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Review Article on Nano Sponges Used in Herbal Preparations

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ABSTRACT: Nanosponges are minuscule particles with nanometres-wide cavities that can encapsulate both hydrophilic and lipophilic drug molecules [2, 3]They offer several advantages over traditional topical formulations, including enhanced stability, reduced side effects, controlled drug release, improved solubility of lipophilic drugs, and increased bioavailability [1, 4].Nanosponges can be prepared using various techniques such as the melt method, solvent diffusion method, solvent evaporation method, and ultrasound-assisted synthesis [16, 17, 24]. Characterization methods include thermoanalytical techniques, microscopy, X-ray diffraction, solubility studies, infrared spectroscopy, and thin layer chromatography [20, 21, 23, 24].Nanosponges are a promising drug delivery technology, especially for topical applications, to improve the solubility, bioavailability, and controlled release of poorly soluble drugs[1].

1. INTRODUCTION:

Approximately 70% of medications in the pharmaceutical business are classified as having poor water solubility since they are produced using synthetic chemistry [1].Formulation scientists work to improve medicine solubility, absorption, and bioavailability. Topical administration is recommended to address problems with solubility, absorption, and bioavailability; new formulations like Nano sponge have been useful in this regard. It is composed of minuscule particles with cavities that are only a few manometers wide[2], allowing pharmacological compounds to be encapsulated[3]. These particles can also transport hydrophilic and lipophilic drug molecules.It has been discovered that topical drug delivery methods including gel, cream, and ointments are less successful at penetrating the skin.Traditional topical treatments like ointments and lotions are linked to unpleasant side effects like burning, contact dermatitis, and stinging sensations because of their poor efficacy and inconsistent medication release. It is now a top priority to develop particle carrier systems, including liposomes and microspheres, to regulate the distribution of drugs to specific areas of the skin. It is anticipated that these mechanisms will control the rate at which drugs are injected, lessen the amount of drugs absorbed into the bloodstream, and limit side effects. Numerous investigations have indicated that liposomal carriers can be substituted with nanoparticle carriers to provide superior cutaneous dispersion. The reason why Nanosponges are a great option for creating topical medications is due to their better product stability, safety, and beauty features. Many topical drugs can be safely contained in nanosponges for controlled release[4].The largest organ in the body, the skin comprises 15% of the adult body weight. The three layers of skin are the dermis, epidermis, and subcutaneous layers. The stratified, squamous epithelial layer that makes up the outermost layer of the skin is termed the epidermis, and it is made up of dendritic cells and keratinocytes. It demonstrated the purpose of keratin synthesis. Present in the skin include Merkel cells, Langerhans cells, and melanocytes. The fibrillar structural protein collagen makes up the dermis, the middle layer of skin. Fibrous, filamentous, and amorphous connective tissue make up the dermis. Little lobes of fat cells called lipocytes are present in the panniculus, a subcutaneous tissue that sits on top of the dermis. The deepest stratum of the skin is called subcutaneous tissue. In the subcutaneous tissue, the development of fat cells starts. These lipocytes, or lobules of fat cells, are separated by fibrous septa made of collagen and big blood vessels. The hypothalamus uses the hormone leptin, which is produced by lipocytes, to control body weight. The nanosponge can enter the body through that skin structure[5]. Drug molecules can be held in nanosponges and released in a controlled manner to target organs or specific places. For dosage forms, topical nanosponge preparations are available in local anesthetic, anti-fungal, anti-acne, and anti-wrinkle varieties[6]. The preparation procedures for the cross-linking, melt, and ultrasonic aided processes[7]. It is possible to construct topical nanosponge formulation for medications and APIs such fenofibrate, indomethacin, and cyclosporin B. The majority of medications used in the creation of nanosponge are classified as Class II pharmaceuticals under the Biopharmac categorization system (BCS) and as having substantial first-pass metabolism[8]. The advantage of the nanosponge is that medications penetrate the skin more effectively. Nanosponges made of a suitable polymer that create three-dimensional networks or scaffolds [9]. These polymers are combined with a cross-linker in a solution and have a natural degradation process to create nanosponge[10].

2. Objectives of Nanosponge dosage form development include:

1. To improve poorly soluble medication solubility.
2. To make the medications more bioavailable.
3. To boost, extend, and regulate a drug's release.

3. ADVANTAGES:

1. The nanosponge functions as an auto-sterilizer.
2. Lipophilic medication solubility is booseted by nanosponges such as Celecoxib[1].
3. They lessen adverse effects.
4. The body may eliminate harmful compounds with the aid of nanosponges.
5. The medication's bioavailability is increased by nanosponges such as HCl erlotinib[11].
6. It lessens the frequency of dose.
7. The molecule is shielded from degradation by nanosponges for instance, doxorubicin[12].
8. Nanosponges provide medication in a regulated fashion.
9. These are chemicals that flow freely.
10. It improves the drug's stability, and this formulation remains stable between pH values.

4. DISADVANTAGES:

1. Nano sponges can only hold small molecules (less than 500 Dalton), hence they are not appropriate for larger molecules[14].
2. Nanosponges are laden with medications that have the ability to modify the level of crystallization.
3. It could result in dosage dumping.

5. DRUG SELECTION FOR TOPICAL NANOSPONGES PREPARATION:

The various classes connected to permeability and solubility are displayed by the biopharmaceutical classification system (Table 1). We can readily segregate a medicine for formulation production from those classes. Drugs that are poorly soluble are made more soluble using nanosponges class 2 (high permeability and poor solubility) is a part of that class in the biopharmaceutical classification system. Drug solubility in that class is low, yet drug penetration through the skin is good because to its high permeability. It can therefore be applied topically to prepare nanosponges.

6. FACTORS INFLUENCES FOR PREPARATION OF NANOSPONGES:

6.1. Kind of Cross-linker and Polymer

The creation and functionality inside nanosponges influenced by the types of polymers utilized in their synthesis. Molecular nanocavities are transformed into three-dimensional nanoporous structures by capable crosslinkers. Depending on the crosslinkers' properties, water-soluble or insoluble nanosponge structures are created[15]. Hydrophilic and hydrophobic nanosponges are the two different varieties in addition to hydrophobic both, nanosponges can be designed for the delivery of active pharmacological molecules using varying crosslinker concentrations[14]. Epichlorohydrin is a cross-linker utilized in hydrophilic nanopsonges that regulates drug release rate and boosts drug absorption across biological barriers. It can therefore be applied to compositions intended for instant release[16]. Cross-linkers in hydrophobic nanosponges include diphenyl carbonate pyrometallic and diisocynates dianhydride, and carbonyldiimidazole.

These nanosponges serve as delivery systems for water-soluble medications, such as proteins and peptides, exhibiting regulated or sustained release characteristics. A medication should be able to be contained within the nanosponge cavity of sufficient size[16]. Drug molecule: A nanosponge ought to include drug molecules. The medication ought to have the following qualities.

a. A pharmacological molecule should have 400 daltons is the molecular weight and a structural structure made up of between the medicqof condensed rings.

b. Less than 10 mg/mL of the medication is soluble in water.

c. The material's melting point ought to be lower than 250°C[14].

6.2. Temperature**:**

Variations can have an impact on how the medication complexes or how nanosponge formulation is made. The degree to which stability constant for medication or the nanosponge complex reduces as temperature rises may be caused by a decrease in the contact forces between the drug and the nanosponges, such as the hydrophobic and Van der Waal forces[14, 16].

6.3Degree of Subsitutions:

The quantity, kind, and location of substituents on the polymeric molecule can all affect how well nanosponges complexate. Different functional groups on the surface of cyclodextrin derivatives are used to provide a kind of substitution that is widely available in different forms, similar to that of β-cyclodextrin derivatives. Various forms of complexed material (β-cyclodextrin nanosponges, cyclodextrin carbonate nanosponges, and cyclodextrin-carbamate nanosponges) are produced when it is complexed with a crosslinker. Since the degree of interconnection and the number of substitutions are directly correlated, it is possible that a higher number of substituents will rise the possibility of experiencing a higher degree of crosslinking, which can result in very permeable nanoparticles because of more polymer interconnections that form a mesh-like network. Additionally, the various conditions of system production affect the substitute position. Modifications during the production process may result in the creation of materials with distinct physicochemical characteristics because functional groups on the parent molecule may occupy different places[15].

7. METHODS OF PREPARATION:

The kind of polymer, drug amount, and cross-linking technique used to load pharmaceuticals into the nanosponge structure all Linker[16].

Methods of preparation of nanosponges:

1. Melt method
2. Solvent diffusion method
3. Solvent evaporation method
4. Ultrasound-assisted synthesis

7.1. Melt Method:

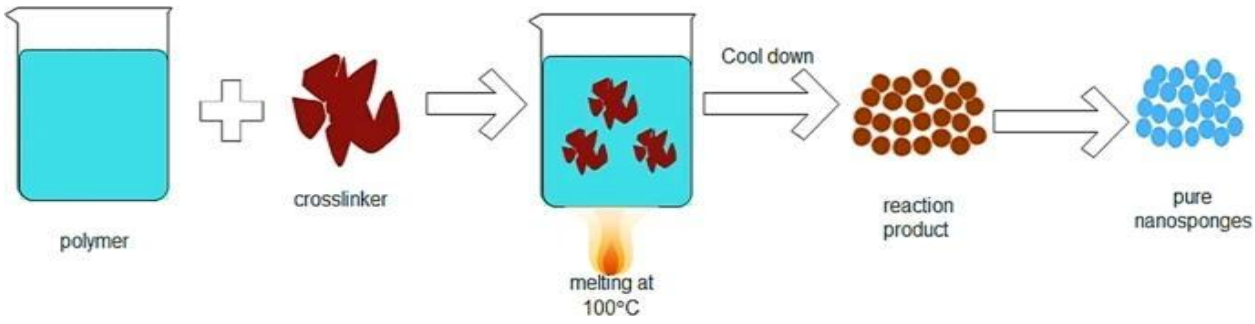


Fig no.1 Melt Method

The cross-linker reaction serves as the foundation for the melt process. To start the reaction, all the materials are placed in a 250 ml flask, heated to a high temperature, and then agitated using a magnetic stirrer. After allowing the mixture to cool, a solvent must be used to wash it. To get unreacted excipient out of the product, repeated washing is necessary[17].

7.2. Solvent Diffusion Method:

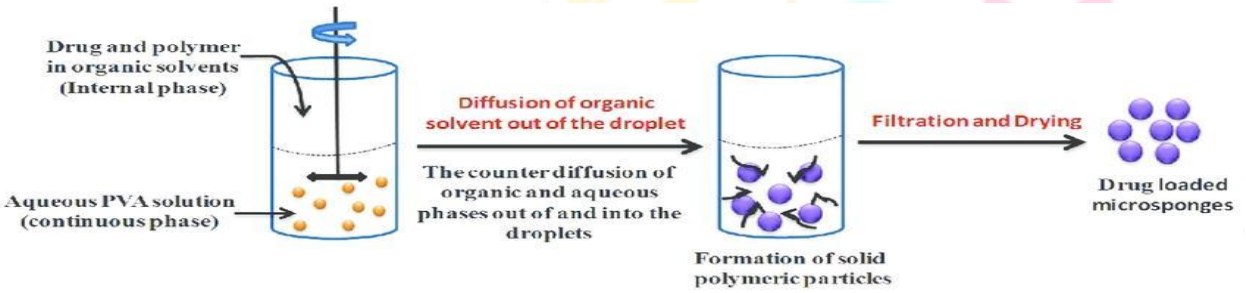


Fig no.2 Solvent Diffusion Method

In this method, both the organic and aqueous phases are employed. The medication and polymer are allowed to dissolve in the organic phase. Alcohol polyvinyl (PVA) and the aqueous phase are commonly employed. The state of organic matter was gradually mixed with the liquid phase while being stirred with a magnetic stirrer. To get rid of undesirable excipients, the generated product will be suitably filtered and cleaned using a suitable solvent. To obtain a dried nanosponge or product, let it dry in a vacuum oven[16].

7.3. Solvent Evaporation Method:

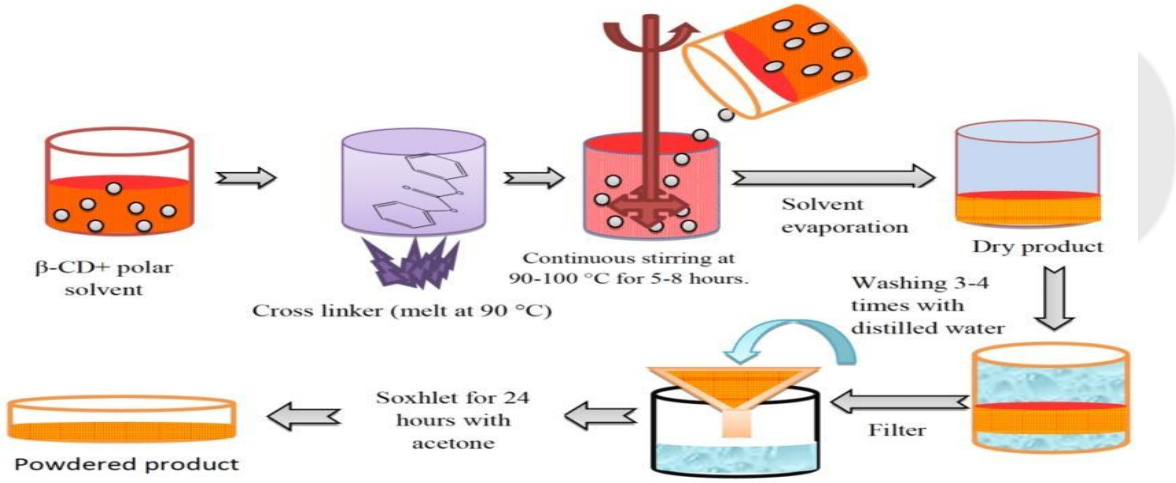


Fig no.3 Solvent Evaporation Method

This approach uses polyvinyl alcohol (PVA) and a chemical to prepare nanosponges. Then, the polymer was dissolved in it to prepare the organic phase. To create an aqueous phase, PVA and deionized water were used. Following that, the organic phase was gradually and dropwise added to the aqueous phase for three minutes. Nanosponge then developed. PVA was then used to stabilize the newly created nanosponge, preventing particle agglomerations. After that, the dispersion was maintained for 24 hours at ambient temperature and atmospheric pressure with continuous stirring at 1000 rpm on a thermostatically controlled magnetic stirrer. The produced nanosponges were cleaned three times with ultra-purified water to remove the adsorbed PVA after the organic phase completely evaporated. The PVA was then obtained after30days of ultracentrifugation at 4°c[24]

7.4. Ultrasound Assisted Synthesis:

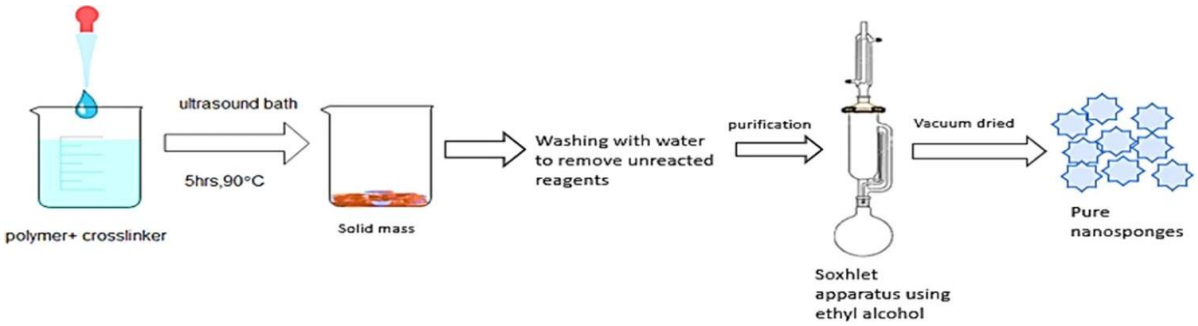
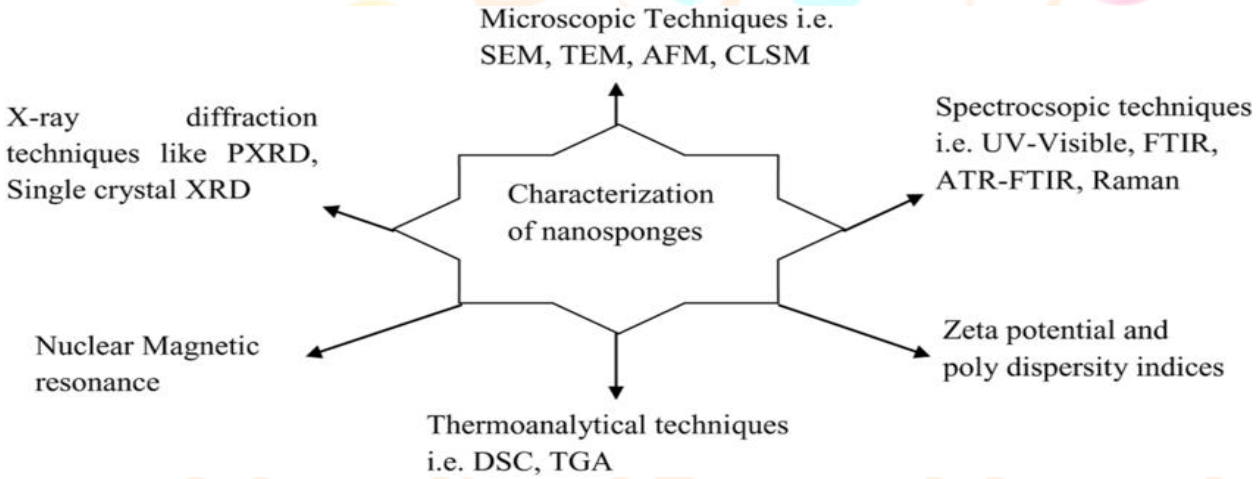


Fig no. 4 Ultrasound Assisted Synthesis

In ultrasound-assisted synthesis, the drug and polymer react without the need for a solvent by reacting with a crosslinker. Additionally, sonication is not used in the process. This involves the polymer reacting with the crosslinker in a flask before the flask is heated to 90°C for five hours in an ultrasonic bath that has previously been filled with water following exposure to ultrasonic, the mixture's solution is allowed to cool to ambient temperature. After that, the product must be adequately cleaned with a non-reacting solvent or polymer and properly filtered to get rid of any undesired excipients. In order to redefine a product mixture, the developed product was extracted using a Soxhlet equipment. After that, a vacuum is used to dry it[19].

8. EVALUATION OF NANOSPONGES:

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods:



8.1. Thermo-analytical method:

Thermoanalytical techniques ascertain if the drug material experiences any modifications prior to the thermal breakdown concerning of the nanosponges. The drug material may undergo melting, evaporation, breakdown, oxidation, or polymorphic transformation. The drug's substance changing suggests the creation of a complex. The thermogram that DTA and DSC produced Observable changes include broadening, shifting, the emergence of new peaks, and the extinction of some peaks. Modifications in weight loss may also offer proof that inclusion complexes are forming[21].

8.2. Microscopic studies:

Transfer and Scanning Electron Microscopy (SEM) the microscopic features of the medication, nanosponges, and product (drug/nanosponge complex) can be studied using electron microscopy (TEM). Under an electron microscope, the raw materials' and the product's different crystallization states show that inclusion complexes are forming[20, 21].

8.3. X-ray diffraction studies:

One technique for identifying inclusion complexation in the solid state is powder X-ray diffractiometry. Since liquids don't have their own diffraction patterns, when a medicine molecule is liquid, its diffraction pattern will obviously differ from that of an uncomplicated nanosponge. The complex creation is shown by this discrepancy in the diffraction pattern. In cases when the drug compound is a solid, it is necessary to compare the diffractogram of the mechanical combination of drug and polymer molecules with that of the assumed complex[21]. While the diffraction patterns of complexes appear to differ from those of each constituent and result in a distinct solid phase, the diffraction patterns of physical mixtures are frequently the sum of those of each componeutilizing various diffractograms. Peaks of diffraction they are helpful in figuring out the chemical breakdown and complex creation of mixtures of chemicals. The drug's crystalline constitution and diffraction patterns are both altered by the complicated synthesis of the drug with nanosponges. A few new peaks emerge, some peaks move, and the old peaks become sharper as a result of the complex creation[21].

8.4. Analysis of the Single Crystal X-ray Structure:

May be applied to ascertain the precise interaction style and inclusion structure. It is possible to pinpoint the precise geometric relationship and identify the interaction between the host and guest molecules[21].

8.5. Studies on Solubility:

The phase solubility method, as defined by Higuchi and Connors, is the most commonly used technique to explore inclusion complexation. It looks at how a nanosponge affects the solubility of a medicine. Diagrams of phase solubility despicts the level of complexation[23, 24].

8.6. Infra-Red spectroscopy:

The interaction between drug molecules in the solid state and nanosponges is estimated using Infra-Red spectroscopy. Bands of the spectrum nanosponges easily mask bands that may be ascribed to the included part of the guest molecules if the fraction of guest molecules contained in the complex is less than 25%. Nanosponge's bands frequently vary only little upon complex formation. In general, the methodology is not appropriate for detecting inclusion complexes and provides less clarity compared to alternative approaches. The use of infrared spectroscopy is restricted to medications that contain certain distinctive bands, including sulfonyl or carbonyl groups. Studies of the infrared spectrum provide information about the role that hydrogen plays in different functional groups. This often causes the band generated by the expanding variation of the group involved in the creation of hydrogen bonds to broaden, intensify, and shift to a lower frequency in the absorbance spectrum. The stretching vibration band shifts most near the hydroxyl group due to the hydrogen bond[21].

8.7. Thin Layer Chromatography:

The RF values of a drug molecule reduces significantly in Thin Layer Chromatography, which aids in determining the complex formation between the drug and Nanosponge. Efficiency of loading you may use to find the loading efficiency (%) of Nanosponge[24].

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

8.8. Particle Size and Polydispersity:

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer Equipped with MAS OPTION particle sizing software. From this the mean diameter and Polydispersity index can be determined[20].

8.9. Zeta Potentia:

Zeta potential is a measure of surface charge. It can be measured by using additional Electrode in the particle size equipment[20].

8.10. Production Yield:

The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of nanosponges[24].

$$\text{Production Yield} = \frac{\text{Practical mass of Nanosponges}}{\text{Theoretical mass (polymer + drug)}} \times 10$$

9. Applications of Nanosponges:

Nanosponges are very versatile and biocompatible, which makes them useful in the pharmaceutical Industry When making tablets, capsules, pellets, granules, suspensions, solid dispersions, or topical dosage forms, they can be utilized as excipients[25]. Table 3 illustrates the range of medications they can contain. In order to improve a product's performance and elegance, as well as its longer release, reduced irritation, and improved thermal, physical, and chemical stability, nanosponges can serve as multifunctional carriers. The applications of nanosponges that demonstrate their versatility are listed below.

Following are the applications of nanosponges which shows versatility of nanosponges.

9.1. Nanosponges as a sustained delivery system:

Because acyclovir effectively treats herpes simplex virus infections, it is a commonly used antiviral medication[26]. Nevertheless, the current formulations of acyclovir cannot provide adequate concentrations of the Agent reaching target areas when administered parenterally or orally. Acyclovir's pharmacokinetics after oral administration are highly varied, and its absorption in the gastrointestinal tract is both slow and incomplete. A prolong discharge of the medication from both types of nanosponges was observed in the in characteristics of in- vitro release profiles of acyclovir, suggesting that the medicine was encapsulated within the nanostructures. After three hours in vitro, between 22% and 70% of the acyclovir was released from the carb-nanosponges and nanosponges, respectively. Both formulation showed no signs of early burst effect, indicating that the drug was not poorly adsorbed onto the surfaces of the nanosponge[27].

9.2. Nanosponges in solubility enhancement:

Swaminathan et al. investigated an itraconazole formulation in Nanosponges[28]. A medication classified as BCS Class II, itraconazole has a limited bioavailability and a sluggish rate of dissolution thanks to nano sponges, medication solubility was enhanced by almost 27 times in the presence of copolyvidonium, this increased by a ratio of 55 include dead as a supporting element to the nano sponges composition . Nanosponges solubilize drugs by either enhancing the drug's wetting, decreasing its crystallinity, or perhaps by hiding the group thata are hydrophobic are of itraconazole[28].

9.3. Nanosponges in drug delivery:

Because of its spherical shape and nanomeric size, nanosponges can be prepared in a variety of dosage forms, including topical, parenteral, aerosol, tablet, and capsule[29]. Telmisartan (TEL) is a BCS Class II medication with poor bioavailability due to its dissolving rate. By using carbonate bonds to cross-link β-CD, BBCD based nanosponges were created. Within the nanosponges, TEL was incorporated. The in vitro dissolution research and saturation solubility of TEL's β-CD complex were compared to those of TEL's plain and nanosponge complexes. It was discovered that adding NaHCO3 to the drug Nanosponges complex enhanced the solubility of TEL by 8.53 times in distilled water, 3.35 times in 1 mol HCl, and 4.66 times in phosphate buffer pH 6.8. A drug release in vitro and maximum solubility were observed in an inclusion complex made of nanosponges and NaHCO3[30]. Paclitaxel is a chemotherapeutic drug for cancer that is poorly soluble in water. Using B-CD-based nanosponges, in cremophor EL, paclitaxel is an alternative to the standard formulation since cremophor decreases the tissue penetration of paclitaxel. When compared to plain paclitaxel, the intracellular concentration of paclitaxel is dramatically increased, and its cytotoxicity is also greatly boosted after a 72-hour incubation. These findings demonstrate how highly nanosponges enhance the biological action of paclitaxel in vitro[31]. Econazole nitrate is an antifungal medication that can be applied topically to relieve the symptoms of dermatophytosis, superficial candidasis, and skin infections. It comes in lotion, cream, and ointment forms. When econazole nitrate is given topically, adsorption is negligible; yet, a high quantity of active ingredients must be included for therapy to be effective. As a result, hydrogel was used to load econazole nitrates nano sponges as a local deport for prolong drug realease; these were made by the emulsion solvent deffusprocess [32].

9.4. Nanosponges for protein delivery:

The effective creation of medications, particularly macromolecular ones like proteins, depends heavily on their long-term stability[33]. However, upon lyophilization, proteins can denature reversibly (or sometimes irreversibly), adopting a conformation that is noticeably different from their initial state. Preserving the native protein structure during formulation and long-term storage is therefore a significant challenge in the

development of protein formulating[34]. Nanosponges 10 and 11, which are cyclodextrin-based swellable poly (amidoamine) nanosponges, were created by cross-linking β-CDs with 2,2-bis-Acrylamidoacetic acid or a brief polyamido-amine chain derived from 2,2-Bisacrylamidoacetic acid and 2-methyl piperazine, respectively. These findings were reported by Swaminathan et al. The developed β-CD based Poly (amidoamine)-nanosponges had a high capacity for protein complexation and were shown to be stable at 300 °C[35].

9.5. Nanosponges in enzyme immobilization:

Since it increases lipases' stability and modifies their selective of enantiomers and reaction speeds, the problem of immobulization of enzyme is very significant[36] new solid support thata are sutaible for this family of enzymes are therefore always needed. Boscolo & Co. discovered that absorbed pseudomonous floroucance lipase on a new kind of nanosponges base on cyclohexatriene exhibited remarkable catalytic capabilities[37].

9.6. Nanosponges as a gas delivery:

In medicine, gases are employed for both medicinal and diagnostic purposes. Hypoxia, or inadequate oxygen delivery, is associated with several illnesses, including as inflammation and cancer. In medical settings, it can be it can be difficult to give oxygen in the proper dosage and type at times. Cavalli et al. developed oxygen delivery methods intended for topical application. Created Combination of nano sponges thata realise and store oxygen graudually [38].

9.7. Nanosponges as a light- or degradation-resistant agent

A blend of ferulic acid ester, gamma-oryzanol has garnered a lot of attention lately as a natural antioxidant. In the cosmetics sector, it is frequently used as a sunscreen and to stabilize raw components for food and medicine. Due to its high instability and photodegradation, its application is restricted. Encapsulating gamma oryzanol in nanosponges demonstrated a strong defence against photodegradation. The gamma-oryzanol-loaded nanosponges were utilized to generate both an O/W emulsion and a gel[39].

CONCLUSION:

1. Hydrophilic and lipophilic pharmacological molecules can be encapsulated in nanosponges, which are minuscule particles with nanometer-wide voids.
2. A variety of techniques, including the melt method, solvent diffusion method, solvent evaporation method, and ultrasound-assisted synthesis method, can be used to manufacture nanosponges.
3. Thermoanalytical techniques, microscopy investigations, X-ray diffraction, solubility studies, infrared spectroscopy, and thin layer chromatography can all be used to assess nanosponges.
4. Nanosponges offer a number of benefits, including enhanced stability, less adverse effects, regulated drug release, enhanced solubility of lipophilic medicines, and greater bioavailability[1].
5. Drugs with substantial first-pass metabolism and BCS Class II (low solubility, high permeability) can be delivered via nanosponges. In conclusion, especially for topical applications, nanosponges are a promising drug delivery technology for increasing the solubility, bioavailability, and controlled release of poorly soluble medications.

REFERENCE:

1. Gangadharappa HV, Prasad SM, Singh RP. Formulation, in vitro and in vivo evaluation of celecoxib nanosponge hydrogels for topical application. J Drug Deliv Sci Technol 2017; 41:488-501.
2. Thakre AR, Gholse N, Kasliwal H. Nanosponges: A novel approach of drug delivery system. J Med Pharm Allied Sci 2016:78-92.
3. Selvamuthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. J Pharm Pharma Sci 2012; 15: 103- 11.
4. Ghanbarzadeh S, Arami S. Enhanced transdermal delivery of diclofenac sodium via conventional liposomes, ethosomes, and transferosomes. Biomed Res Int 2013; 2013:616810. Doi: 10.1155/2013/616810, PMID 23936825
5. Kolarsick P, Kolarsick MA, Goodwin C. Anatomy and physiology of the skin. J Dermatol Nurs Assoc 2011; 3:203-13.
6. Abbas N, Parveen K, Hussain A, Latif S, Zaman SU, Shah PA, et al. Nanosponge-based hydrogel preparation of fluconazole for improved topical delivery. Trop J Pharm Res 2019; 18:215-22. Doi: 10.4314/tjpr.v18i2.1
7. Kaur S, Kumar S. Nanosponges: An innovative drug delivery system. Asian J Pharm Clin Res 2019; 12:60-7.
8. Lee JS, Oh H, Kim S, Lee JH, Shin YC, Choi WI. A novel chitosan nanosponge as a vehicle for transepidermal drug delivery. Pharmaceutics 2021; 13:1329.
9.Kapileshwari GR, Barve AR, Kumar L, Bhide PJ, Joshi M, RK. Novel drug delivery system of antifungal drug-formulation and characterization. J Drug Deliv Sci Technol 2019; 55:101302.
10. Bhowmik H, Venkatesh DN, Kuila A, Kumar KH. Nanosponges: A review. Int J Appl Pharm 2018; 10:1-5
11.Dora CP, Trotta F, Kushwah V, Devasari N, Singh C, Suresh S, et al. Potential of erlotinib cyclodextrin nanosponge complex to enhance Solubility, dissolution rate, in vitro cytotoxicity and oral bioavailability. Carbohydr Polym 2015; 137:339-40
12. Balwe MB. Nanosponge a novel drug delivery system. Res J Pharm Dosage Forms Technol 2020; 12:261-6. Doi: 10.5958/0975-4377.2020.00043.9
13. Sharma R, Pathak K. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through Topical hydrogel formulation. Pharm Dev Technol 2011; 16:367-76. Doi: 10.3109/10837451003739289, PMID 20367024
14.Jain A, Prajapati SK, Kumari A, Mody N, Bajpai M. Engineered Nanosponges as versatile biodegradable carriers: An insight. J Drug Deliv Sci Technol 2020; 57:1-38. Doi: 10.1016/j.jddst.2020.101643
15.Osmani RA, Kulkarni P, Gowda V, Vaghela R, Bhosale R. Cyclodextrin Nanosponges in Drug Delivery and Nanotherapeutics. Ch. 9. Cham: Springer International Publishing; 2018. P. 280-332.
16. Pawar S, Shende P, Trotta F. Diversity of β-cyclodextrin-based Nanosponges for transformation of actives. Int J Pharm 2019; 565:333-50. Doi: 10.1016/j.ijpharm.2019.05.015, PMID 31082468
17. Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based Nanosponges: A critical review. Carbohydr Polym 2017; 173:37-49. Doi: 10.1016/j.carbpol.2017.05.086, PMID 28732878
18.Ahmed MM, Fatima F, Anwer MK, Ibnouf EO, Kalam MA, Alshamsan A, et al. Formulation and in vitro evaluation of topical nanosponge-based gel containing butenafine for the treatment of fungal skin infection. Saudi Pharm J 2021; 29:467-77.
19. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, verma A. Nanosponges: A potential nanocarrier for novel drug delivery-a review. Asian Pac J Trop Dis 2014; 4:S519-26. Doi: 10.1016/S2222-1808(14)60667-8

20.Shankar S, Linda P, Loredana S, Francesco T, Pradeep V, Dino A, Michele T, Gianpaolo Z, Roberta C. Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm, 2010; 74: 193-201.

21. Ramnik S, Nitin B, Jyotsana M, Horemat SN. Characterization of Cyclodextrin Inclusion complexes –A Review. J Pharm Sci Tech, 2010; 2(3): 171-183.

22 .Jenny A, Merima P, Alberto F, Francesco T. Role of β- cyclodextrin nanosponges in polypropylene photooxidation. Carbohydrate Polymers, 2011; 86: 127– 135.

23. Rajeswari C, Alka A, Javed A, Khar R K. Cyclodextrins in drug delivery: an update Review. AAPS pharmSciTech, 2005; 6(2): E329-E357.

24. Moya-Ortega MD, Alvarez-Lorenzo C, Concheiro A, Loftsson T. Cyclodextrin-based nanogels for pharmaceutical and biomedical applications. Int J Pharm, 2012; 428: 152-163.

25. O'Brien JJ, Campoli-Richards DM. Acyclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs, 1989; 37: 233-309

26. Lemboa D, Swaminathan S, Donalisioa M, Civraa A, Pasterod L, Aquilanod D, et al. Encapsulation of acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. Int J Pharm, 2013; 443: 262-272.

27. Swaminathan S, Vavia PR, Trotta F, Torne S. Formulation of betacyclodextrin based Nanosponges of itraconazole. J InclPhenom Macrcycl Chem, 2007; 57(1-4): 89-94.

28. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: a novel class of drug delivery system-review. J Pharm Pharma Sci, 2012; 15(1): 103-111.

29. Rao M, Bajaj A, Khole I, Munjapara G, Trotta F. In vitro and in vivo evaluation of β-cyclodextrin-based nanosponges of telmisartan. J Incl Phenom Macrocycl Chem, 2013; 77: 135-145.

30.Mognetti B, Barberis A, Marino S, Berta G, Francia SD, Trotta F, et al. In vitro Enhancement of anticancer activity of paclitaxel by a cremophor free cyclodextrin-based Nanosponge formulation. J Incl Phenom Macrocycl Chem, 2012; 74: 201-210.

31. Sharma R., Roderick B., and Pathak K., Evaluation of kinetics and mechanism of drug Release from Econazole nitrate Nanosponges loaded carbopol Hydrogel. Indian J of Pharma Edu and research, 2011; 45(1): 25-31.

32. Klibanov AM, Schefiliti JA. On the relationship between conformation and stability in solid pharmaceutical protein formutations. Biotechnol Lett, 2004; 26: 1103-1106.

33. Shewarts D, Sofia S, Friess W. Integrity and stability studies of precipitated rhBMP-2 microparticles with a focus on ATR-FTIR measurements. Eur J Pharm Biopharm, 2006; 63: 241-248.

34. Mateo C, Palomo JM, Fernandez-Lorente G, Guisan JM, Fernandez-Lorente R. Improvement of enzyme activity, stability and selectivity via immobilization techniques. Enzyme Microb Technol, 2007; 40: 1451-1463.

35.Mateo C, Palomo JM, Fernandez-Lorente G, Guisan JM, Fernandez-Lorente R. Improvement of enzyme activity, stability and selectivity via immobilization techniques. Enzyme Microb Technol, 2007; 40: 1451-1463

36. Boscolo B, Trotta F, Ghibaudi E. High catalytic performances of Pseudomonas Fluorescens lipase adsorbed on a new type of cyclodextrin-based nanosponges. J Mol Catal B Enzym, 2010; 62: 155-161.

37. Phatak AA, Chaudhari PD. Development and evaluation of Nanogel as a carried for transdermal delivery of aceclofenac.Asian J Pharm Tech 2012; 2:125-32.

38. Chetan GS, Pramod kumar TM, Venkatesh MP. Intra-articular Delivery of methotrexate loaded nanostructured lipid carrier-Based smart gel for effective treatment of rheumatic diseases. RSC Adv 2016; 16:1-43.

39.Zhang X, Pan W, Gan L. Preparation of a dispersible PEGylateNanostructured lipid carriers (NLC) loaded with 10-hydroxyCamptothecin by spray-drying. Chem Pharm Bull2008; 56:1645-50.