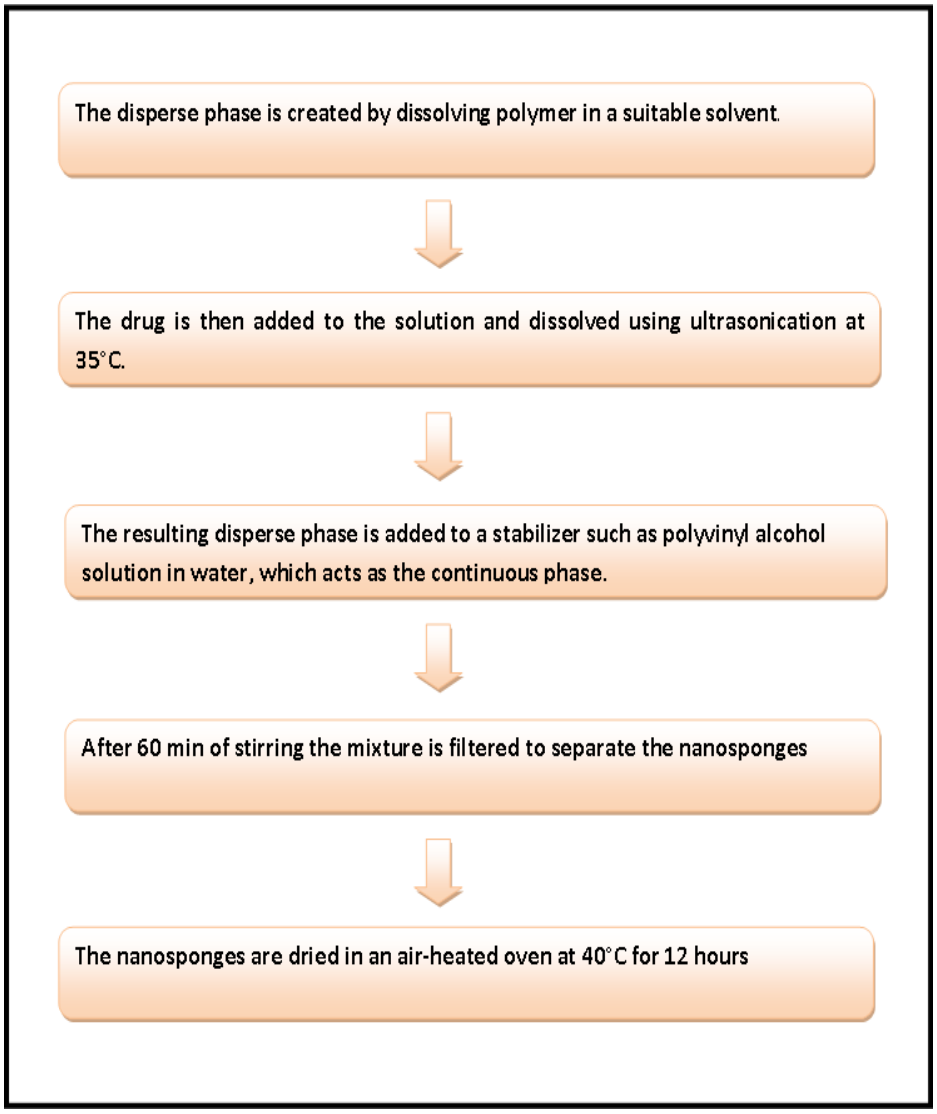
To complex the nanosponges with drugs, an aqueous suspension of nanosponges is prepared and an excess amount of drug is added. The mixture is continuously stirred for a specific

period of time to allow complexation to occur. Uncomplexed drug is then separated from the complexed drug using centrifugation.

The solid crystal structure of the nanosponges plays a critical role in drug complexation. The drug loading capacity of paracrystalline nanosponges is lower compared to crystalline nanosponges. In weakly crystalline nanosponges, drug loading occurs as a mechanical mixture.[19]

Quasi-emulsion solvent diffusion[20]

The Quasi-emulsion solvent diffusion process entails the emulsification of an organic drug solution that is miscible with water and contains stabilizers. When a transient O/W emulsion is shifted into water, the droplets harden quickly due to the diffusion of the organic solvent out of the droplets to the exterior phase.



NANOSPONGES CHARACTERIZATION

1. Particle size determination

Powders that flow freely and have a pleasing look characteristics will be feasible to achieve by adjusting particle size during polymerization. Laser light diffractometry or the Malvern Zeta sizer will be used to analyze the particle sizes of loaded and unloaded nanosponges. To investigate the effect of particle size on drug release, the cumulative percentage drug release from nanosponges of various particle sizes will be plotted versus time. Particles bigger than 30 m in size can give a gritty feeling, hence particles between 10 and 25 m in size are suggested for use in final topical formulations.[21,22]

2. The polydispersity index (PDI)

Dynamic light scattering instruments are used to calculate the polydispersity index. PDI is a width and variation with particle size distribution index. They have a lower PDI value in monodisperse samples, while a higher PDI value implies a wider particle size distribution and the polydisperse character of the sample. The PDI is calculated using the equation below.

PDI=d/davg where d=distribution width the polydispersity index range is shown in the table below:

Index of polydispersity	Dispersion type
0-0.05	Monodisperse standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Mid-range polydispersity
> 0.7	Very polydisperse

3. Porosity

It provides an estimate of the nanocavities produced in nanosponges. Helium pycnometers are employed because helium gas has the potential to penetrate Through inter and intra molecule channels. The extent of helium displacement can be used to calculate the true volume.[23]

$$\% \ Porosity = \frac{Bulk\ volume - True volume}{Bulk\ volume} \times 100$$

4. Loading efficiency[4]

The loading efficiency of a nanosponge particle can be measured by estimating the amount of drug that has been loaded into the nanosponge using a UV spectrophotometer and a high-

performance liquid chromatography technique for the nanosponges. The loading efficiency of nanosponges can be determined using the equation below.

$$\mathbf{LE} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \text{ X } 100$$

5. Determination of production yield

Production yeild (PY) may be calculated by dividing the beginning weight of raw materials by the end weight of nanosponges.[24]

$$\textbf{Production Yield} = \frac{\textbf{Practical mass of nanosponges}}{\textbf{Theoretical mass}} \times 100$$

6. Drug entrapment efficiency[8]

For drug entrapment efficiency, centrifugation at 1300 rpm for 20 minutes is used. The supernatant layer was collected and diluted with appropriate solvent after centrifugation.

% DEE = weight of original drug added in formulation-weight of free into formulation / weight of initial drug added in formulation 100

7. Zeta potential determination[4]

The difference in potential between two layers of fluid (dispersion medium and immobile layer) locked up with dispersed particles is termed as zeta potential. The zeta potential is a major critical indication of colloidal dispersion stability. The zeta potential can be determined by attaching an extra electrode to particle size equipment or a zeta seizer. The higher the value of a colloidal dispersion's zeta potential, the more stable it is.

8. Microscopic studies

SEM and transmission electron microscopy are used to investigate the morphology and surface topography.

9. X-ray diffractometry

Inclusion complexation in solids is detected using X-ray diffractometry.

10. Infrared spectroscopy

The interaction of nanosponges and drugs in solid form Infrared spectroscopy can be used to determine this. Nanosponge Bands can shift slightly during complicated formation. a few visitors molecules linked to complexes that are less than 25%,The spectrum of drugs can

easily obscure the spectrum of nanosponges. The approach is ineffective for determining the inclusion complex out performs the other approaches[26]

11. Thin layer chromatography

The Rf value of a medication candidate is used in TLC evaluation. evaporate, allowing the nanosponges to be identified drug. Nonetheless, it is a reversible procedure. As a result, only the medicine and TLC-plate nanosponges are formed.

12. Fourier Transform Infrared (FTIR) analysis

It is used to ascertain the potential link between the medicine and the polymer. As a reference, a carbon blank is employed and the sample is scanned between 400 and 4000 cm-1. The cleansing Helium is used to clean the detector before to analysis. Pellets of KBr are commonly utilized.[63] Spectra of 4000 to 650 cm-1 polymer, drug, drug polymer physical mixture, drug loaded It is mentioned that nanosponges and blank NS are used to observe any conceivable interaction. This approach also indicates the hydrophilic and hydrophobic properties. NS hydrophobic sites.[27]

13. Moisture analysis

Nanosponges do not absorb moisture. The preservation of during moisture absorption and desorption, the crystal structure changes dynamic vapour sorption investigations can confirm.[24]

14. In vitro release studies

Dissolution characteristics of Nanosponge can be examined by usage with a dissolving apparatus usp xxiii modified basket consisted of 5m stainless steel mesh. Speed of the rotation is 150 rpm.The dissolving medium is selected while considering solubility of actives to ensuresink conditions. Samples from the dissolution media can be evaluated using appropriate analytical method studied by use of the dissolving apparatus USP xxiii with a modified basket consisted of 5m stainless steel mesh. The rotational speed is 150 rpm while the dissolving media is chosen considering active solubility to ensuresing circumstances. Samples from the dissolution media can be evaluated using aadequate analytical procedure.[28]

APPLICATIONS OF NANOSPONGES

Nanosponges have a wide range of application in the pharmaceutical

Because of its biocompatibility and versatility, it is used in the field. In the pharmaceutical industry, nanosponges can be used as an excipient for the formulation of tablets, capsules, granules, pallets, suspensions, solid dispersions and topical dosage forms. Nanosponges are capable of accommodating.

Essentially, those drugs contain both lipophilic and hydrophilic drug molecules substances which belong to the biopharmaceutical classification system (BCS-class II) as well as the medication that is weakly water soluble.[18]

Nanosponges for drug delivery

Because of their small size, nanosponges can transport water-insoluble drugs a very small porous structure. To improve dissolving rate, solubility, and the permeability of drug nanosponges complexes is important. This according to reports, -cyclodextrine-based nanosponges are three or five it is up to ten times more effective at delivering the drug to the intended site. Nanosponges are generally solid in form and can be manufactured for a variety of applications. Oral, parental, topical, and inhalation dosing forms are available. For the formulation of a tablet or capsule for oral administration the nanosponges complexes are dissolved in an appropriate excipient such as lubricants, diluents, and anti-cracking agents are all included.

Nanosponges for cancer therapy

Delivery of anticancer drugs is a significant challenge in the pharmaceutical field due to their low solubility. According to a recent article, nanosponge complexes are three times more effective in reducing tumor growth than direct injection. These complexes are loaded with drugs and targeted using a peptide that binds tightly to a radiation-induced cell layer on the tumor receptor. Upon encountering the tumor cells, the nanosponges adhere to their surface and gradually release the drug molecules. This targeted delivery method offers a more effective therapeutic effect with minimal side effects at the same dosage.[21] To test the encapsulating capacity of β-cyclodextrin-based nanosponges, bovine serum albumin (BSA) was used as a model protein. Since BSA solutions are not stable and can be denatured during lyophilization, they are typically stored in a lyophilized form. However, maintaining the protein's native structure during and after processing is a major challenge in protein formulation and development. Cyclodextrin-based nanosponges can increase the stability of

proteins like BSA and have been used for enzyme immobilization, protein encapsulation, controlled delivery, and stabilization purposes.[22]

Fungal infections of the skin are a significant global health issue.[23] Topical therapy is a popular choice for treating cutaneous infections due to its ability to target drugs directly to the site of infection and reduce systemic side effects. Econazole nitrate (imidazole) is a common topical antifungal used to treat athlete's foot, ringworm, tinea pityriasis versicolor, jock itch, and vaginal thrush. However, the available products of econazole nitrate in the market, such as cream, ointment, lotion, and solution, do not provide significant adsorption when applied to the skin, requiring a high concentration of active agents for effective therapy. To address this issue, econazole nitrate nanosponges were developed using the emulsion solvent method and loaded into a hydrogel as a topical delivery system for sustained drug release.[24-25]

Itraconazole is another antifungal drug that falls under biopharmaceutical classification system class II and has limited dissolution rate and poor bioavailability. The aim of this study was to increase the solubility of itraconazole to overcome the bioavailability issue. By cross-linking β-cyclodextrin with carbonate bonds and loading it with itraconazole, the solubility of the drug can be increased. Nanosponges also have potential applications as absorbents in removing poisonous substances from the bloodstream. Rather than using traditional antidotes, nanosponges can be injected into the blood to soak up toxins by mimicking the appearance of red blood cells. These nanosponges attract toxins to attack them, effectively absorbing the harmful substances. The number of toxin molecules that each nanosponge can absorb varies depending on the toxin.[26]

Nanosponges as Solubility Enhancer

The ideal carrier system for low soluble compounds is nanosponge, which entraps the molecule into its core and improves the solubility and bioavailability of lipophilic medications. Nanosponges are commonly utilized to improve the solubility and dissolution rate of poorly soluble medicines while also giving a controlled release profile.[37]

Nanosponges in Drug Delivery

Because nanosponges have a nanoporous structure, they can transport medicines and/or molecules that are insoluble in water (BCS Class-II drugs). The usage of nanosponge can improve the dissolving rate, solubility, and stability of BCS class II medicines. Certain

medications with low solubility are successfully given by putting them into nanosponges. Because they are solid, they can be prepared as oral, parenteral, topical, or inhalation dose forms.[38]

Nanosponge in protein drug delivery

Nanosponges can be used to immobilize enzymes, encapsulate proteins, and then deliver and stabilize them in a controlled manner. Because bovineserumalubin (BSA) protein is unstable in solution, it is preserved in lyophilized form. Swellable cyclodextrin-based poly (amidoamino) nanosponges improve the stability of proteins such as BSA.[39]

Nanosponges as a Carrier for Delivery of Gases

The gases are important in medicine because they can be used for therapy and diagnostic purposes. Hypoxia (deficiency of appropriate oxygen supply) from inflammation to cancer is associated to different illnesses. The delivery oxygen in appropriate form and doses in clinical practice is Sometimes difficult. Cavalli et al. created Nanosponge formulations for topical oxygen delivery systems that have the ability to store and release oxygen slowly over time.[40]

Topical drug delivery system

Some of the medicinal compounds that can be easily synthesized as topical nanosponges are local anesthetics, antifungals, and antibiotics. In this regard, nanosponges can be generated using several methods such as emulsion solvent diffusion.[41]

In Antiviral Therapy

Nanosponges can be used for ocular, nasal, and pulmonary delivery. Several antiviral drugs are administered using nanosponge in the oral, parentral, and other drug delivery systems. Zidovudine, saquinavir, interferon-, acyclovir, nelfinavir, and other medications are formulated in nano delivery systems.[42]

Modulating Drug Release

The usual, commercially accessible medicines have main downside it is a frequent administration. Hence, a drug loaded into the nanosponge is retained and released slowly over time. According to Vyas et al., hydrophilic cyclodextrin nanosponges can change the drug release rate, increase drug absorption across biological barriers, and act as a potent drug carrier in immediate release formulations. Hydrophobic cyclodextrin nanosponges are used as

sustained release carriers for water soluble drugs, peptide and protein drugs, and anticancer drugs such as doxorubicin, and they also protect the drug during its passage through the stomach. This medication is released very slowly at pH 1.1, however it is released more quickly at pH 7.4.[43]

CONCLUSION

Nanosponges have been identified as a drug delivery system capable of encapsulating or accumulating hydrophilic and lipophilic drugs by forming a compound. They can deliver the medicine to a specific place in a controlled manner. Nanosponges can be used in topical preparations such as lotions, creams, and ointments, as well as in liquid or powder form. The benefit of this technology is that it targets the drug to a specific spot, which decreases side effects, improves stability, increases formulation flexibility, and improves patient compliance. Other applications for nanosponges include cosmetics, biomedicine, bioremediation, agrochemistry, and catalysis, among others.

REFERANCES

1. Yadav GV, Panchory HP. Nanosponges–a boon to the targeted drug delivery system. J Drug Delivery Ther., 2013; 3: 151-5.
2. Pandey P, Purohit D, Dureja H. Nanosponges -A Promising Novel Drug Delivery System. Recent Pat Nanotechnol, 2018; 12(3): 180-191. doi: 10.2174/1872210512666180925102842. PMID: 30251614
3. Bolmal UB, Manvi FV, Rajkumar K, Palla SS, Paladugu A, Reddy KR. Recent advances in nanosponges as drug delivery system. Int J Pharm Sci Nanotechnol, 2013; 6: 1934-44.
4. Bhowmik H, Venkatesh DN, Kuila A, Kumar KH. Nanosponges: A review. International journal of applied pharmaceutics, Jul 7, 2018: 1-5.
5. Thakre AR, Gholse YN, Kasliwal RH. Nanosponges: a novel approach of drug delivery system. J Med Pharm Allied Sci., 2016; 78: 103-11.
6. Rita L, Amit T, Chandrashekhar G. Current trends in β- cyclodextrin based drug delivery systems. Int J Res Ayurveda Pharm., 2011; 2: 1520-6.
7. Ahmed RZ, Patil G, Zaheer Z. Nanosponges–a completely new nano-horizon: pharmaceutical applications and recent advances. Drug Dev Ind Pharm., 2013; 39: 1263-72.
8. Balwe MB. Nanosponge a novel drug delivery system. Research Journal of Pharmaceutical Dosage Forms and Technology, 2020; 12(4): 261-6.

9. Selvamuthukumar, Subramanian et al. Nanosponges: A Novel Class of Drug Delivery System– Review. J Pharm Pharma Sci., 2012; 15(1): 103–111.
10. Singh D, Soni GC, Prajapati SK. Recent advances in nanosponges as drug delivery system: a review. Eur J Pharm Med Res., 2016; 3: 364-71.
11. Usman F, Shah HS, Zaib S, Manee S, Mudassir J, Khan A, Batiha GE, Abualnaja KM, Alhashmialameer D, Khan I. Fabrication and biological assessment of antidiabetic α-Mangostin loaded nanosponges: In vitro, in vivo, and in silico studies. Molecules, Jan, 2021; 26(21): 6633.
12. Selvamuthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. Journal of Pharmacy & Pharmaceutical Sciences, 2012; 15(1): 103-111.
13. Krabicová I, Appleton SL, Tannous M, Hoti G, Caldera F, et al. History of Cyclodextrin Nanosponges. Polymers, 2020; 12(5): 1122.
14. Krabicová I, Appleton SL, Tannous M, Hoti G, Caldera F, et al. History of Cyclodextrin Nanosponges. Polymers, 2020; 12(5): 1122.
15. Tejashri G, Amrita B, Darshana J. Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta pharmaceutica, 2013; 63(3): 335-358.
16. Chilajwar SV, Pednekar PP, Jadhav KR, Gupta GJC, Kadam VJ. Cyclodextrin-based nanosponges: a propitious platform for enhancing drug delivery. Expert opinion on drug delivery, 2014; 11(1): 111-120.
17. Trotta F, Tumiatti V, Cavalli R, Roggero C, Mognetti R and Berta G,2009. "Cyclodextrin-based Nanosponges as a Vehicle for Antitumoral Drugs", WO/003656 A1.
18. Guo L, Gao G, Liu X and Liu F, "Preparation and characterization of TiO2 nanosponge", Mater. Chem. Phys., 2008; 111: 322–325. DOI: 10.1186/1556- 276X-6-551
19. Indira B, Bolisetti SS. Nanosponges: a new era in drug delivery. J Pharm Res., 2012; 5: 5293-6.
20. Embil K, Nacht S, The microsponge delivery system a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. J Microencapsule, 1996; 13: 575–88.
21. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, Vallero R. 2007 Ultrasound-assisted synthesis of Cyclodextrin-based nanosponges. EP 1 786 841 B1.
22. Renuka S, Kamla P. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation Pharm Dev Technol, 2011; 16(4): 367-376.

23. Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: a critical review. Carbohydrate Polymers, 2017; 173: 37-49.
24. Rajeswari C, Alka A, Javed A, Khar R K. Cyclodextrins in drug delivery: an update review. AAPS pharmSci Tech, 2005; 6(2): E329-E357.
25. Prathima Srinivas et. al, Formulation and Evaluation of Isoniazid loaded nanosponges, Pharmaceutical Nanotechnology, 2015; 3: 68-76.
26. Farooq SA, Saini V. Application of novel drug delivery system in the pharmacotherapy of hyperlipidemia. J Chem Pharm Sci., 2013; 6: 138-46.
27. Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: a critical review. Carbohydrate Polymers, 2017; 173: 37-49.
28. Wester R., Patel R., Natch S., Leyden J., Melendres J., and Maibach H, "Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy, J. Am. Acad. Derm, 1991; 24: 720-726.
29. Trotta F, Dianzani C, Caldera F, Mognetti B, Cavalli R. The application of nanosponges to cancer drug delivery. Expert Opinion Drug Delivery, 2014; 11: 931-41.
30. Naga SJ, Nissankararao S, Bhimavarapu R, Sravanthi S, Vinusha K. Nanosponges: a versatile drug delivery system. Int J Pharm Life Sci., 2013; 4: 2920-5.
31. Güngör S, Erdal MS, Aksu B. New formulation strategies in topical antifungal therapy. J Cosmet Dermatol Sci., 2013; 3: 56.
32. Trotta F. Cyclodextrin nanosponges and their applications. Cyclodextrins in pharmaceutics, cosmetics, and biomedicine. Current and Future Industrial Applications, 2011; 323-42.
33. Kaur G, Aggarwal G, Harikumar SL. Nanosponge: New colloidal drug delivery system for topical delivery. Indo Global J Pharm Sci., 2015; 5: 53-7.
34. Renu Kadian. Nanoparticles: a promising drug delivery approach. Asian J Pharm Clin Res., 2018; 11: 30-5.
35. Che-Ming J Hu, Ronnie H Fang, Jonathan Copp, Brian T Luk, Liangfang Zhang. A biomimetic nanosponge that absorbs poreforming toxins. Nat Nanotechnol, 2013; 8: 336–40.
36. Tiwari H et al, A Review on Nanosponges, World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3: 219-233.
37. Swaminathan S et al, Invitro release modulation and conformational stabilization of a model protein using swellablepolyamidoamine nanosponges of cyclodextrin. J InclPhemonMacrocycl Chem., 2010. DOI10.1007/s10847-010-9765-9.

38. Schlichten mayer M and Hirscher M, *J Mater Chem.*, **2012;** 22: 10134-10143.
39. Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosponge formulations as oxygen delivery systems. Int J Pharm., 2010; 402: 254-257.
40. Ansari KA, Torne SJ, Vavia PR, Trotta F, Cavalli R. Paclitaxel loaded nanosponges: in-vitro characterization and cytotoxicity study on MCF-7 cell line culture. Curr Drug Deliv., 2011; 8(2): 194-202.
41. A. Martin, J et al, In: Physical Pharmacy–Physical Chemical Principles in Pharmaceutical Sciences, 1991; 3: 527.
42. Vyas A, Saraf S. Cyclodextrin based novel drug delivery systems. J Incl Phenom Macrocycl Chem., 2008; 62: 23-42.