

Novel nanocarrier: A research article's review on nanosponges

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Abstract

The process of modern medication delivery system development is smooth. Any delivery method that directs a molecule to a specific place is always valued. A specialised drug delivery system can easily target the medicine at the site of action without sacrificing its efficacy and quality, satisfying this criterion. Most novel medications can be administered effectively using a conventional dose form. Benefits from localised, focused distribution of therapeutic substances are thus additional factors influencing the current situation. With the introduction of nanosponge technology, systemic toxicity and extreme reactions can be reduced by helping the drug release gradually and in a controlled manner. With cavities that can be filled with a wide range of hydrophilic and hydrophobic drugs, nanosponges, which are tiny sponges about the size of a virus (250 nm-1µm), can be further incorporated into a pharmaceutical dosage form such as oral, parenteral, topical, or inhalation. The discovery of nanosponge has proven to be a significant stride in the fight against issues including patient unacceptability, medication toxicity, poor bioavailability, and physiochemical instability. There are six different methodologies for the preparation of the nanosponges which follows a particular mechanism for the release of the drug from it. Further, the nanosponges can be subjected to several characterization.

Keywords: Characterization; Mechanism; Methodology; Nanosponges; Target Site

1. Introduction

Researchers have long struggled with how to deliver medications to the correct location in the body while also controlling the drug's release to avoid overdosing. The development of novel, intricate molecules known as nanosponges has the potential to address these issues. A new class of materials called nanosponges is formed of small particles with cavities only a few nanometres wide that can contain a wide range of chemicals. Nanosponges are porous structures with a diameter of one micrometre that resemble sponges and have a three-dimensional network structure. Numerous different medications can be used to fill these nanosponges. When they come across the precise target place, these nanoscale small sponges can wander throughout the body until they cling to the surface and start to release the medicine in a controlled and predictable manner. Drugs that are both lipophilic and hydrophilic can be transported effectively to a target spot using nanosponges. The porous outer surface of nanosponges allows for regulated release, yet optimising the drug's particle size and ensuring controlled drug release on a wide scale are difficult features to implement. By adjusting the polymer-cross linker ratio, drug release can be modified(1). The best drug compounds to manufacture into nanosponges are those with molecular weights between 100 and 400 Da, a water solubility pattern of less than 10 mg/ml, a melting point below 250°C, and a ring count of no more than five condensed rings. Nanosponges can be prepared by using Melt Method (MM), Emulsion solvent diffusion method, Quasi emulsion solvent diffusion method, emulsion solvent evaporation method, ultrasound assisted method and hyper cross-linked β-cyclodextrin method.

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1.1. Features of nanosponges(2)

- The key advantage of these small structures is their aqueous solubility, which encourages the distribution of less soluble medications throughout the body.
- They possess a very amphoteric character and are capable of containing even lipophilic and hydrophilic moieties.
- Similar to a nano mediator for delivering medication molecules for biological purposes, they aid in the removal of pollutants from water.
- They are less poisonous and have greater trapping abilities.
- They are more elegant, more stable, and have the right amount of flexibility.
- They assist in reducing irritation and are neither carcinogenic nor allergenic in nature.
- By adding an immiscible liquid, they can be employed as materials for extended or even continuous release for 12 or 24 hours.
- Even the transformation of liquid into powder produces particles that are spherical and submicron in size.
- They have improved shelf life, better stabilization, and protection from oxygen and air. Depending on the medicine dose, they have more therapeutic properties.

1.2. Types Of Nanosponges(3)

- Beta - Cyclodextrin Based nanosponge
- Carbon - coated Metallic Nanosponges
- Silicon nanosponge particles
- Hyper cross - linked Polystyrene Nanosponge
- Titanium Based Nanosponges

1.3. Advantages(1)

- This method provides ingredient trapping and minimizes negative effects.
- Enhanced formulation flexibility, increased elegance, and improved stability.
- These compositions maintain their stability from PH 1 to 11.
- These formulations are compatible with most vehicles and ingredients and are stable at temperatures up to 130°C.
- Since bacteria cannot pass through their 0.25 nm average pore size, these are self-sterilizing.
- Both the bioavailability and the solubility of poorly soluble drugs are improved.

1.4. Disadvantages(1)

- Nanosponges include only small molecules.
- Depend only upon loading capacities.

1.5. Chemicals used for the synthesis of nanosponges

The important materials used in the synthesis of nanosponges are

- **Polymers:** Hyper cross-linked polystyrenes, methyl β -cyclodextrin, alkyloxy carbonyl cyclodextrin, 2-hydroxy propyl β -cyclodextrin, α -cyclodextrin, β -cyclodextrin.
- **Co-polymers:** Poly (δ -valerolactone-co-allyl- δ -valerolactone), poly (methyl methacrylate) (PMMA), poly vinyl alcohol, hydroxyl propyl methyl cellulose, ethyl cellulose.
- **Apolar solvents:** Ethanol, methanol, dimethylformamide, dimethyl sulfoxide, dimethylacetamide.
- **Cross-linkers:** Diphenyl carbonate, diaryl carbonate, hexamethylene diisocyanate, carbonyl diimidazole, carboxylic acid dianhydride, toluene-2,4-diisocyanates, epichlorhydrin, pyromellitic anhydride, dichloromethane, poly amido amine.

2. Methodology(3)

2.1. Methods Of Preparation of Nanosponges

- Emulsion Solvent Evaporation Method
- Quasi- Emulsion Solvent Diffusion Method
- Emulsion Solvent Diffusion Method
- Melt Method
- Ultra- Sound Assisted Synthesis Method
- Hyper Cross-linked β Cyclodextrin Method

2.1.1. Melt method

The desired quantity of β - cyclodextrin, 100mg of Drug and barium carbonate was taken in a China dish. The hot air oven which is previously heated (60°C - 70°C) and this mixture in a China dish is placed in it for 1 hour. PVA taken in a 100ml of distilled water is heated in a water bath until it forms a clear solution. To a continuous mixing in a magnetic stirrer at 70°C, 10ml of the cooled PVA solution is added slowly to the China dish taken from the hot air oven. As the solution evaporates, it forms a semi-dried mass, and it is collected using a spatula and the sample used for further studies.

2.1.2. Ultrasound- assisted synthesis method

To a Drug- methanol solution was taken. A beaker of β - cyclodextrin, 0.75ml of glutaraldehyde is added. This is placed in a ultrasonicator at 40°C and the Drug is added slowly and continued for 2 hours. The turbidity is formed, and it is filtered, and the product is washed with distilled water. The NS formed is dried in a Hot air oven at 60°C for 30min until a powdery substance is obtained.

2.1.3. Emulsion solvent evaporation method

The method involves 2 phases: an organic phase and an aqueous phase. The organic phase consists of a specific quantity of Drug, with 100mg of Ethyl Cellulose and 20ml of Dichloromethane (DCM) in a beaker. For Aqueous phase, the required quantity of Poly vinyl alcohol powder is added to 100ml of distilled water. The aqueous phase is placed in a digital mixer and rotated with a speed of 1000rpm to 2000rpm while adding the organic phase drop wise using a syringe slowly for about 2 hours. Then the dispersion medium was kept on a thermostatically stabilized magnetic stirrer and the solution is allowed to evaporate slowly under constant stirring until the solution is completely evaporated. The product of nanosponges is collected and stored in an airtight container.

2.1.4. Emulsion solvent diffusion method

To prepare the organic phase, a specific quantity of Drug is mixed with Ethyl Cellulose in 20ml of Dichloromethane (DCM) in a beaker. For Aqueous phase, the required quantity of Poly vinyl alcohol is dissolved into 100ml of distilled water, with the help of a water bath at 60°C – 70 °C until a clear solution is formed. After the solutions of both phases were prepared, the aqueous phase is placed in a digital mixer and rotated with a speed of 1000rpm while adding the organic phase drop-wise using a syringe slowly for about 2 hours. Then the dispersion medium was kept on a thermostatically stabilized magnetic stirrer and the solution is allowed to evaporate slowly under constant stirring until the solution is completely evaporated. The resulting dispersion is then filtered using a filter paper and the residue is then dried in a China dish using hot air oven at 40°C - 50°C for 2 hours. The final product is packed and stored in airtight container.

2.1.5. Quasi emulsion solvent diffusion method

A specific quantity of Eudragit RS 100 polymer is mixed with Drug alongside with Dichloromethane (DCM) in a beaker. In another beaker, Poly vinyl alcohol powder in 100ml of distilled water. The solution of the scopolamine is added slowly drop-wise using a syringe which is kept in a digital mixer and rotated with a speed of 1000rpm for 3 hours. The solution is then filtered and the nanosponges obtained is then dried in a hot air oven for 30 minutes and stored in an airtight container.

2.1.6. Hyper cross-linked beta-cyclodextrin method

Nanosponges were prepared using hyper cross-linked β -cyclodextrin method using different concentration of cross-linker. In this method, anhydrous Dimethyl sulfoxide was placed in round bottom flask and anhydrous β -cyclodextrin was added to achieve complete dissolution.

Then diphenyl carbonate was added and the solution was allowed to react for 4 h at 100°C. Once the condensation polymerization was completed, the transparent block of hyper-cross-linked β -cyclodextrin was roughly ground and excess of deionized water were added to remove Dimethyl sulfoxide. Finally, residual by product or unreacted reagent was completely removed by Soxhlet extraction with ethanol, the white powder thus obtained was dried overnight in an oven at 60°C and subsequently ground in a mortar. The fine powder obtained was dispersed in water. The colloidal part that remained suspended in water was recovered and lyophilized.

2.2. Mechanism of drug release from Nanosponges(3)

The nanosponges particles have an open structure; the active constituent is free to move in and out of the particles into the vehicle until the equilibrium is reached when the vehicle becomes saturated. When the product is applied to the skin, the active constituent already present in the vehicle becomes unsaturated, disrupting the balance. This will initiate the flow of active substance from the nanosponges particle into the vehicle, which will then be applied to the skin until the vehicle has dried or been absorbed. The sponge particle matter that remains on the skin surface (Stratum Corneum) will continue to distribute the active ingredient to the skin even after the vehicle has dried. As a result, the action of the release is prolonged. Even after that, nanosponges particles maintained on the stratum corneum's surface will progressively release active substance to the skin, resulting in a protracted release. If its ingested orally or given parenterally, it releases the drug in a controlled and sustained manner to the site of action. Based upon the type of polymer used it may undergo a diffusion or the dissolution of the drug from its core matrix. The nanosponges being porous in nature the drug molecules which is entrapped inside comes out in a sustained manner.

2.3. Factors influencing Nanosponge formulation(1)

2.3.1. Type of polymer

The performance of nanosponges as well as their production can be influenced by the type of polymer utilised. The cavity size of nanosponges should be suitable to accommodate a drug molecule of a specific size for complexation.

The substance's melting point is below 250°C.

2.3.2. Type of drugs:

To be complexed with nanosponges, drug molecules must Weights of molecules range from 100 to 400. There are less than five condensed rings in drug compounds. Water has a solubility of less than 10 mg/ml.

2.3.3. Temperature

Changes in temperature can impact how well drugs and nanosponges interact. In general, as temperature rises, the strength of the drug/nanosponges complex's apparent stability constant tends to diminish. This could be because drug/nanosponges contact forces such van der Waal and hydrophobic forces may be reduced as a result.

2.3.4. Method of preparation

The way the drug is loaded onto the nanosponges can impact how the drug and nanosponges are complexed. Freeze drying has been proven to be the most effective approach for drug complexation in many circumstances, albeit the efficiency of a method depends on the nature of the drug and polymer.

3. The overview of different literature reported on the nanosponges prepared using various methods are briefly discussed in this study

Mohammed Muqtader Ahmed *et al.*, reported on the Ribociclib-Loaded Ethylcellulose-Based Nanosponges: Formulation, Physicochemical Characterization, and Cytotoxic Potential against Breast Cancer. Ethylcellulose-based ribociclib-loaded nanosponges (RCNs) were prepared using an emulsion-solvent evaporation approach. The polymers used for the preparation of nanosponges are ethylcellulose and polyvinyl alcohol and organic solvent like methylene chloride were added to produce nanosponges. The prepared nanosponges were evaluated by the following techniques like particle size, polydispersity index, zeta potential, drug entrapment loading estimation, FTIR Spectroscopy,

Differential Scanning Calorimetry, X-Ray Diffraction (XRD) Analysis, Morphology by Scanning Electron Microscopy (SEM), *In-Vitro* Drug Release Studies, MTT Assay, Apoptosis Studies by the Annexin V-Propidium Iodide Method, Statistical Analysis. The results obtained after evaluation for particle size were measured in the range of 363.5 ± 4.8 – 734.9 ± 3.1 nm, the drug release value was found to be $57.02\% \pm 0.56$, zeta potential was found to be 18.5 ± 0.05 mV and Entrapment Efficiency is $81.35 \pm 1.64\%$, PDI and ZP values of 0.292 ± 0.012 , and -18.5 ± 0.05 mV, respectively and overall ribociclib-loaded ethylcellulose nanosponges could be a potential nanocarrier to enhance the effectiveness of ribociclib in breast cancer treatment(4).

Lakshmi Devi G et al., had developed Formulation and development of Losartan nanosponge capsules. This nanosponge capsules were prepared by using solvent evaporation method and the preparation of nanosponge was done by using the following polymers and organic solvents and they are β cyclodextrin, HP β -cyclodextrin, polyvinyl alcohol and ethanol. The prepared nanosponges were evaluated by the following techniques like Particle size, Morphology determination by scanning electron microscopy (SEM), Entrapment efficiency, *In-vitro* dissolution studies and FTIR. The nanosponges were evaluated by different techniques and reported and the average particle size of all formulations ranges from 316.4 nm to 454.8 nm which is in increasing order due to the increase in the concentration of polymer. *In-vitro* drug release was found to be 98.24 % in 12 hours. The entrapment efficiency of formulation was found to be in the range of 86.59 to 101.26%. FTIR spectroscopy is used to identify organic, polymeric and inorganic materials of the drug in these nanosponges. Scanning electron microscopy used to identify the spherical nature of the nanosponge in all variations. Then by this Losartan is a BCS class II drug, having a half-life of 1.5-2.5 hours, which wasn't suitable for maintaining constant plasma concentrations. So, Losartan was formulated as a Nanosponge formulation for effective drug release(5).

Mohammed Muqtader Ahmed et al., reported on the Formulation and *in-vitro* evaluation of topical nanosponge-based gel containing butenafine for the treatment of fungal skin infection. BTF loaded NS were prepared by the emulsion solvent evaporation technique using the drug and polyvinyl alcohol, ethyl cellulose and dichloromethane. The evaluation parameters like Particle characterization and zeta potential, Measurement of entrapment efficiency, drug loading, PDI, Fourier transform infrared spectroscopy, Differential scanning calorimetry and Scanning electron microscopy, Drug diffusion, Stability studies, Release kinetics were done. The nanosponges showed size in the range of 310 ± 0.16 nm to 808 ± 0.32 nm and the gel exhibited $89.9 \pm 0.15\%$ drug release sustained for up to 24 h. The Entrapment Efficiency and zeta potential was found to be $71.3 \pm 0.34\%$ and -33.8 ± 0.89 mV respectively. The PDI value and % drug loading was found to be 0.330 ± 0.02 and $22.8 \pm 0.67\%$ respectively. By the reported values, therefore topical gel could be considered as a potential DDS in the treatment of skin-related fungal infections(6).

B. Raja Narendra et al., reported on the Formulation and Evaluation of Anticancer Drug (Doxorubicin) Loaded Nanosponges. The purpose of this research was to prepare Doxorubicin loaded Nanosponge gel for Sustained release of drug, increase the drug solubility, and increase the drug permeability, to reduce the dosing frequency and side effects. Doxorubicin Nanosponges were prepared by Emulsion solvent evaporation method. The polymers used for the preparation of nanosponges are Ethyl cellulose, Polymethyl methacrylate, Dichloro methane, Polyvinyl Alcohol. The prepared nanosponges were evaluated by the following techniques like particle size, Determination of drug content, Determination of drug entrapment efficiency, FTIR, *in-vitro* release studies, Kinetic drug release and Stability study for gel. The results obtained after evaluation for particle size were measured in the range of 370.3nm and the *in-vitro* release of the formulations was observed to be between 15.53% to 45.66%. Entrapment efficiency of the formulations was observed to be from 97.85 to 99.21%. The FTIR studies proved that there was no interaction between the drug and Polymers. Cyclo-octa-amylose -based Nanosponges can be watchful a challenging knowledge preordained for the spreading out of pioneering phrasings, suitable for a variety of management direct for anti-cancer drugs(7).

Chodvadiya Chandrika Upendra et al., have reported on the Topical Nano sponge Gel: New Hope (Tachrolimus). The purpose of this research was to show that the topically applied tacrolimus appears to penetrate the skin sufficiently to effect local immunosuppression. Nano sponge of Tacrolimus was prepared by Emulsion Solvent Evaporation Method using the drug and Ethyl cellulose, Dichloro methane, Polyvinyl Alcohol and Carbopol 938. The evaluation parameters like Particle characterization, SEM, Measurement of entrapment efficiency, FTIR, DSC, and *in-vitro* release studies were performed. The nanosponges showed size in the range of 520-580 nm and highest entrapment efficiency is 80.09%. and the maximum drug release 84.52% in phosphate buffer Ph 6.8. and the results of FTIR and DSC shows that there was no significant change has been observed in chemical and physical properties of Tacrolimus and tacrolimus is compatible with excipients. Topical tacrolimus inhibits experimentally induced allergic contact dermatitis, and preliminary studies have suggested that the drug is effective in the treatment of atopic dermatitis(8).

Umesh et al., reported on the Formulation and evaluation of nanosponge gel containing ketoconazole. Nanosponges were prepared using hyper cross-linked β -cyclodextrin method using different concentration of cross-linker using the

drug, β cyclodextrin, Diphenyl carbonate, DMSO, Ethanol. The evaluation parameters like Particle characterization, zeta potential, Measurement of entrapment efficiency, drug loading, Fourier transform infrared spectroscopy, Differential scanning calorimetry and Scanning electron microscopy were done. The nanosponges showed size in the range of 78.81 ± 0.20 nm – 336.02 ± 0.124 nm. The drug release from nanosponges was found to extend up to 8 h 82–92%. It was found that the DL of the ranged from 39.2 ± 0.22 to $87.3 \pm 0.45\%$ w/w. EE of batches ranged from 22.37 ± 0.25 to $82.71 \pm 0.71\%$ w/w. The percent of ketoconazole release from nanosponge formulation after 8 hrs is 82 to 92% and the prepared nanosponges were made into Gel and evaluation parameter were performed. A sustained release topical drug delivery of ketoconazole developed as a nanosponge loaded gel offers solubilizing matrix for the drug, served as a local depot for sustained drug release, and provided a rate limiting matrix barrier for modulation of drug release(9).

Shankar Swaminathan et al., reported on the Formulation of beta cyclodextrin based nanosponges of itraconazole. Nanosponges were prepared using hyper cross-linked β -cyclodextrin method using different concentration of drug and copolyvidonum. The prepared nanosponges were evaluated by the following techniques like particle size, *in-vitro* drug release, Differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and photon correlation spectroscopy (PCS). The nanosponges showed size in the range of 275–300 nm and drug release were found to be of 71.5%. It was found that the dissolution was fastest in case of ternary complex as compared to binary complexes of nanosponge. Due to more solubilization, the bioavailability of itraconazole can be expected to be more as compared to plain drug. Thus, the objective of the work was achieved using a ternary system of nanosponges and copolyvidonum(10).

S. S. Darandale et al., reported on the Cyclodextrin-based nanosponges of curcumin: formulation and physicochemical characterization. Nanosponges were prepared using hyper cross-linked β -cyclodextrin method using different concentration of drug, Dimethyl carbonate, Dimethyl formamide and ethanol. The prepared nanosponges were evaluated by the following techniques like particle size, *in-vitro* drug release, Photomicrographs, zeta potential, Fourier transformed infra-red (FT-IR) spectroscopy, X-ray powder diffraction and Differential scanning calorimetry (DSC). The particle size analysis by DLS study showed that the nanosponges have average particle size of 487.3 nm and *In-vitro* release study of curcumin from formulation showed sustained drug release and a release of about 25%. The zeta potential of the formulation was found to be (-27 mV). Then it can be concluded that cyclodextrin-based nanosponges of curcumin offers a potential drug delivery system for curcumin in cancer treatment(11).

D. Lembo et al., reported on the Encapsulation of Acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. Nanosponges were prepared using hyper cross-linked β -cyclodextrin method using different concentration of drug, fluoresceine isothiocyanate, carbonyl diimidazole and ammonium acetate, ethanol and DMF. The prepared nanosponges were evaluated by the following techniques like particle size, *in-vitro* drug release, TEM, zeta potential, Fourier transformed infra-red (FT-IR) spectroscopy, Differential scanning calorimetry (DSC) and biological studies were evaluated. NS were spherical in shape with a mean diameter of approx. 400 nm. The percentages of Acyclovir released from Carb-NS and NS after 3 h *in-vitro* were approx. 22% and 70%, respectively. The surface charge of Carb-NS is (-38.3 mV). Enhanced antiviral activity against a clinical isolate of HSV-1 was obtained using Acyclovir loaded in Carb-NS(12).

Kiran Deshmukh et al., reported on the Toluene diisocyanate cross-linked β -cyclodextrin nanosponges as a pH sensitive carrier for naproxen. Nanosponges were prepared using hyper cross-linked β -cyclodextrin method using different concentration of drug, Naproxen, Ethanol, DMF and β -cyclodextrin. The evaluation parameters like Particle characterization, zeta potential, surface characterisation, Entrapment efficiency, *In-vitro* drug release study, *In-vivo* drug release study, Anti-inflammatory activity, X-ray diffraction (XRPD), Fourier transformed infra-red (FT-IR) spectroscopy and Differential scanning calorimetry (DSC). The nanosponges showed size between in the range of 378.45 ± 7.54 nm to 1520.47 ± 7.96 nm. The drug percentages of release showed maximum percentage release in controlled manner ($83.09 \pm 1.03\%$) for 24 h and Zeta potential ranges from (-23.97 \pm 3.280) to (-24.53 \pm 3.31), entrapment efficiency was found to be in range of 90%. *In-vivo* drug release study percentage release in controlled manner ($83.09 \pm 1.03\%$) for 24 h. Toluene diisocyanate crosslinked β -cyclodextrin based nanosponges showed sensitive and effective approach for controlled delivery of naproxen by oral route for anti-inflammatory action(13).

Padmini Iriventi et al., reported on the development and evaluation of nanosponge loaded topical herbal gel of Wrightia tinctoria. The main objective of this study was to develop Nanosponge (NS) based Topical gels of Wrightia tinctoria extract using cross-linker and polymer by melting method. The polymers used was β -cyclodextrin and the cross linker was Dimethyl carbonate. The prepared nanosponges were evaluated for entrapment efficiency, *in-vitro* drug diffusion study, Scanning electron microscopy (SEM), Particle size and zeta potential analysis. The optimized formulation showed drug release of 92.15% in 24 h, particle size was around 192.5 nm, The zeta potential was found to be 21.5 mv which indicated that particles are moderately stable and the entrapment efficiency was 52.28 ± 0.020816 . The authors have stated that the entrapment efficiency changes according to the variation in drug: polymer ratio and depends upon the

cross-linker used in the formulation. Further, the optimized NS were incorporated in the gel to formulate nano topical gel and the Evaluation studies include homogeneity, viscosity, spreadability, pH and *In-vitro* studies were carried out for all gel formulations. The authors had concluded that the constituents responsible for treating psoriasis are present in the obtained extract and prepared NS based topical gel has significant effect in providing sustained drug release(14).

Khalid Anwer et al., In this study, the objective was to find out the efficiency of Abemaciclib-loaded ethylcellulose based nanosponges for sustained cytotoxicity against MCF-7 and MDA-MB-231 human breast cancer cells lines. The authors have prepared the nanosponges by solvent emulsification-ultrasonication technique by using the chemicals like ethyl cellulose (EC), Koliphore P-188 which acts as the stabilizer and solvents like dimethyl sulfoxide (DMSO) and dichloromethane (DCM). The Abemaciclib-encapsulated NSs were Characterized for the following evaluations such as Particle size analysis, Entrapment efficiency, drug loading, Fourier-transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) studies, X-ray powder diffraction (XRD) studies, Scanning electron microscopy (SEM), *In-vitro* diffusion study, Stability study and MTT assay. It was reported that the NSs showed particle size, PDI, and zeta potential in the range of 366.3 – 842.2 nm, 0.448 – 0.853, and -8.21 to -19.7 mV, respectively and the drug entrapment efficiency (%EE) was found to be between 48.45–79.36%. After 24 h of release studies, the optimized formulation exhibited 77.12% of drug release, which followed Higuchi-Matrix model of release kinetics with asymmetrical non-Fickian release. The authors have concluded that the developed NSs would be an efficient carrier to sustain the release of AC in order to improve efficacy against breast cancer(15).

Ms. Ayesha N. Shaikh et al., reported on the Formulation and Evaluation Nanosponges Loaded Hydrogel of Luliconazole. In this literature, the ethyl cellulose based nanosponges were prepared using Emulsion solvent diffusion method and then the drug luliconazole was loaded into the previously prepared ethyl cellulose based nanosponges using solvent evaporation technique. Then the prepared nanosponges were evaluated for the following studies such as Physical appearance, Production yield, Drug entrapment efficiency, Actual drug content, Swelling and Water uptake, Infrared spectroscopy and Particle size. The results reported for Entrapment efficiency (EE%) was in the range from 62.87 to 77.06%, for (%) production yield it was observed in wide range from 65.45 to 73.65% and the Particle size of optimized batch was found to be 173.3nm. Then the synthesized nanosponges were loaded to prepare hydrogel and then evaluation were carried out for the prepared nanosponges loaded hydrogel. Hence, it was concluded that nanosponges topical gel for the antifungal activity can be best suitable approach in novel drug delivery system than conventional gel(16).

Poornima et al., reported on the Formulation and Evaluation OF Gastroretentive Floating Tablets Enclosing Nanosponge Loaded with Lafutidine for Gastric Ulcer. The nanosponges were synthesized using emulsion solvent diffusion method and 3² factorial design approach was employed to assess the influence of two independent variables, which are ethyl cellulose: Poly vinyl alcohol (PVA) ratio and sonication time. Then the prepared nanosponges were evaluated for Particle size, Zeta Potential, PDI, % Entrapment Efficiency, % Yield and the results obtained for Particle size, Zeta potential, PDI and % Entrapment Efficiency are 234.5 to 284.1 nm, -26 to -38 mV, 0.1-0.25 and 50-70% respectively. Then the authors have prepared floating of nanosponge loaded with lafutidine using effervescent technology by direct compression method and have performed the characterization for the same. The conclusion given by the authors is that the floating tablet of nanosponge loaded with lafutidine can be an effective drug delivery system for gastric ulcer with controlled drug release(17).

Aditee Ghose et al., have carried out Development and Evaluation of Polymeric Nanosponge Hydrogel for Terbinafine Hydrochloride. The NS was developed by the emulsion diffusion method, from which the optimized formulation was obtained using Box Behnken Design. The parameters such as polyvinyl alcohol, ethyl cellulose and tween 80 were taken as factors and the responses were particle size, polydispersity index (PDI), and entrapment efficiency (%EE). The results obtained for the optimized formulation were 448.4 ± 12.6 nm, 0.3 ± 0.04, 85.45 ± 3.7% for Particle size, PDI, Entrapment efficiency respectively. Further, these nanosponge was then incorporated into the hydrogel and characterized. Finally in this literature It was concluded that, nanosponge hydrogel formulation is a potential carrier for efficient topical delivery of terbinafine hydrochloride(18).

Pushpalatha D et al., reported on the Formulation and evaluation of lovastatin loaded nanosponges. The Main objective of the study was to prepare lovastatin loaded nanosponges and to evaluate them. The nanosponges were prepared by carrying out the Emulsion solvent diffusion method and the polymers used were Ethyl cellulose, Polyvinyl alcohol, β-cyclodextrin, Pluronic F68, Hydroxy Propyl β- cyclodextrin. For the selected polymers the FT-IR studies were carried out to make sure there was no interaction between the drug and the polymers. Then various evaluation was carried out for the prepared nanosponges, which are the particle size, PDI, zeta potential, SEM, entrapment efficiency and invitro drug release. The characterization results indicated that the obtained nanosponges had the particle size ranged from 295.5 to 578.8 nm, PDI ranged from 0.189 to 0.465, zeta potential from -17.3 to -35.96 mV and entrapment efficiency

was ranged from 78.38 to 95.77 % and the cumulative percentage release from all nanosponges varied from 66.86 to 96.60% after 12 hours. Thus, the author concluded that the formulation of the Lovastatin nanosponge delivery system, which used widely used and physiologically acceptable polymers, was able to display controlled release properties for a period of 12 hours. Thus, they may decrease the number of doses needed, thereby reducing the likelihood of side effects, enhance bioavailability, and boost the drug's effectiveness(19).

K. Rodrigues et al., reported on the preparation of the hesperetin (HT) loaded colloidal nanosponges for sustained delivery was assisted by the QBD approach, where a 4^2 factorial design was used. The synthesis was done by the quasi-emulsion solvent diffusion method. The independent and dependent variables was Drug: polymer ratios, solvent volume, PVA concentrations, stirring time and % yield, drug content and entrapment efficiency respectively. Then, the prepared Hesperetin loaded colloidal nanosponges have been evaluated for various parameters which was Drug content, entrapment efficiency determination, Photo microscopy, scanning electron microscopy (SEM), transmission electron microscope (TEM), Fourier transform infrared (FT-IR) studies, X-ray diffraction studies, Particle size, Polydispersity Index, zeta potential analysis, Porosity analysis, Dissolution studies. The results obtained for the optimized formulation after the evaluation for Particle size, PDI, Zeta potential, Entrapment Efficiency (%) and dissolution studies was 105.08nm, 0.09, -1.35 mV, 85% and 39.98% of the drug release at the end of 8h respectively. Then, these nanosponges were further loaded in gel and then was further evaluated. Finally, the authors have concluded that the nanosponges significantly retarded the topical delivery and could circumvent the bioavailability issues associated with HT(20).

D Shruthika Reddy et al., In this study the main aim was to formulate gliclazide tablets loaded with nanosponges which were further evaluated. The gliclazide loaded nanosponges were prepared by using emulsion solvent diffusion method, the chemicals used were Polyvinyl alcohol (PVA), Dichloromethane (DCM) and Ethyl cellulose. Then, these nanosponges has been evaluated for Percentage Yield, Entrapment efficiency, Surface morphology, Solubility studies, Compatibility Studies such as FT-IR & DSC and *In-vitro* drug release studies of nanosponge formulations. The results obtained after SEM evaluation revealed that the nanosponges were spherical to oval resembling a porous nature in a size range of 0.298 - 0.813 μ m and for *In-vitro* it was about 98.29 % drug release in 24 hrs. Then, the formulation which had the best results with sustained release pattern were further selected for preparation of tablet using direct compression method and the prepared nanosponge loaded tablets has been further evaluated. In this literature it has been concluded that, Gliclazide tablets loaded with nanosponges has increased its efficacy of sustained release and thereby improving its solubility(21).

Sarvesh Mishra et al., In this study, Box Behnken design was used For Optimisation of the Nanosponges. The nanosponges containing deflazacort were created utilising the quasi-emulsion solvent diffusion, using polymers like Eudragit S-100, Poly-methyl methacrylate (PMMA), Ethanol, Dichloromethane (DCM) and Polyvinyl Alcohol (PVA). Then, the prepared nanosponges has been subjected to Characterization namely, Size of the particles, Efficiency of entrapment, Shape and surface morphology, drug content determination, and *in-vitro* drug release. The results obtained for Particle size, Drug entrapment, *In-vitro* drug release for the optimized formulations was 170.45 nm, 73.42 % and 90.33 % in colonic fluid with 4 percent w/v caecal content for a 24- hour period. Eventually, the authors have concluded that, the generated polynomial equations and contour plots helped in forecasting the values of chosen independent variables to produce the best controlled release colon focused formulation of Deflazacort with the required features(22).

Madhuri Dinde et al., reported on Development and Evaluation of Cinnarizine Loaded Nanosponges, the objective of this study was to formulate and evaluate Cinnarizine loaded nanosponges. The drug loaded nanosponges has been prepared by using quasi emulsion solvent diffusion method. The 3^2 Full factorial design taking Eudragit RS 100 and cold PVA as independent variables and entrapment efficiency, particle size, percent yield, drug release, zeta potential as dependent variables was generated for the experimental design of Cinnarizine loaded nanosponges. Then the prepared drug loaded nanosponges have been evaluated for various characteristics among those the results obtained for Particle size analysis, Polydispersity index, Zeta potential, Entrapment efficiency (%), percent yield and *In-vitro* diffusion study for optimized batch were 492.33nm, 0.08103 \pm 0.04, 5.67mV, 70.85 \pm 0.41%, 60.89 \pm 0.18% and 97.65 \pm 2.15%. respectively. Finally, the authors have concluded that it was possible to prepare nanosponges of Cinnarizine by using quasi emulsion solvent diffusion method to obtain the best possible formulation(23).

KVNR Aishwarya et al., The authors have reported on the preparation and evaluation of lansoprazole nanosponges whose main objective has been to formulate the lansoprazole loaded nanosponges for controlled release application. In the study the nanosponges have been prepared by Quasi emulsion solvent diffusion method using Eudragit Rs 100 and dichloromethane which acted as a polymer and as crosslinker respectively. Then, the prepared nanosponges have been evaluated for Average particle size distribution, Entrapment efficiency, Estimation of drug content and Drug release

study and the results obtained for Particle Size, Entrapment Efficiency and Drug release Studies were 1435 μ m, 73.6-86.7 %, and Lansoprazole release from all the nanosponges prepared was slow and spread over 7 h respectively, which was diffusion controlled and followed first order kinetics respectively(24).

Nensi Raythatha et al., The Literature reported on the Development of benzoyl peroxide loaded nanosponges gel. The main aim of this study was to develop Benzoyl peroxide (BPO) nanosponges using various polymers and to improve stability, lessen side effects, change medication release patterns, and deliver a pharmaceutically active substance effectively at a low dose. The chemicals which have been used in this study other than the drug are HPMC K4M, Eudragit S100, Eudragit RL100 dichloromethane, Ethyl Cellulose and Poly Vinyl Alcohol. The Nanosponges have been prepared using quasi-emulsion solvent diffusion method which has been further evaluated for Particle size, Production yield and Loading efficiency. The results for the evaluations carried out was better for certain formulation (F9), the results are 80-200nm, 82.1 \pm 2.31 and 87.9 \pm 1.38, so this batch was loaded into the gel and which has been evaluated further. Finally, the authors have concluded that nanosponge delivery system work efficiently for topical delivery of Benzoyl Peroxide(25).

4. Characterization of nanosponges

4.1. Solubility Studies

Inclusion complexes are a technique for determining medication solubility and bioavailability. This is the most used technique for analyzing the inclusion complexes of nanosponges. The plot of phase solubility might reveal the degree of completion. Solubility studies are carried out to determine the pH of the drug, the solubilization process, and the factors influencing drug solubility(26).

4.2. Particle size and polydispersity index

One of the crucial factors for determining the particle size of nanosponges is the diameter of the particles. A measure of variance or dispersion within the particle size distribution is the PDI. Monodisperse samples have a lower PDI value, whereas polydisperse samples have a greater PDI value, which suggests a wider particle size dispersion. Dynamic light scattering employing a 90 Plus particle sizer outfitted with MAS OPTION particle sizing software, laser light diffractometry, or Malvern Zeta sizer are three methods for determining the particle size and polydispersity index (PDI). This allows for the calculation of the polydispersity index and mean diameter(27).

4.3. Zeta Potential

The instrument zeta sizer determines the surface charge and type of nanosponges, and the zeta potential aids in this determination. The primary critical measure for stability is zeta potential. The study benefits from the potential charge of about ± 30 Mv(2).

4.4. Microscopic studies

Two studies, (SEM) Scanning Electron Microscopy and (TEM) Transmission Electron Microscopy, can be used to determine the microscopic evaluation of nanosponges in order to innovate the morphological aspects of nanosponges. This research allows us to determine the extent of crystallinity of several produced inclusion complexes(2).

4.5. Assessment of Loading efficiency and Percentage yield

The loading efficiency (%) of the sponges can be calculated from an equation:

$$\text{Loading efficiency} = \text{actual drug content} / \text{Theoretical yield} \times 100$$

The percentage yield of the sponges can be determined from the initial weight of the sponges and to the final weight of sponges(2).

$$\text{Percentage yield} = \text{Practical mass of nanosponges} / \text{Theoretical mass (polymer + drug)} \times 100$$

4.6. Determination of true density

With the use of an ultra-pycnometer and helium gas, the density of the nanosponges can be measured. The mean value can then be calculated after performing a mean repetition(2).

4.7. Infrared Spectroscopy

Infrared spectroscopy is used to estimate the interaction between drugs, polymers, and nanosponges in the solid state. The peaks that were found are typical of the functional groupings that were present in the sample. This method is less clear than other methods and is not suitable for locating inclusion complexes(27).

4.8. X-ray diffractometry

Powder X-ray diffractometry is mostly employed for solid moieties with inclusion complexes. Sponge diffraction patterns can reveal a variety of physical properties about a substance. Complexation is indicated by the broadening or addition of peak patterns. It is simpler to distinguish between the uncomplicated and complex species from the peaks(2).

4.9. Morphology and surface topography

By covering the nanosponges with gold-palladium and maintaining them at room temperature with argon gas, the morphology and surface topography of the nanosponges are determined(2).

Thermal analysis techniques:

It can be determined using thermo-analytical techniques whether the drug material changes in any way prior to the thermal destruction of the nanosponge. The drug substance can alter by melting, evaporating, decomposing, oxidizing, or going through a polymorphic transition. The drug substance's alteration suggests the creation of a complex. One can look for broadening, shifting, the introduction of new peaks, or the elimination of specific peaks, in the thermogram produced by DTA and DSC. The development of inclusion complexes can also be supported by changes in weight loss(28).

4.10. FTIR (Fourier Transform Infrared Analysis)

To determine the combining bonds of polymer and drug interactions, FTIR analysis is performed. By obtaining IR samples between 400 and 4000 cm^{-1} , the drug samples and drug sponges are identified. To reduce moisture content, helium gas is utilized as a purge for the detector, and carbon black is used as a reference to take high signal and IR readings. Determined are the chemical vibrations, linked vibrations, extra bands, etc (2).

4.11. Thin Layer Chromatography

The R_f values of a drug molecule significantly decrease in thin layer chromatography, which aids in recognizing the complex formation between the drug and nanosponge(28).

4.12. Dissolution test

The USP Dissolution Test Apparatus II, with a modified basket made of 5 m stainless steel mesh and a rotational speed of 150 rpm, can be used to study the dissolution profile of nanosponges. In order to ensure sink conditions, the dissolution medium is chosen while taking the actives' solubility into account. A suitable analytical method can be used to analyze samples from the dissolution medium(27).

4.13. Resiliency

Sponge's viscoelastic qualities can be generated by transforming them into softer beadlets as needed for the final composition. The release profile gets shorter when crosslinkers are added.

Therefore, the release of crosslinkers with the polymers with regard to time can be adjusted to select, study, and optimize the sponges that are needed(2).

4.14. Drug release kinetics

The release data was analyzed using the Zero order, first order, Higuchi, Peppas, Hixon Crowell, Kopcha, and Makoid-Banker models to learn more about the process of drug release from the Nanosponge. The data can be examined with the help of the graph pad prism software. The programme determines the non-linear function's parameters based on which experimental results and non-linear function fit together most closely(27).

5. Conclusion

Drugs that are both lipophilic and hydrophilic can be added to nanosponges. At the target spot, nanosponges can release them in a controlled and predictable manner. The nanosponge formulation's particle size and release rate can be adjusted by adjusting the polymer to cross-linker ratio. Nanosponges make it easier to utilise insoluble compounds and can shield the active components from physiochemical deterioration from the outside world. Nanosponges can be created in a variety of dosage forms, including parenteral, topical, aerosol, tablets, and capsules, due to their small size and spherical shape.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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