International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 06-01-2024, Accepted: 21-01-2024, Published: 05-02-2024
Volume 9, Issue 1, 2024, Page No. 12-16

Nanosponge based hydrogel for enhancement of permeation and retention of anti-fungal drugs: A review

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Abstract
The creation of a targeted medicine delivery system is the result of recent advancements in nanotechnology. However, a specialised drug delivery system is needed to successfully target a molecule to a specific place utilising a drug delivery system. Because they can accommodate both hydrophilic and hydrophobic drugs, the development of nanosponge has become a crucial step in solving some issues such as drug toxicity, low bioavailability, and predictable drug release. Because of their porous nature, nanosponges have the unusual capacity to capture drug moieties and provide a benefit of desire release. Nanosponges are microscopic sponges that can move throughout the body to target areas and adhere to surfaces to release drugs in a predictable and regulated way. Crosslinking polymers produces nanosponges, which are three-dimensional drug delivery systems at the nanoscale. One of their advantages is that they can accommodate a large variety of different sized medications. There are numerous sizes and shapes for nanosponges. Their differentiation stems from the kind of polymer employed, the research methodology employed, and the potential medication composition. Because they can administer drugs with targeted distribution and a regulated release pattern, nanosponges are superior to alternative delivery technologies. Different polymers with varying concentrations, such as carbopol 940, hydroxypropyl methyl cellulose, methyl cellulose, pectin, and pluronic P407, were used to manufacture the gel. Physical characteristics such as colour, syneresis, spreadability, pH, drug concentration, and rheological properties were assessed for ten distinct formulas.

Keywords: Nanosponges, antifungal, hydrogel

Introduction

Nowadays, fungus-induced skin infections are among the most prevalent dermatological issues. Physicians can choose from a variety of therapy options, including liquid dosage formulation, semisolid dosage form, and solid dose form. Clear, transparent gels are a popular topical formulation in the cosmetics and pharmaceutical industries. Clinicians and patients have access to a wide range of vehicle preparations, from solids to semisolids and liquids, for the topical treatment of dermatological diseases as well as skin care. Transparent gels are one of the main categories of semisolid preparations, and their application in pharmaceutical and cosmetic preparation has increased [1]. Systemic and superficial fungi have historically been considered two separate kinds of fungal diseases. As a result, the main antifungal medications are divided into topical and systemic forms.7 Chemical structure is the basis for the classification of antifungal medications, which include azole, polyene, allylamine, echinocandin, and others [2]. When compared to creams and ointments, gels frequently offer a quicker release of the drug's ingredient, regardless of the drug's water solubility. They are readily administered, do not require removal, and are extremely biocompatible with a reduced chance of inflammation or negative reactions. Thixotropic, greaseless, readily spreadable, quickly removed, emollient, non-staining, compatible with several excipients, and water soluble or miscile are only a few of the advantageous qualities of gels for dermatological use [3]. Topical gel delivery systems employ a variety of hydrophilic polymers, including carbopol 940, hydroxy propyl methyl cellulose (HPMC), and sodium alginate [4].

Nanosponge: Recently, a potential delivery mechanism in the pharmacological and cosmoceutical domains has emerged: nanosponges, a novel family of encapsulating nanoparticles [5]. These are virus-sized, sponge-like nanoparticles with a non-collapsible structure and a porous surface, with an average diameter of less than 1 μm [6, 7]. The definition of nanotechnology is the production and modification of materials at the nanoscale level to produce finished goods with unique characteristics. It comprises a range of formulations, such as nanocrystals, nanoparticles, nanocapsules, nanospheres, nanosponges, and nanosuspensions**.** Nanoparticles are available in different dosage forms such as polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, dendrimers, etc. Nanoparticles have applications like biocompatible materials, textile functionalization and coating against microbial degradation, drug delivery, DNA delivery, etc [8]. Nanosponges are small, innovative class colloidal structures that resemble microscopic meshes and are based on hypercrosslinked polymers. The core of these structures contains a wide range of medicinal compounds. Due to their inclusion and non-inclusion behaviour, they have been shown to have a spherical colloidal character and a very high solubilization capacity for antifungal medicines (drugs that are weakly soluble). They have just lately been created and suggested for the delivery of drugs. The nanosponges are roughly the size of viruses, with a naturally degradable polyester scaffold serving as their backbone [9]. The lengthy polyester stands are combined with cross-linkers, which are tiny molecules that have a preference for particular polyester segments, in a solution. The polyester is divided into segments and cross-linked to create a spherical shape with numerous pockets. of medications is able to be stored [10]. Topical hydrogels can also contain nanosponges, which have the advantage of better skin retention, less side effects, and less irritation when compared to traditional

topical delivery methods [11–14]. Thus, it is possible to view nanosponges as a futuristic delivery system that has great promise for the distribution of oral and topical medications. It has the ability to stabilise easily degradable chemicals, increase the solubility of lipophilic drugs, and transport active ingredients in a regulated way [6,14].

Advantages of nanosponges

- Boost the drug's aqueous solubility; • Allow the drug molecules to be released by nanosponges in a predictable manner.
- Bacteria cannot pass through the nanosponges' minuscule 0.25 µm pore size, which causes them to function as self-sterilizers.
- The drug delivery methods used by Nanosponges are non-toxic, non-mutagenic, and non-irritating.
- Nasosponges aid in the body's removal of poisonous and venomous substances.
- The Nanosponges medication delivery technology reduces adverse effects.
- Strengthen the formulation's stability and improve its adaptability.
- Lower the frequency of dose.
- Increased patient adherence [15–17].

Hydrogel: Water serves as the dispersing agent in networks of hydrophilic polymer chains, which make up hydrogels. These are networks of natural or artificial polymers that are very absorbent. Their highwater content also makes them fairly flexible.

These gels have distinctive physicochemical characteristics, such as:

- Hydrogel has strong mechanical qualities and resists breaking even after repeated exposure to pressures as high as 1 kPa.
- Absorbs large volumes of aqueous fluid (usually 100 times the original mass) while maintaining a three-dimensional structure.
- Hydrogel is incredibly flexible [18].

Method of Preparation

a. Solvent method

By combining the polymer with polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), nano sponges are created by the solvent method. Then, in a 1:4 ratio, a crosslinker is added to this mixture. To reflux the solvent's temperature for a duration of one to forty-eight hours, the aforementioned reaction should be carried out at a temperature of 10˚C. After the reaction is finished, the mixture is allowed to cool to room temperature, and the resulting product is then mixed with bi-distilled water. The product is recovered using vacuum-separated filtration, Soxhlet extraction with ethanol, and drying [19, 20].

b. Nanosponges prepared from hyper-cross linked β-cyclodextrins

Made from β-cyclodextrins, these nanoporous materials functioned as drug delivery carriers. As a result, three-dimensional networks are created, which could resemble a roughly spherical structure the size of a protein with interior channels and pores. using a cross linker, such as di-isocianates, diaryl carbonates, carbonyl di-imidazoles, etc., to react with cyclodextrin. The porosity and surface charge density of sponges determine their size and ability to adhere to various molecules. Depending on the cross linker employed, neutral or acidic nanosponges can be created. They are made up of solid particles that have been transformed into crystals. The ability of nanosponges to encapsulate drugs with varying solubility and shapes. They are employed to make medications that aren't very soluble in water more soluble in water [21].

c. Emulsion solvent diffusion method

In this method, different proportion or amount of ethyl cellulose and polyvinyl alcohol are used to prepare nanosponges. Two phases are used in this method–dispersed and continuous. The dispersed phase consists of ethyl cellulose and the drug, which is then dissolved in 20 ml of dichloromethane and some amount of polyvinyl alcohol (PVA) is added to 150 ml of the continuous phase (aqueous). Then, the mixture is stirred at the speed of 1000 rpm for about 2 h. The product i.e. the nanosponges are collected by filtration. Finally, the product is dried in an oven at a temperature of 400˚C [22].

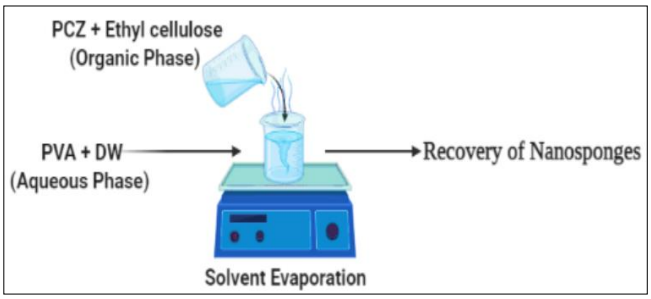

Fig 1: Emulsion Solvent Diffusion Method

d. Ultrasound-assisted method

The polymer ultrasonics junction is used in the ultrasound-assisted synthesis process. Polymer crosslinking results from ultrasonic vibrations, and crosslinking can be obtained without the use of any solvent. The polymer and crosslinker were mixed at a suitable molar ratio in a flask. The ultrasonication technique involved placing the flask in an ultrasound bath for five hours at a temperature of ninety degrees Celsius. After sonication, the temperature of the collected mixture was lowered. The product was then roughly separated and cleansed with an excessive amount of water to remove unreacted chemicals and polymer [23]. Using Soxhlet extraction, the cleaned solid was refined with ethyl alcohol. Prior to the next drug loading, the filtered NS was carefully processed, hoover dried, and stored [24].

Materials used in preparation of nanosponge

Table 1

Polymer	Co-polymer	Cross-linker
Hypercross-linked polystyrenes, cyclodextrin and its derivatives like methyl β-cyclodextrin, 2-hydropropyl β-cyclodextrin	Ethyl cellulose (EC), polyvinyl alcohol (PVA)	Di-phenyl Carbonate (DPC), diary carbonate, di-isocyanates, pyromellitic anhydride, carbonyl diimidazole, 22-bis (acrylamide) acidic acid and dichloromethane [25, 26]

Formulation of Nanosponge-Loaded Hydrogels

A gel-forming polymer, 1 gm of Carbopol 934, is submerged in 100 ml of water for a duration of 12 hours. After that, agitate the mixture using a magnetic stirrer to achieve a homogeneous dispersion. In order to release all of the trapped air, the dispersion is allowed to settle for fifteen minutes. Before being employed as a preservative, propylparaben is dissolved in enough water to warm it up. The pH of the polymer aqueous solution is then neutralised by adding triethanolamine drop by drop while continuously mixing [27].

Evaluation of nanosponges

a. Microscopic studies

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to examine a drug's or product's microscopic features. The development of inclusion complexes is indicated by the difference in the crystallisation state [28].

b. Loading efficiency

It can be found by quantitatively estimating the drug injected into the nanosponge using an HPLC technique or a UV spectrophotometer. One can compute the loading efficiency using [29].

$$Loading\ efficiency = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug}} \text{ X } 100$$

c. Zeta potential

The surface charge is determined by measuring the zeta potential. With particle size measurement equipment, it can be measured with an extra electrode [30].

d. Solubility study

approach that Higuchi and Connors describe that aids in figuring out how nanosponge affects the drug's solubility. The phase solubility diagram showed the degree of complexation [31].

e. Particle size and polydispersity

The particle size of a nanosponge formulation can be determined by dynamic light scattering using 90 plus particle sizer equipped with MAS OPTION particle sizing software. From the data obtained mean diameter and polydispersity index can be determined [32].

f. X-ray diffraction study

Powder X-ray diffractometry can be used to find the inclusion complexation for the solid state. The diffraction pattern of a newly produced material obviously differs from that of an uncomplicated nanosponge when the drug molecule is liquid and liquid has no diffraction pattern of their own. The complex development is indicated by this variation in the diffraction pattern. It is necessary to compare the diffractogram of the complex with that of the mechanical combination of the drug and polymer molecules when the drug compound is a solid**.** While the diffraction patterns of complexes appear to differ from those of their constituents and produce a new solid phase with distinct diffractograms, the diffraction patterns of physical mixtures are frequently the sum of those of each component. It is possible to ascertain the chemical breakdown and complex creation of a mixture of compounds by looking at their diffraction peaks. The drug's crystalline constitution and diffraction pattern are both altered by the complicated synthesis of the drug with nanosponge. Certain peaks change and others become sharper as a result of the complicated creation [33].

g. Infra-red spectroscopy

The primary use of this spectroscopic technique is to quantify the solid-state drug molecule-nanosponge interaction. When a complex forms, the bands of the nanosponge tend to fluctuate frequently, and if the proportion of guest molecules contained in the complex is less than 25%, the bands of the nanosponge spectrum readily obscure any bands that may be associated with the included portion of the guest molecules. The use of infrared spectroscopy is restricted to medications that have distinctive bands like sulfonyl or carbonyl groups. Studies of infrared spectra provide information about the role of hydrogen in different functional groups [34].

h. Thermo-analytical method

Thermoanalytical methods determine whether the drug compound changes before the Nanosponge heats up and breaks down. These modifications to the drug's composition could result via melting, evaporating, breaking down, oxidising, or going through a polymorphic transition, among other processes [35].

i. Dissolution test

The USP-II dissolving device can be used to investigate the dissolution properties of nanosponges (NSs). This is using a specially made container that rotates at 100 revolutions per minute (rpm) and is made of five metres of steel cable that is resistant to corrosion. The choice of dissolve medium guarantees the preservation of sink conditions, which is necessary to evaluate the bioactive substance's dispersibility. The available analytical techniques are then applied to the resultant samples for analysis [36].

Evaluation of hydrogel

1. Physical appearance

The prepared hydrogel formulation was evaluated for appearance and homogeneity by visual observation.

2. pH determination

A pH metre was used to measure the hydrogel's pH. In order to do this, one percent of the hydrogel is made in deionized water, and the pH was measured at 25 degrees Celsius.

3. Viscosity

The viscosity of the hydrogel formulation is measured with a Brookfield viscometer at 25 °C and 100 rpm spindle speed. Three copies of the viscosity determination were made [37].

4. Spreadability

Spreadability is a crucial component to take into account when creating gels. If the prepared gel has a moderate to low viscosity, the result will have a high spreadability; if the gel is excessively viscous, it will have a very poor spreadability. As a result, spreadability and viscosity have an inverse relationship. The produced nanosponge hydrogel formulation should have a spreadability between 2.150 ± 0.017 and 2.219 ± 0.009 cm [38].

Role of nanosponges for treatment of fungal infections

One of the most serious diseases in the world is fungus-induced skin infections [39]. Due to its many benefits, including the ability to target the exact site of infection and lessen systemic side effects, topical therapy is a popular option for treating coetaneous infections. A topical antifungal or pharmaceutical fungicide called econazole nitrate (imidazole) is used to treat vaginal thrush, ringworm, athlete's foot, jock itch, and tinea pityriasis versicolor. Econazole nitrate is accessible as cream, ointment, lotion, and solution across the market. When applied topically, econazole nitrate does not significantly adsorb; successful therapy requires a combination of highly concentrated active drugs. Because of this, econazole nitrate nanosponges were created using the emulsion solvent procedure and then injected into a hydrogel for topical distribution of the medication that would release over time [40, 41]. Another antifungal medication, itraconazole, belongs to class II of the biopharmaceutical classification system and has a low bioavailability and restricted dissolving rate. Therefore, the goal of this work was to make itraconazole more soluble in order to address the issue of bioavailability. Itraconazole's solubility can be enhanced in these nanosponges by loading it with itraconazole and using β-cyclodextrine that has been cross-linked with carbonate bonds [42].

Conclusion

Nanosponges have been recognized as drug delivery system to encapsulate or accumulate for both hydrophilic and lipophilic drug by forming a complex. They can effectively deliver the drug in a controlled manner at a target site. Nanosponge-based hydrogel formulations of antifungal drugs revealed a sustained released pattern of the antifungal drugs. This system provided potential benefits such as reduced frequency of application, leading to increased patient compliance because nanosponge-based hydrogel offered better drug retention ability and made antifungal drugs more efficient for the treatment of fungal infections topically.

Acknowledgment

The authors are thankful to Aicte New Delhi for providing the financial support during M. Pharm study tenure. also, thankful to the principle of Government College of Pharmacy, Karad for allowing to publish this article and gave us other facilities.

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