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Nanosponge: An Overview

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A B S T R A C T

The "Pharmaceutical Nanotechnology" subfield of pharmaceutical sciences, which is now in its infancy, offers new tools, prospects, and horizons with potential applications in the field of therapy and diagnostics of disease. Pharmaceutical nanotechnology consists of items that are nanosized and may be altered in many ways to enhance their properties. According to the administration method, the nanoporous particles are NSs that may entangle a wide variety of materials before being absorbed into a suitable formulation. They delay the drug's release in a regulated manner, stop the drug's protein from degrading, and disperse the drug where it is needed. They can move about the body, connect to the skin, and release the medicine at the intended target spot in a regulated and predictable way. They have excellent aqueous solubility, making them a carrier for medications with poor water solubility. When compared to other nanocarriers, they have greater drug loading capabilities. They are therefore appropriate for addressing issues with active ingredient stability, solubility, and delayed release. The main benefit of nanosponges of weakly water soluble medicines. They can function as biocatalysts in the administration of enzymes, proteins, vaccines, and antibodies and can administer medications via a variety of routes, including oral, topical, parental, etc.

Keywords: Nanosponges, Cyclodextrin, Cross linking agents, targeted delivery, etc.

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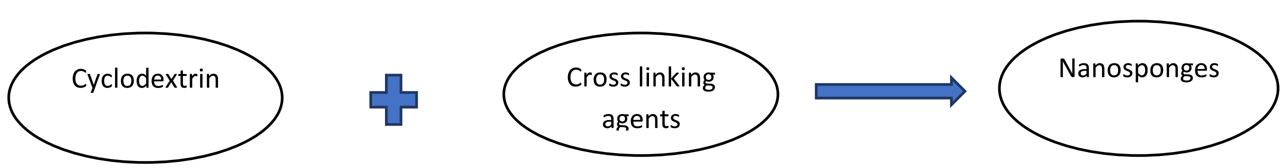
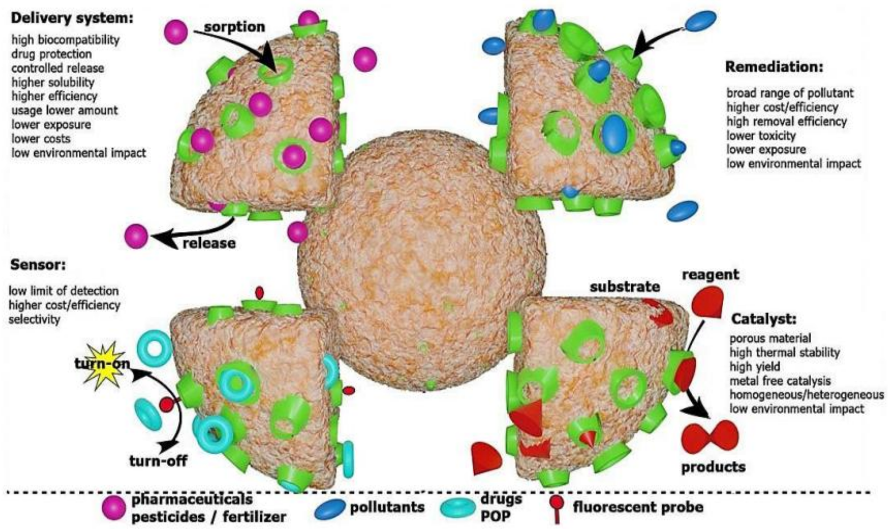
INTRODUCTION

In the past, nanotechnology has created a variety of formulations, including nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, and nano-erythosomes, among others. The manufacture and nanoscale manipulation of materials to create products with distinctive properties is the definition of nanotechnology. Recently, there has been a lot of interest in nanomaterials. In 1959, Richard P. Feynman, a researcher at Cal Tech, predicted the existence of nanomaterials. He expressed the notion that scaling down to the nanoscale and starting at the very bottom was the key to future gains in nanotechnology, saying "There is plenty of room at the bottom. Materials with at least one dimension between 1 and 100 nm are known as nanomaterials. NSs are many, interconnected spongy spheres. These NSs may bind insoluble medications inside the matrix and boost their bioavailability, and they have a significant potential to entrap a range of active compounds [2,3].By combining cyclodextrin with best-fit crosslinkers, an NSs may be produced [4]. They can contain a wide range of molecules by producing inclusion and non-inclusion complexes [5, 6]They can transport both hydrophilic and lipophilic medicinal substances because of their outside hydrophilic branching and inside lipophilic chambers.. By initiating a reaction of cyclodextrin with a suitable crosslinker and resulting in hyper crosslinked cyclodextrin, a special nano-sized substance called as NSs may be formed [7,8]. They have the power to solidify liquid substances and mask off-putting tastes .The crosslinkers in the NSs enable them to unite where they are needed. They have strong personalities and may be used on many different routes [8].



Formation of Nanosponges

Polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, NSs, carbon nanotubes, micellar systems, and dendrimers are a few types of nanoparticles that have been identified(9). The sponge builds a three-dimensional network or scaffold. The backbone is made of long lengths of polyester. It is dissolved in a cross-linker-containing solution to produce the polymer. Spherically shaped particles with cavities that might contain therapeutic compounds are the end product. The polyester dissolves over time in the body since it is biodegradable. It disintegrates with a predictable pharmacological payload. It is feasible to make nanosponges of a certain size and shape that release drugs gradually by altering the cross-linker to polymer ratios. The main issue with nanosponges is that they can only hold very small molecules [2].



Characteristics features:[10, 11]

1. Nanosponges offer a range of sizes (1 m or less) with a polarity-adjustable chamber.
2. The crosslinker to polymer ratio may be changed to produce nanosponges of a certain size.
3. They might take on crystalline or paracrystalline forms depending on the processing conditions. The complexation of drugs with nanosponges depends on their crystal structure.
4. 4.The degree of crystallisation affects the drug loading capacity.
5. A variety of drug loading capacities may be shown using paracrystalline nanosponges.
6. They contain non-toxic, porous particles that are stable up to 300 °C and insoluble in the majority of organic solvents.
7. They can resist pH values ranging from 1 to 11.
8. They produce a transparent, opalescent suspension in water.
9. Simple thermal desorption, solvent extraction, microwave, and ultrasonic technologies can be used to produce them.
10. Chemical linkers help nanosponges adhere to the target area more successfully.
11. By combining with different medications, nanosponges can produce complexes that include inclusions and do not.
12. By including magnetic particles into the reaction mixture, magnetic properties may also be imparted to nanosponges.
13. Nanosponges are porous particles that are highly soluble in water and are most frequently employed to encapsulate drugs that are not easily soluble in water.
14. These Nanosponges can carry drugs that are both lipophilic and hydrophilic.
15. 15.They guard the drug against physicochemical deterioration.
16. They can remove organic impurities from water.

Advantage:[11,12]

1. Drug delivery to a specified target spot.
2. These compositions maintain their stability between pH 1 and 11.
3. These compositions are temperature-stable.
4. Because bacteria cannot pass through their 0.25 mm average pore size, they are self-sterilizing.
5. This method offers higher stability, increased elegance, decreased side effects, and increased formulation flexibility through the trapping of components.
6. Extended release action can last up to 12 hours.
7. Less negative side effects as a result of medication interaction with healthy tissue being reduced .
8. Hydrophobic drug can be contained within nanosponge particles after being coupled with an adjuvant reagent since they are soluble in water.
9. An anticipated release.
10. Biodegradable.

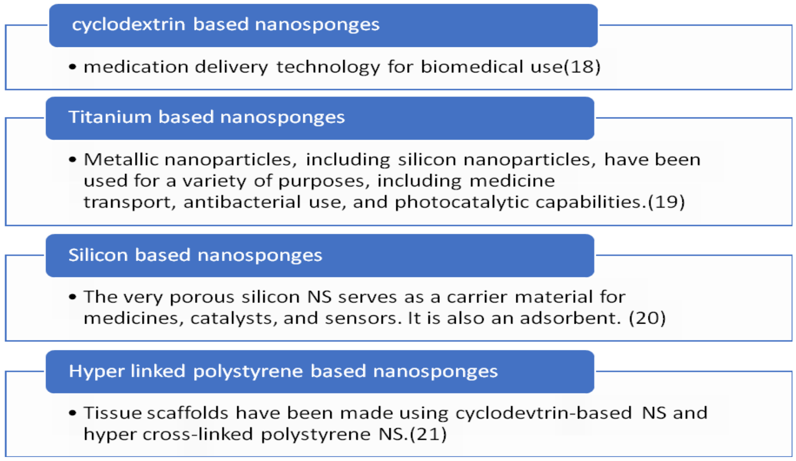
Disadvantages:

1. Only tiny molecules may be included by nanosponges.
2. The crystalline or paracrystalline character of nanosponges is possible.
3. The primary factor affecting the loading capacity of nanosponges is the degree of crystallisation.
4. Different loading capacities may be demonstrated by paracrystalline nanosponges.

Marketed preparation of nanosponges:[13]

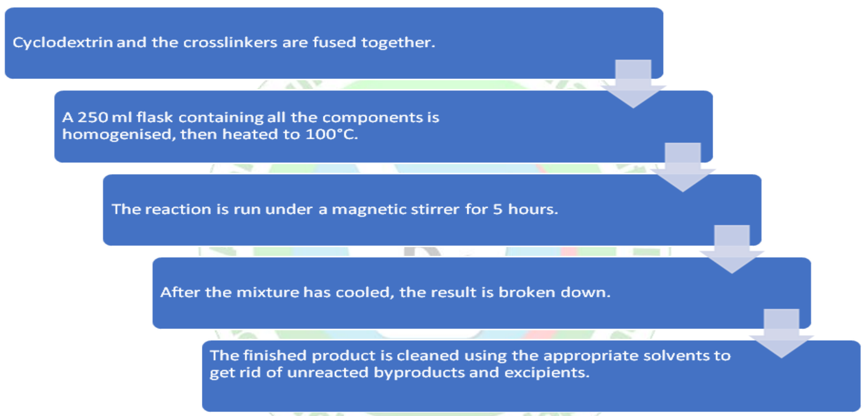
Drug	Administration route	Marketed formulation
Dexamethasone	I.V.	Dexamethasone sodium phosphate
Alprostadil	I.V.	Alprostadil injection IP
Piroxicam	Oral	Piroxicam – 20
Tamoxifen	Oral	Tamodex 20

Types of nanosponges and their applications:[14-17]

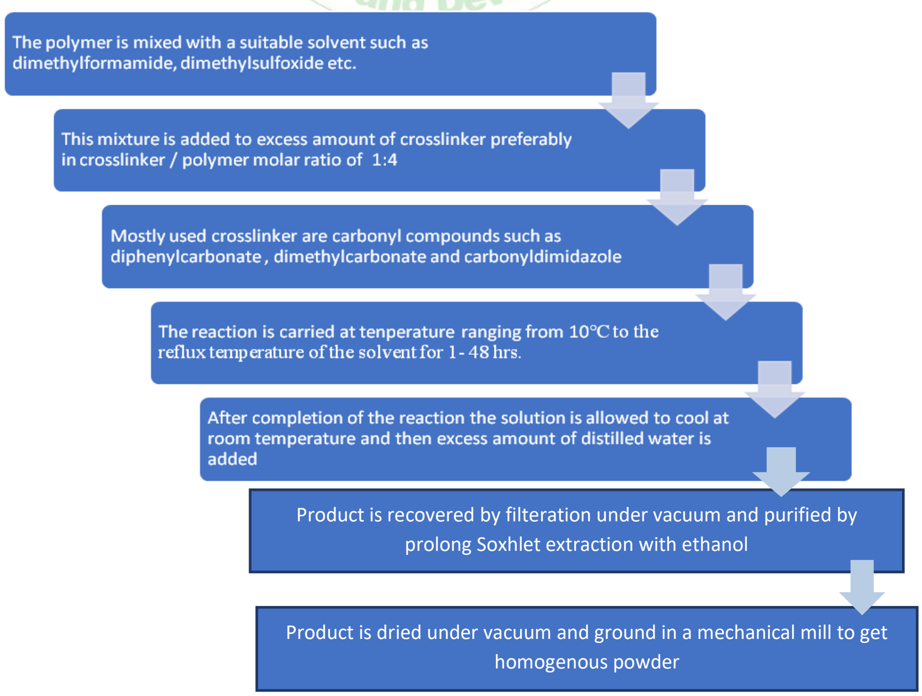


METHOD OF PREPARATION:

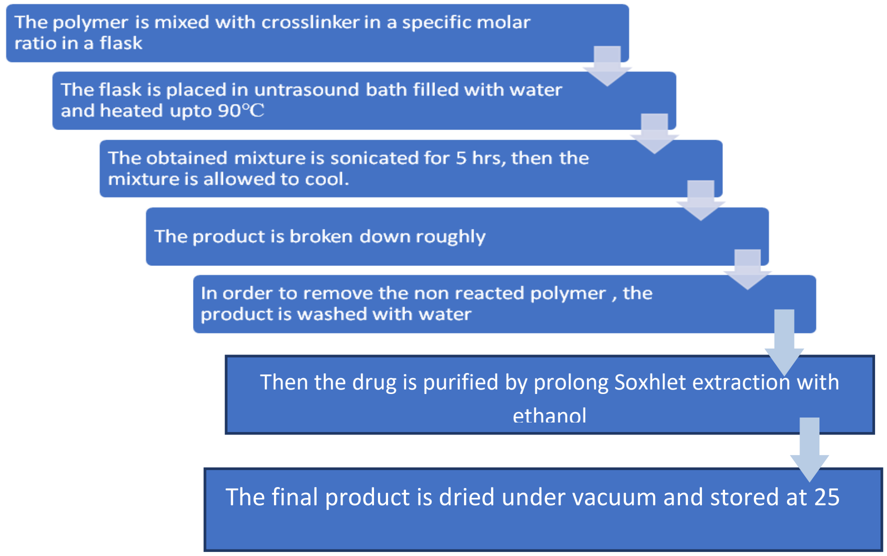
1. Melt method: [22]



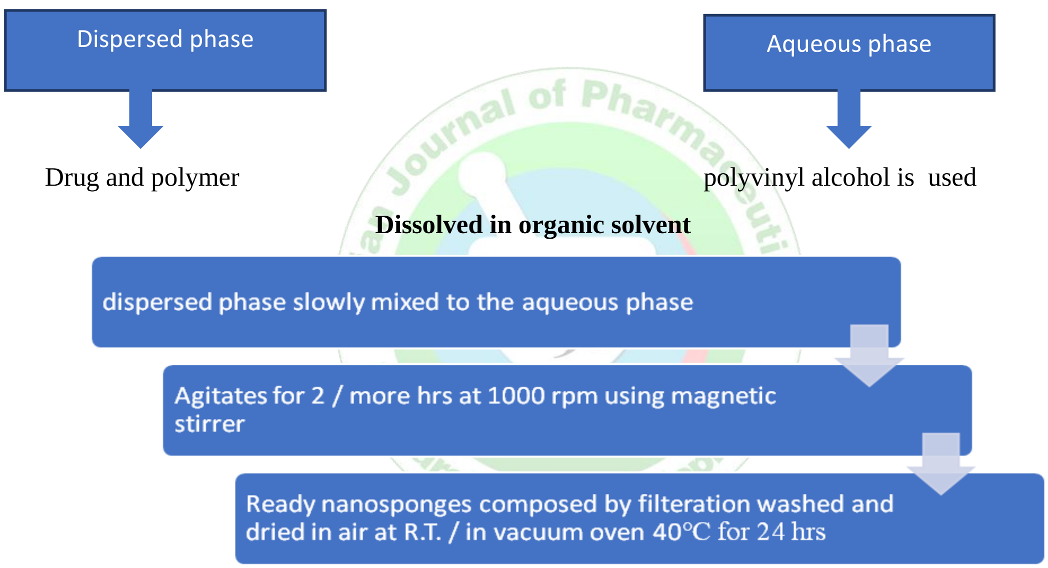
2. Solvent method:[23,24]



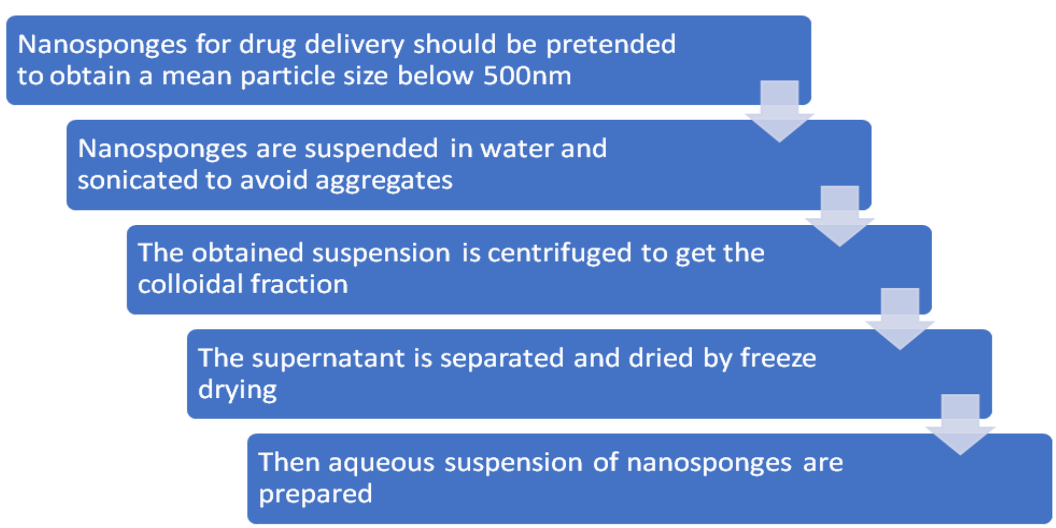
3) Ultrasound assistated synthesis:[24,25]

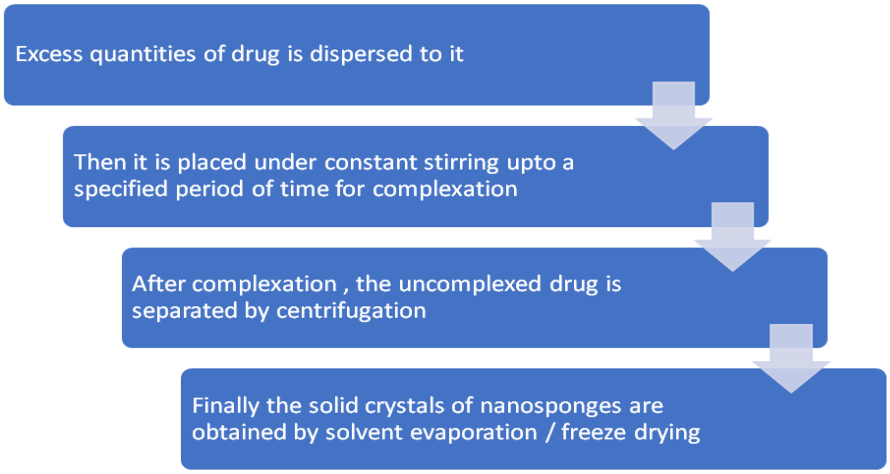


4) Emulsion solvent diffusion method:[26,27,28]



5) Loading drug into nanosponges:[17,23,24]





Characterization and evaluation of nanosponges:

1. Solubility studies:[29]

The phase solubility technique developed by Higuchi and Connors, which investigates the impact of a nanosponge on drug solubility, is the most used method for studying inclusion complexation. Diagrams of phase solubility show the level of complexation.

2. Loading efficiency and production yield:[30]

The following equation can be used to determine the nanosponges' loading efficiency (%).

$$\text{Loading efficiency} = \frac{\text{Actual drug content in NS}}{\text{Theoretical drug content}} \times 100$$

After accurately establishing the beginning weight of the raw materials and the end weight of the produced nanosponge, the production yield of the nanosponges may be estimated using the equation below.

$$\text{Production yield: } \frac{\text{Practical mass of NS}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

3. Porosity :

The sequence of nanochannels and nanocavities are confirmed by this investigation. Since helium gas has the ability to penetrate both the inter- and intra-specific channels of substances, helium pycnometers are used to check the porosity of NSs. Equation [31,32] specifies the percent porosity.

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

4. Microscopy studies:

Studies of the microscopic features of the drug, nanosponges, and the finished product (drug/nanosponge complex) can be conducted using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Under an electron microscope, the contrast between the raw materials' and the finished product's crystallisation states reveals the presence of inclusion complexes [33].

5. Particle size and polydispersity index:

The Malvern Zeta sizer, laser light diffractometry, or 90 Plus particle sizer equipped with MAS OPTION particle sizing software can all be used to estimate the particle size. This allows for the calculation of the polydispersity index and mean diameter [34].

6. Zeta potential : (35,36,37)

Zeta sizer is used to calculate the surface charge or zeta potential of prepared NSs [35,36]. The NSs emulsion is added to the electrophoretic cell after being diluted with water [37].

7. Drug release kinetics :(37)

The kinetic behaviour of the NSs' in vitro drug release mechanisms is also examined in order to determine how it affects the release of NSs [58]. In order to examine the mechanism of drug release from NSs, models such as the zero-order, first-order, Higuchi, and Korsmeyer-Peppas are utilised.

8. Swelling and water uptake :

The swelling uptake of swellable polymers like polyamidomine NSs, water, and swelling uptake may be determined using the following formula [38].

$$\text{Percentage of swelling} = \frac{\text{Making of the cylinder at specified time point}}{\text{Initial marking before swelling}} \times 100$$

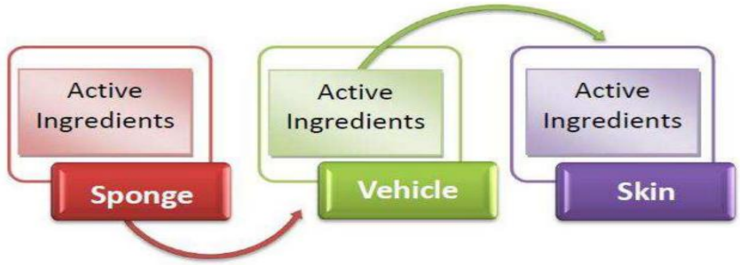
$$\text{Percentage of water uptake} = \frac{\text{Mass of hydrogel after 72 hrs}}{\text{Initial mass of polymer}} \times 100$$

9. In Vitro release studies:[39]

Using a multi-compartment rotating cell with a dialysis membrane (cut-off 12,000 Da), it is possible to analyse the drug release from the improved nanosponge formulation. The drug-loaded nanosponge complex in distilled water makes up the donor phase. The same medium is present in the receptor phase as well. After predetermined time intervals, the receptor phase is entirely removed, appropriately diluted with distilled water, and then examined using a UV spectrophotometer.

Mechanism of drug release :

The active is unrestricted in its ability to flow into and out of the open-structured sponge particles and into the vehicle until equilibrium is reached. In the case of topical distribution, the active that is already in the vehicle will be absorbed into the skin when the completed product is applied, depleting the vehicle, causing it to become unsaturated, and upsetting the balance. Once the vehicle is either dried or absorbed, the active will move from the sponge particle into the vehicle and from there to the skin (Figure 1). Even after that, the sponge particles that were left on the stratum corneum's surface would keep gradually releasing the active ingredient into the skin, offering a longer release period time (40)



Drug release mechanism in topical delivery

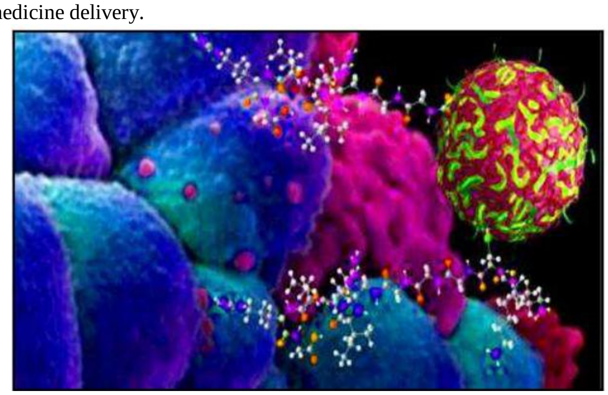
List of drug molecules encapsulated with nanosponges:

Category	Nanosponge vehicle	Drug
Anticancer	β–Cyclodextrine	Paclitaxel Camptothecin(41)
Breast cancer	β–Cyclodextrine	Tamoxifen(41)
Inflammation	β–Cyclodextrine	Resveratrol(41)
Brain tumour	Poly (valerolactoneallylvalerolactone) and poly (valerolactoneallylvalerolactone –oxepanedione)	Temozolamide(42)
Antifungal	Ethyl cellulose Polyvinyl alcohol β-Cyclodextrine	Econazole nitrate Itraconazole(42)
Cancer therapy	Sodium alginate	Antisense(43)
Brain tumour	β–Cyclodextrine	Dexamethasone(43)
Oligonucliotides	Poly L-lysine	Viral infection Pathologic disorder(43)

Applications:

1. Anti-cancer Therapy

Researchers at Vanderbilt University have created nanosponges that may be utilised as a delivery mechanism for anticancer medications to tumours, thereby slowing tumour development. They assert that compared to direct medication injection, the approach is three to five times more successful in slowing cancer development. The small nanosponges have a drug load inside of them and reveal a targeting peptide that binds to the tumor's radiation-induced cell surface receptors. The sponges are prompted to discharge their contents when they come into contact with cancer cells. Less adverse effects and more effective therapy at the same dose are two advantages of targeted medicine delivery. Researchers at Vanderbilt University have created nanosponges that may be utilised as a delivery mechanism for anticancer medications to tumours, thereby slowing tumour development. They assert that compared to direct medication injection, the approach is three to five times more successful in slowing cancer development. The small nanosponges have a drug load inside of them and reveal a targeting peptide that binds to the tumor's radiation-induced cell surface receptors. The sponges are prompted to discharge their contents when they come into contact with cancer cells. Less adverse effects and more effective therapy at the same dose are two advantages of targeted medicine delivery.



2. Topical Agents :

For the regulated and prolonged release of skin-retaining medications, NS in drug delivery technique is an important technology. Traditional dermatological and personal-care solutions often offer active ingredients in quite high concentrations, but they also have a relatively quick time to action. Instances of these include short-term overmedication followed by long-term undermedication. The skin-penetrating active components may result in rashes and other adverse effects. Contrary to conventional technology, the NS-based drug delivery system permits a consistent and constant rate of medication release, minimising discomfort while maintaining efficiency.An articulated product can have a wide variety of ingredients, including cream, liquid, gel, ointment, powder, and lotion (45)A topical antifungal medication called econazole nitrate is used to treat superficial candidiasis, skin and vesicular infections, and dermatophytosis. It comes in ointment, solution, cream, and lotion forms. Since econazole's adsorption is minimal, a large concentration of the active ingredients must be incorporated into the skin for successful therapy.The econazole nitrate NSs incorporate hydrogel as a local depot for continuous drug release and were made utilising the emulsion solvent diffusion method.(26, 40). For use in tropical climates, the produced hydrogel NSs were combined with the lipophilic and poor water solubility celecoxib. The produced formulations of NS-4 were shown to be non-irritating on mouse skin during pharmacokinetic investigations. Therefore, the formulation may be used for topical drug release for the application of celecoxib [46] and can satisfy the standards for human exposure.

3. Nanosponges for Solubility Enhancement

The efficacy of drug formulations is significantly impacted by the solubility in water, which is a critical component required for the formulation of pharmaceuticals. By using NS as a carrier system, which helps to entrap the drug into a specific pore and increases the bioavailability and solubility of drug formulations in regulated release profiles, this may be corrected. In comparison to conventional cefpodoxime proxetil, the medication cefpodoxime proxetil NS demonstrated enhanced dissolving rate. Additionally, cholesterol was linked through disulfide linkages to the arm-termini, and these cholesterol-terminated arms may combine with beta-cyclodextrin (beta-CD) to produce a star architectural NS [47,48]. The addition of the substance -cyclodextrin NS has drawn more attention since it improves the bioavailability and solubility of medications. By speeding up drug dissolution and enhancing drug solubility, NSs based on cyclodextrin can enhance the permeability of hydrophobic medicines. In order to deliver NS into the membrane without disturbing the lipid layers of the biological barrier, this makes the NS accessible on the surface of the barrier. Additionally, because it aids in improving the bioavailability and solubility of medications like naproxen and ketoprofen, -cyclodextrin NSs have drawn more attention [49]. Resveratrol's solubility was also improved by being entrapped in cyclodextrin-based NS [50] Solvent evaporation was used to load the medication into the produced NS, and the findings demonstrated a threefold improvement in dissolution using ternary complexes. In the rat trial, utilising this NS-loaded rilpivirine, the oral bioavailability improved twofold [51]. Ferulic acid (FA), a weakly soluble anticancer drug with antioxidant capabilities, was made more soluble utilising cyclodextrin-based NS. Using diphenyl carbonate as a cross-linker, the beta-cyclodextrin NSs were employed to encapsulate FA at a ratio of 1:4 (FA:NS). The solubility of FA was increased by NS encapsulation up to 15-fold [52]. A non-steroidal anti-inflammatory medicine (NSAID) called meloxicam can lower the hormone levels that cause pain. Due to its low solubility, which affected the action, cyclodextrin-based NSs were created in a research to encapsulate meloxicam. The NS encapsulated medication increased the analgesic and anti-infammatory properties, which were both investigated using the carrageenan-induced rat paw edoema model and acetic acid-induced writhing, respectively [53].

5. Other Applications

Pawar et al. and Pandey et al. [54,55] provide descriptions of the additional uses of NSs. The mesh-like architectures of NSs constructed of solid nanoparticles that contain holes allow them to encapsulate a variety of compounds, including proteins and peptides, genetic materials, antineoplastic drugs, and volatile oils, have been described in detail by Pawar et al. These NSs may now be employed for a variety of applications, including protein delivery, explosive detection, water filtration, chemical sensors, and agriculture. Pawar et al. [55] reviewed the NS patents from 2006 to 2018 and the several cyclodextrin-based NS uses in cancer treatment, vaccine delivery, water purification, and fre engineering. According to Pandey et al., NSs have the ability to transport both hydrophilic and lipophilic medicines. Different qualities, benefits, patents, preparation techniques, and characterisation techniques were also covered [54]. Gamma-oryzanol, a ferulic acid ester combination and natural antioxidant, is typically used to stabilise food, medicinal raw materials, and even sunscreens in the cosmetics sector. NSs operate as a preventative agent against deterioration. . When a virus that infects the respiratory tract, such as the rhinovirus and influenza virus, is encountered, the nanocarriers can carry the antiviral medication to the lungs or nasal route. Zidovudine and saquinavir are two medications made with the help of NSs that were utilised as an antiviral agent to target the drug in the nasal and pulmonary tracts [56]. With sizes ranging from 40 to 100 nm, five distinct kinds of nanoparticles (NSs) containing five different quantities of -cyclodextrin and diphenyl carbonate were used to encapsulate the chemical quercetin. When compared to quercetin alone, the NS-loaded quercetin was shown to have enhanced solubility and antioxidant activity.

CONCLUSION:

Finally, it was determined that NSs are tiny mesh-like structures that may be used to treat a variety of disorders and that nanotechnology is 4-5 times more effective than the traditional technique in delivering pharmaceuticals. They can be used in several forms, including parenteral, aerosol, topical, tablets, and capsules, due to their small size. NSs easily penetrate the skin since they are colloidal bearers with nanoscale dimensions. They advise ingesting both lipophilic and hydrophilic medications, and discharging them at the target place in a regulated and predictable way. This nanotechnology improves the solubility of pharmaceuticals that are currently weakly soluble, in particular BCS Class II medications.

REFERENCES:

1. Bhatia S. Nanoparticles Types, Classification, Characterization, Fabrication Methods and Drug Delivery Applications. Natural Polymer Drug Delivery Systems, Springer International Publishing Switzerland, 2016.
2. Dhavala PB, Tenneti VS. An interesting nanosponges as a nanocarrier for novel drug delivery: A review. Int J Pharm Med Res 2017; 5:1-7.
3. Bezawada S, Charanjitha, Reddy VM, Naveena. Nanosponges: A concise review for emerging trends. Int J Pharm Res Biomed Anal 2014;3:1-6.
4. Chilajwar SV, Pednekar PP, Jadhav KR, Gupta GJ, Kadam VJ. Cyclodextrin-based nanosponges: A propitious platform for enhancing drug delivery. Expert Opin Drug Deliv 2014;11:111-20.
5. Jyoti P, Tulsi B, Popin K, Chetna B. An innovative advancement for targeted drug delivery: Nanosponges. Indo Glob J Pharm Sci 2016;6:59-64.
6. Swaminathan S, Darandale S, Vavia PR. Nanosponge-aided drug delivery: A closer look. Pharm Formul Qual 2012;14:12-5.
7. Szejtli J. Cyclodextrin Technology. Berlin: Springer Science and Business Media; 1988. p. 450.
8. Salisbury D. Nanosponge Drug Delivery System more Effective Than Direct Injection. Nashville: Vanderbilt University; 2010. Available from: http://www.news.vanderbilt.edu/2010/06/nanosponge-drugdelivery-system-more-effective-thandirect-injection-116839. [Last accessed on 2012 Dec 20].
9. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system – review. J Pharm Pharm Sci 2012;15:103-11.
10. Targe BM, Patil MP, Jahagirdar Baliram D. Nanosponges- An emerging Drug Delivery System. Int J of Insti Pharm and Life Sci. 2015; 5(6):160-173.
11. Patel EK, Oswal RJ. Nanosponge and Microsponges: A Novel Drug Delivery System. International Journal of Research in Pharmacy and Chemistry, 2012.
12. Subramanian S, Sinireddy A, Krishnamoorthy K, Rajappan M. A Novel Class of Drug Delivery System
13. Nanosponges ; a boon to the targeted drug delivery system from slideshare
14. Guo L, Gao G, Liu X, Liu F. Preparation and characterization of TiO2 nanosponge. Mater Chem Phys., 2008, 111; 322-325.
15. Farrell D, Limaye S, Subramanian S. Silicon Nanosponge Particles. U.S. Pat 0, 251, 561A1., 9 Nov 2006.
16. Dakankov V, Llyin M, Tsyurupa M, Timofeeva G, Dubronina L. From a dissolved polystyrenecoil to intramolecularly hyper-crosslinked nanosponges. Macromolecules., 1998, 29; 8398-8403.
17. Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D et al. Cyclodextrin based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm., 2010; 74:193-201
18. Bergal, A., Elmas, A., & Akyüz, G. (2019). A new type and efective approach for anti-cancer drug delivery application - A nano sponge. Nano Research & Applications, 5(3:1), 1–10. https://doi.org/10.36648/24719838.5.1.43
19. Navarro-Gázquez, P. J., Muñoz-Portero, M. J., Blasco-Tamarit, E., Sánchez-Tovar, R., Fernández-Domene, R. M., & García-Antón, J. Original approach to synthesize TiO2/ZnO hybrid nanosponges used as photoanodes for photoelectrochemical applications. Materials, 2021; 14(21):6441.
20. Farrell D., Limaye S. Y., Subramanian S. (2009). U.S. Patent No. 7,569,202. Washington, DC: U.S. Patent and Trademark Office Davankov, V. A., Ilyin, M. M., Tsyurupa, M. P., Timofeeva, G. I., & Dubrovina, L. V. (1996). From a dissolved polystyrene coil to an intramolecularly-hyper-cross-linked "nano sponge." Macromolecules, 29(26), 8398–8403. https://doi.org/10.1021/ma951 673i
21. Tejashri G, Amrita B, Darshana J. Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta Pharm., 2013; 63:335-358
22. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, Vallero R. inventors; Sea Marconi Technologies Sas, assignee. Ultrasound assisted synthesis of cyclodextrin based nanosponges. EP 1786 841 B1. 2007.
23. Lala R, Thorat A, Gargote C. Current trends in β-cyclodextrin based drug delivery systems. Int J Res Ayur Pharm., 2011;2(5):1520-1526.
24. Alongi J, Poskovic M, Frache A, Trotta F. Role of β-cyclodextrin nanosponges in polypropylene photooxidation. Carbohyd Polym., 2011;86; 127-135.
25. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system – review. J Pharm Pharm Sci 2012;15:103-11
26. Osmani RA, Thirumaleshwar S, Bhosale RR, Kulkarni PK. Nanosponges: The spanking accession in drug delivery – An updated comprehensive review. Pelagia Res Lib Pharm Sin 2014; 5:7-21.
27. Patel B, Bagade O, Ramteke K, Patel R, Awsarker V. An assessment on preparation, characterization and poles a part appliances of nanosponges. Int J PharmTech Res 2014; 6:1898-907.
28. Maravajhala V., Papishetty S., Bandlapalli S., Nanotechnology in the development of drug delivery system,International journal of pharmaceutical sciences & research 2012; 3(1).
29. Srinivas P, Sreeja. K. Formulation and Evaluation of Voriconazole Loaded Nanosponges for Oral and Topical Delivery. Int J Drug Dev Res. 2013; 5(1):55-68.
30. Patel EK, Oswal RJ. Nanosponge and microsponges: A novel drug delivery system. Int J Res Pharm Chem 2012; 2:237-44.
31. Singh R, Bharti N, Madan J, Hiremath SN. Characterization of cyclodextrin inclusion complexes – A review. J Pharm Sci Technol 2010; 2:171-83.

32. Jyoti P, Tulsi B, Popin K, Chetna B. An Innovative Advancement for Targeted Drug Delivery: Nanosponges, Indo Global J Pharm Sci. 2016; 6(2):59-64.
33. Khan KA, Bhargav E, reddy KR, Sowmya C. Nanosponges: A New Approach for Drug Targetting. Int. J pharm. pharm. res. 2016; 7(3):381-396
34. Seema G, Kumar SA, Manoj B. Development and evaluation of curcumin loaded nanosponges for colon drug delivery. World J Pharm Res 2015; 4:1650-66.
35. Rajeswari C, Alka A, Javed A, Khar RK. Cyclodextrins in drug delivery: An update review. AAPS Pharm Sci Tech 2005; 6:E329-57.
36. Morsi N, Ghorab D, Refai H, Teba H. Preparation and evaluation of alginate/chitosan nanosdispersion for occular delivery. Int J Pharm Pharm Sci 2015; 7:234-40.
37. Manyam N, Reddy Budideti KK, Mogili S. Formulation and in vitro evaluation of nanosponges loaded extended release tablets of Trimethoprim. Unique Pub J Pharm Med Health Sci 2018;1:78-86
38. Ansari K., Torne S., Vavia P.R., Trotta F., Cavalli R., Cyclodextrin - Based Nanosponges for Delivery of Resveratrol: In Vitro Characterization, Stability, Cytotoxicity and Permeation Study, AAPS Pharm Sci Tech,2011;12(1).
39. Mandava SS, Thavva V, Int J Pharm Sci Res, 2012; 3(4):967-980.
40. 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.
41. Gidwani B, Vyas A. A comprehensive review of cyclodextrinbased carriers for delivery of chemotherapeutic cytotoxic anticancer drugs. BioMed Res Int 2015; 15:1-15.
42. Vyas A, Saraf S, Saraf S. Cyclodextrin based novel drug delivery systems. J Inclusion Phenom Macrocyclic Chem 2008; 62:23-42
43. Shivani, S., & Poladi, K. K. Nano sponges-novel emerging drug delivery system: A review. Int J Pharmaceutical Sci Res,2015; 6(2):529–540. https://doi.org/10.13040/IJPSR.0975-8232.6(2). 529-40
44. Gangadharappa, H. V., Prasad, S. M. C., & Singh, R. P. (2017). Formulation, in vitro and in vivo evaluation of celecoxib nano sponge hydrogels for topical application. J Drug Delivery Science Technology, 41, 488–501. https://doi.org/10.1016/j.jddst.2017.09. 004
45. Wadhwa, A., Mathura, V., & Lewis, S. A. Emerging novel nano pharmaceuticals for drug delivery. Asian J Pharmaceutical Clinical Res,2018; 11(7):35–42.
46. Setijadi, E., Tao, L., Liu, J., Jia, Z., Boyer, C., & Davis, T. P. Biodegradable star polymers functionalized with β-cyclodextrin inclusion complexes. Biomacromolecules, 2009; 10:2699–2707.
47. Tejashri, G., Amrita, B., & Darshana, J. Cyclodextrin based nano sponges for pharmaceutical use: A review. Acta Pharmaceutical, 63(3), 335–358. https://doi.org/10.2478/ acph-2013-0021
48. Ansari, K. A., Vavia, P. R., Trotta, F., & Cavalli, R. Cyclodextrin-based nanosponges for delivery of resveratrol: In vitro characterisation, stability, cytotoxicity and permeation study. An Ofcial Journal of the American Association of Pharmaceutical Scientists, 2011; 12:279–286.
49. Rao, M. R. P., Chaudhari, J., Trotta, F., & Caldera, F. (2018). Investigation of cyclodextrin-based nanosponges for solubility and bioavailability enhancement of rilpivirine. An Ofcial Journal of the American Association of Pharmaceutical Scientists, 19(5), 2358–2369. https://doi.org/10.1208/s12249-018-1064-6 .
50. Rezaei, A., Varshosaz, J., Fesharaki, M., Farhang, A., & Jafari, S. M. Improving the solubility and in vitro cytotoxicity (anticancer activity) of ferulic acid by loading it into cyclodextrin nanosponges. International Journal of Nanomedicine, 2019; 14:4589–4599. https://doi.org/10.2147/IJN.S206350
51. Shende, P. K., Gaud, R. S., Bakal, R., & Patil, D. (2015). Efect of inclusion complexation of meloxicam with β-cyclodextrin- and β-cyclodextrin-based nanosponges on solubility, in vitro release and stability studies. Colloids and Surfaces B: Biointerfaces,2015;136:105–110. https://doi.org/10.1016/j.colsurfb.2015.09.002
52. . Pandey, P., Purohit, D., & Dureja, H. Nanosponges -A promising novel drug delivery system. Recent Patents on Nanotechnology, 2018; 12(3):180–191. https://doi.org/10.2174/1872210512 666180925102842
53. . Pawar, S., & Shende, P. A comprehensive patent review on β-cyclodextrin cross-linked nanosponges for multiple applications. Recent Patents on Nanotechnology, 2020; 14(1):75–89. https:// doi.org/10.2174/1872210513666190603083930
54. Patil, T. S., Nalawade, N. A., Kakade, V. K., & Kale, S. N. Nano sponges: A novel targeted drug delivery for cancer treatment. International Journal for Advance Research and Development, 2017; 2(4):55–62