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Review Article

ASSESSMENT AND OUTCOME ON PREPARATIONS, CHARACTERIZATION OF TOPICAL TARGETED NANOSPONGE BASED DRUG DELIVERY: CRITICAL REVIEW

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ABSTRACT

The pharmaceutical Industry, and most of the drugs which come from synthetic chemistry possess poor water solubility and approximately 70% of drugs fall under such category. To improve solubility, drug absorption and bioavailability are a critical lookout for the formulation scientist. The current research activity for the development of dosage forms is concentrated on the development of particulate carrier systems such as microspheres and liposomes. Nanosponge is being prioritized to control the delivery of drug/APIs/phytoconstituents to particular the skin targetting. The drug delivery to skin can be prevented through the development of nanosponge. Topical nanosponge preparation can be delivered in the form of local anesthetics, anti-fungal, anti-acne, anti-wrinkle, etc. drugs. The present study highlights the developmental stages for the topical targeted nanosponge drug delivery. The review covers a different method of preparation, and evaluation of topical nanosponge drug delivery systems.

Keywords: Topical targeted, Nanosponge, Particulate drug delivery.

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INTRODUCTION

The pharmaceutical industry, most of the drugs which come through synthetic chemistry possess poor water solubility, and approximately 70% of drugs fall under such category [1]. Improving solubility, drug absorption, and bioavailability is a task for the formulation scientist.

To overcome solubility, absorption and bioavailability issues topical route is preferred, and novel formulations such as nanosponge have been found beneficial. It is made up of microscopic particles having a few nanometers wide cavities in which drug substances can be encapsulated [2] and possess carrying capacity for hydrophilic and lipophilic drug molecules [3].

Conventional topical drug delivery systems such as gel, cream, and ointments are found to be less effective for permeation through the skin. Due to their low effectiveness and unpredictable drug release, traditional topical methods such as ointments and creams are associated with unpleasant side effects such as burning, contact dermatitis, and stinging sensations. The development of particulate carrier systems such as microspheres and liposomes is being prioritized to control the delivery of medications to particular skin regions. These systems are expected to regulate drug input rate, reduce drug absorption into the systemic circulation, and minimize undesirable effect. Several studies have demonstrated that nanoparticle carriers can replace liposomal carriers to provide better cutaneous distribution. Nanosponges an excellent choice for the producing of topical medicines because of their enhanced cosmetic qualities, improved safety, and product stability. Nanosponges can safely contain a variety of topical medications for controlled release [4]. The skin makes up 15% of the adult body weight, making the biggest organ in the body. Skin is composed of three layers, that is, The Epidermis, Dermis, and subcutaneous layers. The outermost layer the epidermis a stratified, squamous epithelium layer composed of keratinocytes and dendritic cells called keratinocytes. It showed the function to synthesizing keratin. Epidermis also contains other cell populations such as melanocytes, Langerhans cells, and Merkel cells.

Collagen, a fibrillar structural protein, makes the middle layer of the skin that is Dermis. The Dermis is fibrous, filamentous, and amorphous connective tissue. The panniculus is a subcutaneous tissue that include tiny lobes of fat cells known as lipocytes, are placed on top of the dermis. Subceutaneous tissue is the innermost layer of the skin. The fat cells begin to develop in the subcutaneous tissue. These fat cell lobules, also known as lipocytes, are divided by fibrous septa comprised of collagen and large blood arteries. The hormones leptin is produced by lipocytes that, regulates body weight by way of the hypothalamus. From that skin structure, the nanosponge can pass into body [5].

Nanosponges can hold drug molecules and deliver them to specific sites or organs in a controlled release manner. Topical nanosponge preparation can be provided in the form of local anesthetics, anti-fungal, anti-acne, and anti-wrinkle types for dosage form [6]. The methods for preparing the Melt method, ultra sound assisted method, and cross-linking method [7]. Topical nanosponge formulation can be formulated for drugs/APIs such as cyclosporin B, Indomethacin, and fenofibrate. Most drugs for the formulation of nanosponge belong to the biopharmac classification system (BCS) Class II drugs and the drugs which possess extensive first-pass metabolism [8]. The nanosponge has the advantage of improved skin penetration of drugs. Nanosponges forming 3-dimensional networks or scaffolds developed using a suitable polymer [9]. These polymers can degrade naturally and are mixed with a cross-linker in a solution to form nanosponge [10].

Objectives of Nanosponge dosage form development include:

1. To enhance the solubility of poorly soluble drugs.
2. To increase the bioavailability of the drugs.
3. To increase, prolong, and control release of a drug.

Advantages

1. Nanosponge acts like a self-sterilizer.
2. Nanosponges increase solubility of lipophilic drugs. e.g., Celecoxib [1]
3. They help to reduce side effects.
4. Nanosponges help to remove toxic substances from the body.
5. Nanosponges increase the bioavailability of the drug. e.g., Erlotinib hydrochloride [11].
6. It reduces dosing frequency.
7. Nanosponges protects the molecule from degrading. e.g., Doxorubicin [12].
8. Nanosponges release drugs in a controlled manner.
9. These are free-flowing substances.

10. It increase stability of the drug, and this formulation stable over a pH range of 1-11. e.g., Econazole nitrate [13].
11. It can be cost-effective.

Disadvantages

1. Nanosponges encapsulate small molecules (< 500 Dalton),which is not suitable for larger molecules [14].
2. Nanosponges are loaded with drugs, These can affect the degree of crystallization.
3. It may cause dose dumping.

DRUG SELECTION FOR TOPICAL NANOSPONGES PREPARATION

Biopharmaceutical classification system shows the different classes, related to solubility, and permeability (Table 1). From that classes, we can easily divide a drug for making formulation.

Nanosponges improve the solubility of poorly soluble drugs. In the biopharmaceutical classification system, that class includes Class II (low solubility and high permeability). In that class, the solubility of drugs is poor, but it has high permeability, so the drug permeation through the skin is good. Due to this, it can be used for the topical preparation of nanosponges.

FACTORS INFLUENCES FOR PREPARATION OF NANOSPONGES

Type of polymer and cross-linker

Different types of polymer used in preparation can influence the formation and performance of nanosponges. Capable crosslinkers switch molecular nanocavities into three-dimensional nanoporous structures. Water-soluble or insoluble nanosponge structures are formed depending on the nature of crosslinkers [15]. There are two types of nanosponges, that is, hydrophilic and hydrophobic. Using the different concentrations of crosslinker, both the hydrophilic or hydrophobic nanosponge can be formulated for the delivery of active drug molecules [14].

In hydrophilic nanopsonges, epichlorohydrin is a cross-linker used for synthesis nanosponges which modulates the drug release rate and increases absorption of drug through biological barriers. Therefore, it can be used for immediate release formulations [16]. In hydrophobic nanosponges, cross-linkers include pyromellitic dianhydride, diisocyanates, carbonyldiimidazole, and diphenyl carbonate. These nanosponges function as carriers for water-soluble drugs to exhibit sustained or controlled release profiles, including proteins and peptides. The size of the nanosponge cavity should be large enough to entrap a drug [16].

Drug molecule

Drug molecules should be incorporated inside a nanosponge. The drug should possess the following characteristics.

a. The molecular weight of the drug molecule should be up to 400 daltons and molecular structure should consist of < 5 condensed rings.
b. The solubility of the drug in water is < 10 mg/mL.
c. The melting point of the substance should be under 250°C [14].

Temperature

Temperature changes can affect the complexation of the drug or nanosponge formulation. Increasing the temperature decreases the extent of the stability constant of the drug or the nanosponge complex, which may be due to the reduction of interaction forces such as hydrophobic forces and Van der Waal forces of drug/nanosponges with an increase in the temperature [14,16].

Table 1: Biopharmaceutical classification system

Class	Solubility	Permeability
Class I	High	High
Class II	Low	High
Class III	High	Low
Class IV	Low	Low

Degree of substitution

The ability of nanosponges complexation may get influenced by the number, position, and type of the substituent on the polymeric molecule. Kind of substitution like β-cyclodextrin derivatives is broadly available in various forms using differing functional groups present on the surface of cyclodextrin derivatives. When it is complexed together with a crosslinker, different types of complexed material (β-cyclodextrin nanosponges, cyclodextrin carbonate nanosponges, cyclodextrin-carbamate nanosponges). The degree of crosslinking and number of substitutions present is directly proportional to each other, therefore suggesting that a higher number of substituents could led to a greater probability of undergoing a higher degree of crosslinking that can yield highly porous nanosponges as an outcome of more interconnections between polymers, resulting in the mesh type network formation. Furthermore, the substitution position depends on the diverse conditions of system production. Changes in the process of production could lead to the formation of materials with different physicochemical properties due to the occupancy of varying positions by functional groups on the parent compound [15].

Method of preparation

The method employed for loading drugs into the nanosponge structure is dependent on the nature of the polymer, drug proportion, and cross-linker [16].

Methods for preparation of nanosponge:

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

Melt method

The basis for the melt method is to carry out a reaction with a cross-linker. All ingredients are put in a 250 ml flask and heated an elevated temperature, and stirred on a magnetic stirrer to proceed with the reaction. The prepared mixture is allowed to cool down and needs to wash by using a solvent. Repeated washing is required to remove unreacted excipient from the product (Table 2) [17].

Solvent diffusion method

In this technique, the organic and aqueous phase is used. In the organic phase, the drug and polymer are allowed dissolve. The aqueous phase and polyvinyl alcohol (PVA) is widely used. Aqueous phase is slowly added to the organic phase and kept on a magnetic stirrer for agitation. The formed product will be appropriately filtered and washed with a suitable solvent to remove unwanted excipients. Then allow it to dry in a vacuum oven to get a dried nanosponge/product [16] (Table 3).

Solvent evaporation method

In this method, nanosponges are prepared using drug and polyvinyl alcohol (PVA). Then, the organic phase was prepared by dissolving polymer in it. An aqueous phase was designed by using PVA and deionized water. After that organic phase was dropwise and slowly added into the aqueous phase for 3 min. Then, nanosponge was formed. Then, formed nanosponge was stabilized by PVA, which avoids particle agglomerations. Then, the dispersion was kept on a thermostatically controlled magnetic stirrer using continuous stirring at 1000 rpm under atmospheric pressure and temperature for 24 h. after complete evaporation of the organic phase, formed nanosponges were washed three times with ultra-purified water to remove the adsorbed PVA, it collected by ultracentrifugation at 4°C for 30 min [24] (Table 4).

Ultrasound-assisted synthesis

Ultrasound-assisted synthesis involves the reaction of the polymer with the drug is reacted with a crosslinker in the absence of solvent. In the process, sonication is also absent. In that, the polymer reacts with the

crosslinker in a flask and then places that the flask in an ultrasound bath previously filled with water, and heats it to 90°C for 5 h. The solution of the mixture is removed from ultrasound and taken to cool down at room temperature. Then, the product will be adequetly washed properly with a non-reacting solvent or non-reacting polymer and it need to filter properly to remove unwanted excipients. The product developed extracted with Soxhlet apparatus to redefine a product mixture. Then, it is dried under a vacuum [29] (Table 5).

Characterization of nanosponges

Solubility studies

The effect of nanosponge formulation on drug solubility is evaluated by the phase solubility technique. The Phase solubility method is described by Higuchi and Connors [29]. Phase solubility diagram indicates the degree of complexation. Solubility studies need to be performed to check the solubility at different pH conditions [19].

Microscopy studies

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are used for microscopy studies. These techniques are used to observe the morphological parameters such as size, shape, crystallinity, and surface topography of a plain drug and formulated nanosponge. Any variation in the crystallization state of the developed nanosponge can be easily detected through comparing it with the basic drugs by microscopic studies [29].

Particle size determination and zeta potential

Particle size determination is an critical parameter for the optimization of nanosponge. The drug solubility affects the particle size. Particle size is determined by the process of dynamic light scattering using 90 Plus, which is equipped with particle size-determining software. Dynamic light scattering (DLS) is a technique used to find out the size distribution profile of nanoparticles and mean particle size. The polydispersity index is an index of width within the particle size allotment. A higher polydispersity index indicates polydisperse particle size distribution, and a lower polydispersity Index monodisperse particle size distribution.

Zeta potential measures the surface charge from prepared nanosponges using a Malvern zeta sizer. Zeta potential can be defined as the difference of potential between two layers fluids (dispersion medium and

Table 2: Literature for nanosponge prepared using melt method

Drug	Excipients	Outcome	References
Gabapentin	Ethylcellulose, diphenyl carbonate, Polyvinyl pyrrolidine, xanthan gum, sucrose, talc, citric acid, and methylparaben	It shows a sustained release effect	[18]
Curcumin and caffeine	dimethyl carbonate (DMC), guar gum and Carbopol-934	Sustained drug release was achieved till the end of 12 h by preparing NS-based topical gel.	[19]
Econazole nitrate	β-cyclodextrin, N, N-carbonyl diimidazole (CDI), Carbopol 934, triethanolamine, methylparaben, propylene glycol, n-methyl-2-pyrrolidone	It works as a permeation enhancer.	[20]
Paracetamol, aceclofenac, caffeine	β -cyclodextrin, dimethyl carbonate, cross povidone	It enhances drug solubility.	[21]

Table 3: Literature for nanosponge prepared using solvent diffusion method

Drug	Excipients	Outcome	Reference
Luliconazole	sodium hydroxide, dichloromethane, triethanolamine, propylene glycol	Improve dermal availability of the drug	[9]
Econazole Nitrate	Ethylcellulose, polyvinyl alcohol, propylene glycol, dichloromethane, triethanolamine	Improve stability of the drug	[13]
Celecoxib	sodium hydroxide, five acetonitrile N, N-Dimethyl formamide (DMF), methanol	Improve solubility of the drug	[1]
Oxybutynin	polyvinyl alcohol, sodium dihydrogen phosphate, disodium hydrogen phosphate	Increased bioavailability of the drug	[22]
Sertaconazole Nitrate	ethyl cellulose and polymethyl methacrylate	Drug shows controlled release effect	[23]

Table 4: Literature for nanosponge prepared using the solvent evaporation method

Drug	Excipient	Outcome	References
Econazole nitrate	Ethylcellulose, polyvinyl alcohol, dichloromethane, and Carbopol 934	It shows extended-release effect.	[25]
Telmisartan	β-cyclodextrin, Diphenyl carbonate	Enhance solubility and bioavailability of drug	[26]
Lemon grass oil	Ethyl cellulose, polyvinyl alcohol, Carbopol 940	It shows a sustained release effect.	[27]
Efavirenz	β-cyclodextrin, sodium lauryl sulfate (SLS), and diphenyl carbonate (DPC)	It enhances the solubility and dissolution of the drugs.	[28]

Table 5: Literature for nanosponge prepared using ultrasound-assisted synthesis

Drug	Excipients	Outcome	Reference
Camptothecin	β-cyclodextrin, diphenyl carbonate	It increased stability and prolonged drug release kinetics.	[30]
Clobetasol propionate	Potassium dihydrogen phosphate, diphenyl carbonate, sodium chloride, and triethanolamine	It shows a controlled release effect.	[31]
Methotrexate	Diphenyl carbonate (DPC), β-CD, and Pluronic F-127	Drug intra-articular retention time improved by this method	[32]

Table 6: Current research in the formulation of the topical nanosponge-based topical targeted drug delivery

Drug	Excipient	Method of preparation	Result	References
Fluconazole	Ethylcellulose, polyvinyl alcohol (PVA), ethanol, carbopol-940, propylene glycol, and triethanolamine	Emulsion solvent diffusion method	The better retention ability of nanosponge, and improved patient compliance.	[4]
Butenafine Hydrochloride	Ethylcellulose, Polyvinyl Alcohol, Dichloromethane, and Carbopol 934P	Emulsion solvent evaporation technique	It improves the therapeutic efficiency of the drug in the target site deeper into the skin layers to completely eradicate of fungal infections.	[24]
Clobetasol propionate	Carbopol 934 and diphenyl carbonate, Sodium chloride, and triethanolamine.	Ultrasound-assisted method	Significant pharmacological action and epidermal thickness change were discovered.	[31]
Curcumin and Caffiene	Dimethyl carbonate (DMC), guar gum, and Carbopol-934	Hot melt method	NS in topical gel show therapeutically better effects in treating psoriasis than the conventional marketed formulation	[19]
Lapatinab and Saquinavir	Ethylcellulose, polyvinyl alcohol, Methanol, and Acetonitrile	Emulsion solvent diffusion method	To enhance its aqueous solubility and bioavailability.	[37]
Terbinafine Hydrochloride	Polyvinyl alcohol, ethylcellulose, Dichloromethane, Tween 80, Carbopol 940, and Ethanol	Emulsion diffusion method	It enhanced skin retentivity	[38]
Econazole nitrate	β-cyclodextrin, N, N-carbonyl diimidazole (CDI), Carbopol 934, triethanolamine, methylparaben, propylene glycol, n-methyl-2-pyrrolidone	Melt method	It improves skin permeation and the stability of the drug.	[13,20]
Lemon grass oil and ethyl cellulose	Polyvinyl alcohol (PVA), Mowiol® 40–88 and cabal-940	Emulsion solvent evaporation method	It enhanced the antifungal effect and decreased irritation.	[27,40,41]
Luliconazole	Ethylcellulose, Poly vinyl alcohol, DMSO Carbopol 940, HMPC, sodium alginate, acacia, methyl Paraben, propyl Paraben	Emulsion solvent diffusion method	It improved therapeutic effect, better dispersibility, and storage	[42,43]
Wrightia tinctoria	Dimethyl carbonate and Carbopol	Melt method	It shows sustained release activity	[44-47]
Flurbiprofen	Ethylcellulose, polyvinyl alcohol, dichloromethane, carbapol	Solvent diffusion method	It improves the controlled release of drug.	[48,49]
Doxorubicin	Ethylcellulose and Poly methyl methacrylate	Emulsion solvent evaporation method	It increases the drug solubility, and increase the drug permeability,	[50]
Lansoprazole	Ethylcellulose, Polyvinyl alcohol, Dichloromethane, HPMC	Emulsion solvent evaporation method	It reduces gastric activity and increase extended-release.	[51,52]
Posaconazole	Ethylcellulose, polyvinyl alcohol (PVA), and dichloromethane	emulsion solvent diffusion method	Drug released in a controlled fashion and also to enhance the bioavailability.	[53-55]
Lornoxicam	Polyvinyl alcohol (PVA) and dichloromethane, ethyl cellulose, Carboxyl methylcellulose sodium	Emulsion solvent evaporation method	It improved and controlled the effect of the topical application	[56-58]
Ketoconazole	β-cyclodextrin and Carbopol 940	Emulsion solvent evaporation method.	It shows sustained release.	[59-61]
Oxiconazole nitrate	Ethylcellulose, β- cyclodextrin	emulsion solvent diffusion method	It enhances the drug efficacy, bioavailability, reduce toxicity, and improves patient compliance.	[62,63]
Celecoxib	β- cyclodextrin, Dimethyl carbonate and Carbopol	Melt technique	It shows sustained release of the drug.	[64]
Besifloxacin Hydrochloride	Ethylcellulose, polyvinyl alcohol	Emulsion solvent evaporation technique	It exhibited sustained release and significant anti-microbial activity.	[64-66]
Resveratrol and carbonyl diimidazole	β-cyclodextrin, anhydrous dimethylformamide (DMF)	Emulsion solvent evaporation method.	It increases the solubility, stability, and permeation.	[67-71]
Etodolac	Ethylcellulose, dichloromethane	Emulsion solvent diffusion method.	Improved bioavailability of the drug	[72,73]
Voriconazole	Poly methyl methacrylate, Ethyl Cellulose, Poly Vinyl Alcohol, Dichloromethane, Triethanolamine, Carbopol 971P, and N-methyl-2- pyrrolidone	Emulsion solvent evaporation technique	Good potential for prolonged drug release	[74,75]
Cinnamon oil	Polyvinyl alcohol (PVA), Carbopol 940, and ethylcellulose	emulsion solvent diffusion technique.	effective, stable topical dosage form with improved and sustained release characteristics	[76,77]
Tazarotene	β-Cyclodextrin and diphenyl carbonate	Freeze drying technique	It shows controlled drug release, better skin permeation, and good storage stability.	[78]

(Contd...)

Table 6: ***(Continued)***

Drug	Excipient	Method of preparation	Result	References
Tenoxicam	Ethylcellulose, polyvinyl alcohol, dichloromethane, Carboxyl methylcellulose sodium	Emulsion solvent evaporation method	It improved and controlled TX release for 6 h.	[57,79]
Tizanidine Hydrochloride	β-cyclodextrin, diphenyl carbonate, DMSO, Triethanolamine, Carbopol 934, Propylene Glycol, and alcohol	Emulsion solvent evaporation method.	It improves the solubility and bioavailability.	[80,81]
Lovastatin	Ethylcellulose, Polyvinyl alcohol, βcyclodextrin, Pluronic F68, Hydroxy Propyl β- cyclodextrin	Emulsion solvent diffusion method	It improves bioavailability and increases the effectiveness of the drug.	[82,83]
Tamoxifen	Ethylcellulose, Polymethyl methacrylate, Polyvinyl alcohol, Dichloromethane, Dimethyl sulfoxide,	Emulsion solvent diffusion method	It shows Sustained release of the drug, increased the drug solubility, and increases the drug permeability.	[84]
Etoricoxib	Ethylcellulose (EC) and polyvinyl alcohol	Emulsion solvent diffusion method	It increases solubility of the drug	[85-87]
Benzoyl peroxide	HPMC K4M, Eudragit S100, Eudragit RL100 dichloromethane, EthylCellulose, and Poly Vinyl Alcohol	The Quasi-emulsion solvent diffusion method	It improves stability of the drug.	[88,89]
Lamotrigine	Ethylcellulose, polyvinyl alcohol	Emulsion solvent diffusion technique	It enhances the solubility and dissolution rate	[90]
Gliclazide	Polyvinyl Alcohol (PVA), Dichloromethane (DCM), Triethyl citrate	Emulsion solvent diffusion method.	It improves the dissolution and bioavailability profile of the poorly water-soluble drug.	[91-94]
Dasatinib	β-Cyclodextrin, Polyvinyl alcohol (PVA), Poloxamer, Ethyl Cellulose, Dichloromethane	Solvent evaporation technique	It improves efficacy of the drug.	[95,96]

immobile layer) locked up with dispersed particles. The seta potential is the primary key that indicate the stability of the colloidal dispersion. The higher the value of zeta potential of a colloidal dispersion more is its stability. Samples to be analyzed were suitably dispersed in double distilled water a clear disposable zeta cell. Zeta potential in water should be about ± 30 mV [24,33,34].

XRD and DSC

XRD studies help in determining the crystallinity and polymorphism, if any for the drug. In general, the metastable or amorphous form of medicine dissolves quicker when compared to the crystalline form due to more tremendous internal energy and molecular motion. The complex formation of the drug with nanosponges alters the diffraction patterns and changes the crystalline nature of the drug. The XRD pattern of the sample is determined as a function of the scattering angle [35]. The thermal properties of nanosponge formulation were determined on the DSC instrument by synchronization method. Analyses are carried out by DSC instrument to assess the interaction pattern, crystallinity, and nature of the developed nanosponges [36]. The thermogram can be analyzed for broadening, shifting, and appearance or disappearance of specific peaks.

Drug loading efficiency

The drug loading efficiency of nanosponge particles can be determined by the quantitative estimation of the drug loaded into nanosponges by Ultraviolet (UV) spectrophotometer and high-performance liquid chromatography (HPLC) methods. Drug loading deals with nanoparticles after their separation from the medium and to estimate their drug content [29]. Drug loading efficiency (%) of nanosponges can be calculated by the following equation [22].

$$\text{Drug loading efficiency}(\%) = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} \times 100$$

Production yield

The production yield of nanosponges by measuring initial weight of raw material and the final weight of nanosponges is determined by this formula [32]:

$$\text{Production yield} = \frac{\text{Practical mass of nanosponges}}{\text{Theoretical mass}\left(\text{drug} + \text{polymer}\right)} \times 100$$

Entrapment efficiency

Entrapment efficiency means the amount of drug successfully trapped into nanosponge particles. The entrapment efficiency was determined through centrifugation with methanol at 10,000rpm for 30 min [37]. The concentration of the drug was determined using a UV spectrophotometer. The percentage of drug entrapment is calculated by [31]:

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Porosity

The porosity study checks the extent of nanochannels and nanocavities formed in nanosponges. Porosity is assessed using a helium pycnometer; Hence, helium gas can penetrate inter- and intra-particular channels of material. The actual volume of material is determined by helium displacement method [35].

Percent porosity is given by the following equation:

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

FTIR spectroscopy

FTIR is used to determine possible functional groups present in the structure. Fourier transform infrared spectroscopy quantifies the interaction between drug molecules, drugs with excipients, and any changes in the prepared nanosponge formulation [35].

Characterization of topical nanosponges

pH determination

pH meter is used to determine the pH of the formulation. A digital pH meter is used to determine the nanosponge gel. If slight deviations in pH were noted, it was adjusted to skin pH using the dropwise addition of triethanolamine solution [38].

Viscosity determination

Viscosity was measured using a Brookfield viscometer [31]. In that the spindle was dropped down vertically into the formulation but in such a way that the spindle did not contact the container. The spindle was rotated at chronological speed from 0.5 to 100 pm, followed by viscometer measurements after 1 min. And record the stable reading and note it down [39].

Determination of spreadability

Take a glass slide with having length of 7.5 cm. Then draw a 1cm circle on glass plates and put the formulation on the glass slides. The different weights, that is, 15, 20, 30, 50, 70, 100, 150, and 200 (gm), were allowed to rest on the formulations, respectively, for 1 min, resulting in spreading of the gel on the glass slide. The extension is measured using a linear scale [20].

$$\text{Spreadability} = \frac{\text{Weight} \times \text{Length}}{\text{Time}}$$

Skin irritation test

Acute skin irritation was evaluated on the albino Wistar rats by guidelines, and permission was taken from the institutional animal ethics committee (IAEC). These rates are shaved before 24 hr of formulation application. Three experimental groups of rats are arranged randomly in that Group I for control, Group II for optimized formulation, and Group III for marketed formulation. In that formulation applied to the dorsal side at 4cm^2 length. Then leave it for 24 h, 48 h, and 72 h. Then observe the rashes or red patches on the skin. With this method, skin irritation test was done [38].

Texture analysis

Texture analysis can be checked in gel formulation. It provides information related to the hardness, cohesiveness, and adhesiveness of prepared gel formulations. The research based on the probe at a predefined force, depth, and analysis [31].

Drugs used for topical preparation of nanosponges are as follow

The following table highlights the excipient used, various methods of preparation of nanosponge, and outcome of the research work is carried out by multiple researchers (Table 6).

CONCLUSION

Nanosponges are nano-sized colloidal barriers, so easily penetrate the skin. Nanosponge-based drug delivery was found to be excellent for the poorly soluble drugs, and for medicines which possess extensive first-pass metabolism. For targeting of the drug (lipophilic or hydrophilic) and to achieving desired drug release in a predictable manner, nanosponge was found to be excellent.

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AUTHORS CONTRIBUTION

The review paper was combined the efforts and contributions of all authors.

CONFLICTS OF INTEREST

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