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NANOSPONGES- A POTENTIAL NANOCARRIER: A REVIEW

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ABSTRACT

The development of a targeted drug delivery system has been made possible by recent developments in nanotechnology. To successfully target a molecule to a specific site using a drug delivery system, however, a specialized drug delivery system is required. The development of nanosponge has become an essential step in resolving concerns related to drug toxicity, limited bioavailability, and predictable drug release since they can accommodate both hydrophilic and hydrophobic medicines. Nanosponges has a unique ability to trap drug moieties and offer the benefit of desired release due to their porous structure. Nanosponges are microscopic sponges that may adhere to surfaces and move throughout the body to target locations in order to deliver medications in a controlled and predictable manner. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility. Utilizing crosslinkers to link the polymer, nanosponges can be created. The distribution of oral and topical drugs has been the subject of much research on nanosponge technology. This review focuses on the general overview of nanosponge, their manufacturing method, characterization, and their application in drug delivery systems.

KEYWORDS: Nanosponges, Targeted drug delivery, Polymer, Poor solubility.

INTRODUCTION

The hunt for an efficient drug delivery system is an enigma in itself. Our medical researchers and formulation scientists are always dealing with challenges related to medication targeting, drug release, overdose, solubility, permeability, activity, and bioavailability. As a result, the development and improvement of pharmaceutical delivery techniques is an ongoing research topic. The ability of nanotechnology to combine features that are difficult to attain by utilizing a drug alone has recently attracted a lot of interest.[1] The production and manipulation of materials at the nanoscale level to produce goods with unique features is known as nanotechnology. Materials with at least one dimension in the 1-100 nm range are referred to as nanomaterials.[2]

Target oriented administration with improved therapeutic efficacy, fewer side effects, and an optimized dose regimen will be the key developments in therapeutics. Targeted drug delivery entails selective and effective localization of pharmacologically active moiety at a preidentified (preselected) target in therapeutic concentration while limiting its access to non-target normal cellular linings, thereby minimizing toxic effects and increasing the drug's therapeutic index. Medical experts have long struggled with drug delivery, namely how to get them to the proper area in the body and manage the drug's release to avoid overdoses. The development of new and sophisticated molecules known as nanosponges has the potential to alleviate this problem.[3]

Nanosponges are tiny mesh like structures, resembling mesh that can hold a vast array of chemicals. Nanosponges resemble scaffolds or networks in three dimensions. The backbone is a long piece of polyester that is dissolved in a solution containing microscopic molecules known as crosslinkers, which function as tiny grappling hooks to bind the polymer's constituent pieces together.[4] A wide range of chemicals can be enclosed in the tiny particles that make up nanosponges, a novel class of materials. The cavities in these particles are only a few nanometres across.[5]

Nanosponges are solid, three-dimensional, porous, biocompatible, and flexible drug delivery systems that can overcome the issues of drug toxicity and low bioavailability by encasing both hydrophilic and hydrophobic medications. The development of nanosponges has proven to be a crucial step in addressing the complexity of the newly emerging systems. Because of their tiny size and porous structure, nanosponges have the ability to bind poorly soluble medications within the matrix, increasing their bioavailability at particular target sites. They can also

attach to the surface and start releasing the medication in a predictable and controlled manner.[6]

NS are small, spherical polymeric delivery systems that distribute the medication in a more controlled and predictable manner. Numerous other benefits, such as reduced adverse effects, adjustable dosage forms, non-irritating properties, and enhanced elegance, render them a desirable method for formulations with sustained release. These encapsulated formulations have compatibility with many constituents and vehicles so they can carry an extensive choice of drugs. In this instance, NS stabilizes the formulation by protecting against the drug's early degradation. The formulation scientists are also interested in targeted medication delivery systems, flavour masking, and improving bioavailability.[7]

These microscopic sponges can move through the body until they reach the desired area, where they adhere to the surface and start to release the drug in a steady and controlled manner. The medication will work better for a given dosage since it can be released exactly where it is needed rather than spreading throughout the body. A crucial characteristic of these nanosponges is their aqueous solubility, which enables the effective application of these systems for drugs with poor solubility.[8]

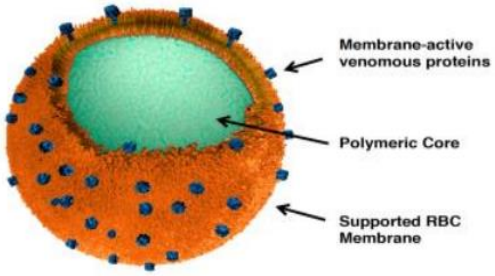

Fig. No. 1: Structure of Nanosponges showing Loading of drugs.

ADVANTAGES

- Increase aqueous solubility of the poorly water-soluble drug.
- The drug molecules can be released by nanosponges in a predictable manner.
- Because of their microscopic pore size (0.25 µm), bacteria cannot penetrate the nanosponges and they act like a self-sterilizer.
- The drug delivery by Nanosponges is non-toxic, non-mutagenic, and non-irritating.
- Nanosponges aid in the body's removal of poisonous and venomous substances.
- Nanosponges drug delivery system reduces side effect.
- Strengthen the formulation's stability and improve its flexibility.
- Decrease the frequency of dose.
- Improved patient adherence.
- Nanosponges complexes remain stable at temperatures up to 130 °C and across a broad pH range (i.e., 1– 11).[9]

DISADVANTAGES

- Nanosponges are only capable of encapsulating small molecules, making them unfit for bigger molecules.
- Dosing dumping may occur.[10]

FEATURES OF NANOSPONGES

- It's a kind of encapsulating nanoparticle that has the capacity to contain the medication molecule within its core.
- The crosslinker's functional groups and concentration have an effect on the NSs' porosity and provide flexible polarity.
- The crosslinker facilitates the formation of cavities in the framework, which opens up the possibility of modifying the pattern of drug release.
- NSs remain stable and non-lethal at temperatures as high as about 300 °C.
- NSs medicines are available in oral, parenteral, topical, and inhalational forms.
- They have less side effects, are extremely stable, elegant, and have good aqueous solubility, which makes it possible to administer medications that are poorly soluble in water. Their formulation flexibility has been improved.[11]
- Depending on the agent utilized as a crosslinker, nanosponges can be manufactured as neutral, acidic, or swellable. Overall, the result is the formation of spherically shaped particles that are filled with cavities where drug molecules can be stored.
- To enhance drug loading and achieve a tailored release profile, the cross-linking can be changed during preparation. Higher drug loading is made possible by the very porous nanometric nature of the drug molecules, which allows them to orient themselves in the inclusion of the nanosponge as well as interact non-inclusion fashion.
- The nanosponges are made of solid material. They may be used as a potential carrier for drug delivery because it has been determined that they are safe for both oral and invasive routes. The

pulmonary and venous transport of nanosponges is made possible by their tiny shape.[12]

MATERIALS USED FOR THE SYNTHESIS OF NANOSPONGE[13]

Various chemicals have demonstrated positive results and can be employed in the production of Nanosponges, depending upon the intended Nanosponge type and the necessary level of crosslinking. The crosslinking quantity, which depends on crosslinker concentration, is an essential part of Nanosponges because of its effect on drug encapsulation and release pattern. The various ingredients that are used in producing nanosponges are listed below.

Table No. 1: Materials used for the synthesis of Nanosponges.

Polymers	Cyclodextrin and its derivatives, hyper crosslinked polystyrenes, Eudragit RS100, acrylic polymers, etc
Copolymers	Polyvinyl alcohol, Poly Valero lactone allylvalerolactone, Ethyl Cellulose etc
Crosslinkers	Carboxylic acid dianhydrides, Carbonyl diimidazoles, dichloromethane, diphenyl carbonate, Glutaraldehyde, etc.,

MECHANISM OF DRUG RELEASE FROM NANOSPONGES

The active drug component enters and exits the sponge particles' open structure and travels into the vehicle until equilibrium is maintained. When a topical dosage form is applied to the skin, the active medication that was previously in the vehicle will be absorbed into the skin. This will cause the vehicle to become unsaturated and upset the balance. When the vehicle is either dried up or absorbed, the active medication will begin to seep from the sponge particles into it and then into the skin. Following that, the sponge particles will remain on the stratum corneum's surface, where they will continue to progressively release the active to the skin, providing sustained release of the drug overtime.[14]

HOW NANOSPONGES ARE BETTER THAN OTHER VESICULAR SYSTEMS?

Some colloidal drug delivery systems with nanometric sizes are liposomes, niosomes, ufasomes, bilosomes, ethosomes, transferosomes, and nanosponge. Compared to nanosponges, some of these vesicular systems have stability issues. While hydrolysis of the medication enclosed in niosomes is caused by oxidation of cholesterol and phospholipids, transferosomes are chemically unstable due to their susceptibility to oxidative destruction. These are a few of the typical issues that vesicular systems face. A new family of colloidal structures based on hyper-crosslinked polymers, known as nanosponges, are made up of solid nanoparticles with colloidal diameters and nanosized voids. Polymers, crosslinkers, and surfactants make up their composition. Chemically and physically stable, nanosponges change drug release, lessen side effects, and boost dosage form bioavailability.[15]

FACTORS AFFECTING FORMULATION OF NANOSPONGES

1. Type of polymer

Type of polymer used can influence the formation as well as the performance of Nanosponges. The polymer used in the formulation determines the size of the nanosponge cavity and drug complexation. The selection of polymer depends on the required release and the drug to be enclosed. The polymers can be utilized to interact with the drug material or to enclose the drug. The polymer must possess the ability to bind with particular ligands in order to facilitate the intended drug release.

2. Type of Drug

Certain properties listed below are required for drug molecules to be complexed with nanosponges.

- The number of condensed rings in the medication molecule's structure shouldn't exceed five.
- The medication must have a melting point of no more than 250°C.
- A drug's solubility in water should not exceed 10 mg/ml.
- Molecular weight should be between 100 and 400 Daltons.[16]

3. Temperature

Variations in temperature can have an impact on the drug and nanosponge complexation. decreases the magnitude of the perceived stability by a factor of two. The drug and Nanosponge complex's steady temperature rise may be caused by the drug and Nanosponge contact forces, which are expected to decrease with temperature.

4. Method of Preparation Nanosponges

The complexation between the drug and the nanosponge may alter when the drug is loaded into the nanosponge. In any case, the kind of medication and polymer used determines how well a procedure works. In many circumstances, the most successful method for drug complexation has been found to be freeze drying.[17]

METHOD OF PREPARATION

1. Solvent method

Combine the polymer [β-CD, ethyl cellulose (EC), alginates, Eudragit, polyvinyl alco (PVA)] and a suitable solvent, particularly an appropriate solvent, preferably a polar aprotic solvent like dimethyl sulfoxide or dimethylformamide. The combination should then be added to the surplus crosslinker, ideally in a crosslinker/polymer molar ratio of 4 to 16. Conduct the reaction for a duration of one to forty-eight hours at a temperature between 100C and the solvent's reflux

temperature. Carbonyl compounds, such as dimethyl carbonate and carbonyl diimidazole, are the preferred crosslinkers. Following the reaction's conclusion, let the mixture cool to room temperature. Then, add the result to a huge excess of by distilled water, recover the product by vacuum-assisted filtration, and finally purify it using prolonged Soxhlet.

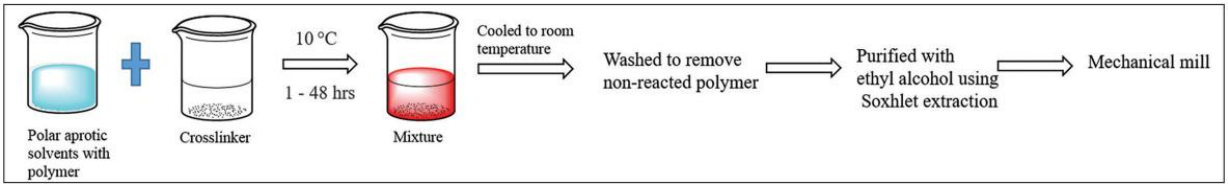

Fig. no. 2: Solvent method.

2. Ultrasound-assisted synthesis

NS is made in this technical method by sonicating the polymers with the cross-linkers without using a solvent. the NS is spherical and homogeneous in size, when made using this technique. A flask was filled with the polymer and the cross-linker at a certain molar ratio. After that, it was held for 5 hours under continuous effective sonication in an ultrasound bath device filled with water that had been heated to the temperature up to 90°C. The non-reacted polymer was then effectively removed by adding too much water, then by using ethanol it was extracted for a long-time. It is possible to obtain NS with a narrow particle size distribution by high-pressure homogenization technique. Finally, the product was then desiccated at 25°C under a vacuum.[18]

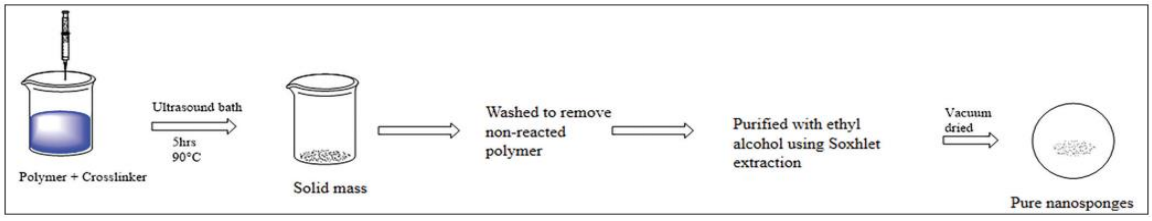

Fig. no. 3: Ultrasound-Assisted synthesis.

3. Quasi emulsion solvent method

This process makes use of two phases—the organic and aqueous phases—in varying ratios to create nanosponges. Polyvinyl alcohol is employed in the aqueous phase, whereas a medication and polymer solution are used in the organic phase. After choosing the polymer and dissolving the medication in an appropriate organic solvent, the mixture is gradually introduced to the aqueous phase. The resulting solution is agitated at 1000 rpm for almost two hours. After formulation, the nanosponges are dried, cleaned, and filtered.

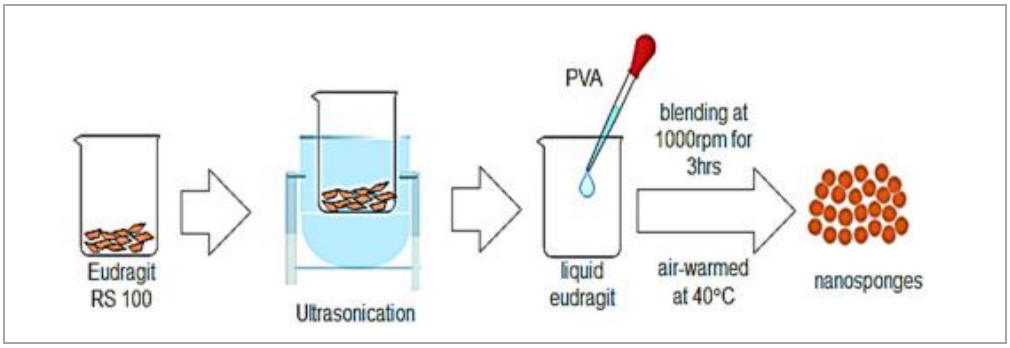

Fig. no. 4: Quasi emulsion solvent method.

4. From hyper cross- linked β-cyclodextrin

βcyclodextrin can act as a carrier for the drug in this situation. When cyclodextrin and a cross linker combine, nanosponges can be produced. This leads to the creation of 3D networks, which might resemble a roughly spherical structure with holes and channels inside that is the size of a protein. The porosity and surface charge density of cross linkers, like diisocyanates or diary carbonates, which help the sponges stick to other molecules, control how big the sponges get when cyclodextrin reacts with them. Neutral or acidic nanosponges can be produced. The average diameter of a nanosponge is less than 1 µm, although fractions lower than 500 nm can be employed. They are used to increase the water solubility of drugs that aren't highly soluble in it. They are produced up of solid particles that have been transformed into crystals.[19]

5. Emulsion Solvent Diffusion Method

Different ratios of polyvinyl alcohol (PVA) and ethyl cellulose (EC) can be used to create nanosponges. A specific volume of polyvinyl alcohol was gradually added to 150 ml of aqueous continuous phase after the dispersed phase containing the medication and ethyl cellulose had been dissolved in 20 ml of dichloromethane. For two hours, the reaction mixture was agitated at 1000 rpm. The resulting nanosponges were gathered through filtering and dried for 24 hours at 400 c in an oven. To guarantee that all remaining solvents were eliminated, the desiccated Nanosponges were kept in vacuum desiccators.[20]

LOADING OF DRUG INTO NANOSPONGES

Pre-treating the nanosponges is necessary to get a particle size of less than 500 nm. These ranges of particle sizes are achieved by dissolving or suspending the nanosponges in water. Strong sonication is applied to the suspended nanosponges. The colloidal fraction is obtained by centrifuging the suspension. After separating the supernatant, the sample is freeze-dried. A suspension in water was made. For the complexation to happen, too much medication is added to the suspension and it is constantly agitated. The uncomplexed and complexed drugs are separated by centrifugation. Either freeze drying or solvent evaporation are used to produce the solid crystals of nanosponges.[21]

CHARACTERIZATION OF NANOSPONGES

1. Particle size determination

For the purpose of creating free-flowing powders with exquisite visual qualities, the size of the particles is maintained throughout the polymerization process. NSs, both loaded and unloaded, have their particle sizes analysed using a Malvern Zeta Sizer or laser light diffractometry. The ideal particle size for delivery is less than 500 nm.

2. Entrapment efficiency

To ascertain the drug-loaded NSs' entrapment efficiency, the UV Spectrophotometric technique was employed. Centrifugation at 1000 rpm for 30 minutes was used to assess the concentration of drug in the supernatant layer and examine the amount of medication in the suspension. We employed UV spectrophotometric analysis to estimate the drug's concentration.[22]

3. Scanning & Transmission Electron Microscopy

To examine the microscopic features of the medication, nanosponges, and product (drug/nanosponge complex), two methods can be utilized: scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Even if there is a noticeable difference between the raw material and the product obtained by co-precipitation, the difference in crystallization states of the raw materials and the product observed under an electron microscope suggests the creation of the inclusion complexes.

4. Zeta potential

Surface charge is measured by zeta potential. An additional electrode in the particle size apparatus can be used to measure it.[23]

5. X-Ray Diffraction Studies

An X-ray diffractometer operating at 40 kV and 40 mA, respectively, was used to record XRD investigations of drugs and nanoscale particles. This research is helpful in examining how medications and NSs alter in crystallinity. Samples were spread out on a low background sample holder, and at a rate of 5°C/min, XRD patterns in the 2θ geometry and step 0.020 size were recorded.

6. Fourier Transform Infrared (FTIR) Analysis

In order to confirm that there could be a chemical bond interaction between the medication and the polymer, Fourier transform infrared analysis was performed. Between 400 and 4000 cm-1, samples were scanned using carbon black as a reference. Carefully purging the detector with clean, dry helium gas raised the signal level and decreased moisture.[24]

7. Thermo analytical methods

Thermoanalytical techniques determine whether the drug material undergoes any modifications prior to the thermal degradation of the nanosponge. The drug substance may undergo polymorphic transition, oxidation, melting, evaporation, or decomposition. The drug's composition changing suggests the creation of a complex. The thermogram obtained by differential thermal analysis and differential scanning calorimetry can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Alterations in the rate of weight loss may also offer proof that inclusion complexes are forming.[25]

Table No. 2: List of drug molecules encapsulated with nanosponges.[26,27]

Category	Nanosponge vehicle	Drug
Anticancer	β–Cyclodextrine	Paclitaxel Camptothecin[26]
Breast cancer	β–Cyclodextrine	Tamoxifen[26]
Brain tumour	Poly (valerolactoneallylvalerolactone) and poly (valerolactoneallylvalerolactone –oxepanedione)	Temozolamide[27]
Antifungal	Ethyl cellulose Polyvinyl alcohol β-Cyclodextrine	Econazole nitrate Itraconazole[27]

APPLICATIONS

Nanosponges in Cancer treatment

Using nanosponges to deliver anticancer drugs represents a promising approach to overcoming some of the challenges faced in traditional cancer treatment. Nanosponges can help ensure that drugs reach their intended target site in sufficient quantities.[28]

Paclitaxel is a chemotherapeutic drug for cancer that is poorly soluble in water. Since Cremophor decreases the tissue penetration of paclitaxel, β-CD based nanosponges provide an alternative to the standard formulation in Cremophor EL for paclitaxel delivery. Nanosponges dramatically improve the biological action of paclitaxel in vitro: after 72 hours of incubation, not only is its cytotoxicity significantly improved, but its intracellular paclitaxel concentration is also significantly increased in comparison to plain paclitaxel.[29]

Nanosponges for Solubility enhancement

The controlled release profiles and enhanced solubility and dissolution rate of poorly soluble medicines have been achieved with the use of nanosponges. Nonetheless, the size and conformation of molecules are crucial factors that impact inclusion complexation in nanosponges; hence, their universal applicability may be limited. To increase the pace at which cefpodoxime proxetil (CP) dissolves, nanosponges of CP have been created.[30]

The formulation of itraconazole in Nanosponges was explored by Swaminathan et al. A medication classified as BCS Class II, itraconazole has a low bioavailability and a limited rate of dissolution. The drug's solubility was enhanced by nanosponges by more than 27-fold. This increased by a factor of 55 when copolyvidonum was included as a supportive ingredient in the nanosponge formulation. By potentially hiding the itraconazole's hydrophobic groups, improving the drug's wetting, or reducing its crystallinity, nanosponges solubilize medication.[31]

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, β-CD based nanosponges were created. Within the nanosponges, TEL was added. 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 NaHCO to the drug-nanosponges complex enhanced TEL's solubility by 8.53 times in distilled water, 3.35 times in 1 mol HCl, and 4.66 times in phosphate buffer pH 6.8 compared to TEL alone. The inclusion complex made of nanosponges and NaHCO showed the maximum solubility and in vitro drug release.[32]

Nanosponges for Sustained delivery system

Comparing modified-release dosage forms to a drug's normal release formulation reveals several benefits. A modified-release product's design often aims to maximize the treatment plan by delivering the medication gradually and continuously throughout the whole dose interval. This enables the administration of a lower dose, modification of the pharmacokinetic profile, and reduction of side effects. Various drug delivery devices have been developed to alter the kinetics of medicine release. Nanosponges can yield drug release kinetics with a sustained release profile over an extended period of time. According to earlier in vitro research, flurbiprofen was released from β-CD nanosponges gradually, taking 130 minutes to achieve a percentage of less than 10%.

When doxorubicin was incorporated to nanosponges, the same result was seen. Doxorubicin was released in vitro relatively slowly at pH 1.2 (about 1% after 120 minutes), and the percentage rose with pH levels. At pH 7.4, a about 29% release of doxorubicin was observed. This behaviour might indicate that the medicine can be delivered in the intestinal system by the nanosponge formulation protecting it from the stomach environment.[33]

Nanosponges for Oral delivery systems

Oral bioavailability of a solid medication is limited by its rate of dissolution. The dissolving process controls the rate and degree of absorption for hydrophobic medicines by acting as a rate-limiting phase. Many hydrophobic medications exhibit inconsistent and insufficient absorption from the gastrointestinal system.

Bakliwal AA, *et.al*., developed to create extended-release nateglinide nanosponges for oral delivery to improve solubility. The nanosponges were formulated using ethyl cellulose and dichloromethane, and the nanosponges were tested for drug content and particle size. The optimized formulation had a particle size of 51.79 nm and 79.43% drug content. The nanosponges were then used to create tablets for oral delivery, with all formulations showing zero-order release kinetics. This finding suggested that the developed nanosponge tablets may offer controlled and sustained release of nateglinide, potentially enhancing its therapeutic efficacy and patient compliance.[34]

Trimethoprim, an antibiotic used for bladder and urinary tract infections, has low solubility, affecting oral bioavailability. To improve solubility, Manyam N, *et.al.*, created Trimethoprim Nanosponges loaded extended-release tablets. These nanosponges, filled with drug molecules, delay drug release at the urinary tract. Eight formulations were tested, with six formulations selected for further evaluation. All formulations showed a maximum drug release of 98.43 ± 0.1% after 10 hours. The nanosponge technique presents a promising approach for enhancing drug solubility of poorly soluble drugs.[35]

Nanosponges for Topical delivery systems

NS can be incorporated in gels and creams for topical drug delivery. Among the classes of medications that are easily made into topical nanosponges include antibiotics, local anaesthetics, and antifungals.

Econazole nitrate is accessible as cream, ointment, lotion, and solution across the market. When applied topically, econazole nitrate does not significantly adsorb; instead, successful therapy requires a combination of highly concentrated active drugs. Because of this, econazole nitrate nanosponges were created using the emulsion solvent approach and then put into a hydrogel for topical delivery of the medication for controlled release of the drug.[36]

The research shows that clobetasol propionate (CP) can be effectively managed with nanosponges, a type of hydrogel. The nanosponges, loaded with CP, showed good payload and controlled release, demonstrating anti-inflammatory and immune modulatory properties. They also exhibited pseudoplastic behaviour, acceptable spreadability, and mechanical properties, making them more effective for topical application. The treatment alleviated side effects of CP in Swiss mice and improved its therapeutic effectiveness.[37]

Nanosponges as a Carrier for Delivery of Gases

In diagnostic, treatment purpose gases play a key role in medicine. A lack of sufficient oxygen supply, or hypoxia, is linked to a number of diseases, including cancer and inflammation. In clinical practice, it can occasionally be challenging to administer oxygen in the right form and dosage. In order to create oxygen delivery systems for topical application, Cavalli et al. created nanosponge formulations with the capacity to gradually store and release oxygen.[38]

Nanosponges in taste masking

Bitter taste was an issue faced with paediatric oral liquid dosage form, Gabapentin, a well-known anti-epileptic drug is not preferred due to drawbacks of bitter taste, short biological half-life and compromised bioavailability. Therefore, to overcome the limitations of this drug NS-based paediatric controlled release dry suspension of Gabapentin was formulated.[39]

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 and spherical shape. 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 controlled and predictable way. This nanotechnology improves the solubility of pharmaceuticals that are currently weakly soluble, in particular BCS Class II medications and nanosponges can shield the active moieties from external physiochemical degradation and enable the usage of insoluble compounds. Because of their adaptability, nanosponges can serve as multipurpose carriers, improving solubility, protecting fragile chemicals, and achieving sustained and controlled release.

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