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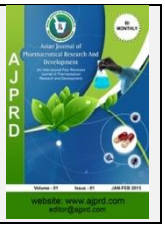

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Review Article

New Trends in Emerging Novel Nanosponges Drug Delivery

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A B S T R A C T

Medical professionals have long had trouble delivering medications to the correct location in the body and controlling their release to prevent overdose. Nano-sponges are novel and complicated molecules, which have the ability to alleviate these challenges. Utilizing nano-sponges allows for precise drug delivery to the desired location. Nano-sponge technology gets better patient compliance by delivering drugs to strategic locations while also extending dosing intervals. Various drug delivery techniques, such as parenteral, transdermal, oral, and immunosuppressive drugs, involve Nano-sponges. In today's world, nanosponges are used in gastro-retentive drug delivery systems.

Keywords: Nano-sponges, hydrophilic, lipophilic, Cyclodextrin, drug delivery, antifungal, cancer therapy

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INTRODUCTION

The Nano-sponges are approximately the size of a virus, with a 'backbone' (a scaffolding structure) comprised of biologically bio-degraded polyester. Cross-linkers are tiny molecules that connect to specific regions of the polyester and break down large polyester strands in a solution. They 'cross link' polyester portions to create a spherical shape with multiple drug pockets (or cavities). The polyester bio-degrades in a predictable way. As a result, it degrades steadily in the body and releases its drug payload in a predictable pattern. These microscopic sponges can move throughout the body until they come into contact with the intended target, where they will then stick to the surface and begin to release the medication. [1]

Background

Nano-sponges one novel type of substance is composed of microparticles with large cavities a few nanometers in size that can encapsulate a variety of compounds. These particles may transfer both lipophilic and hydrophilic compounds while as well as enhancing Poorly water-soluble compound solubility. Nano- sponges comprise small mesh-like formations with the potential to revolutionize effective treatment of disease conditions. Preliminary studies showed that this technology was nearly five times more effective than traditional techniques of administering medications for breast cancer.

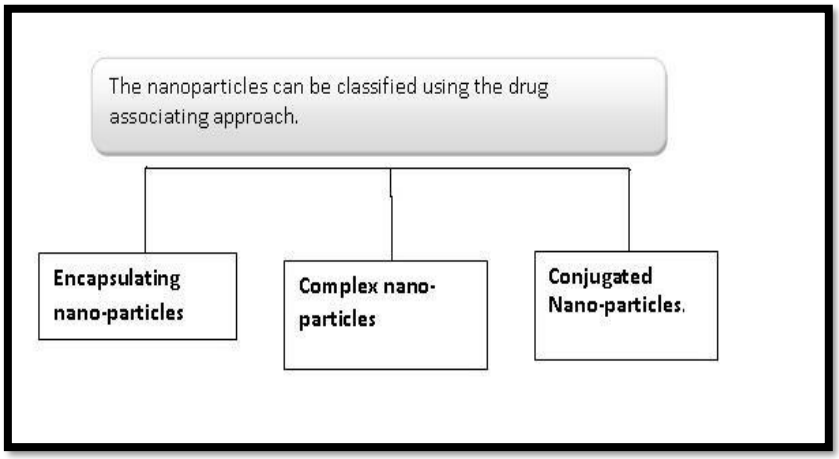


Figure 1:-Classification of Nanoparticles using drug associating approach.(1)

Nanosponges and nanocapsules are examples of the first category. Nano-sponges, such as alginate nanosponges, are nano-particles that similar to sponges with numerous pores that transport medicinal molecules. Poly(isobutyl-cyanoacrylate) (IBCA) nanocrystals are also used to enclose nano-particles. They can effectively absorb drug molecules in their hydrophilic core. The 2nd group consists of complex nanoparticles that attract molecules through electrostatic interaction. Conjugated nano-particles, are 3rd type which form covalent connections with drugs. These nanosponges are a new type of nano-particle created by naturally occurring compounds. When compared to other nanoparticles, they are insoluble in both organic and water-based solvents, porous, non-poisonous, and resistant to elevated temperatures of up to 300°C. They can acquire, transfer, and probably release a wide range of molecules because of their three- dimensional structure, which comprises cavities of nano metric size and variable polarities. (2)

The Key Properties of Nanosponges

- Nanosponges are available in a variety of sizes (1 m or even less) and different polarities. (3)
- By altering the cross linker to polymer proportion, Nanosponges of variable sizes and polarities can be formed. (3)
- Depending on the process parameters, they may be They might be crystallized or Para-crystallized. The crystal structure of nano-sponges is critical in their drug complexation. The drug encapsulation ability of nanosponges is mostly determined by the degree of crystallization The drug encapsulation ability of para-crystalline nanosponges have varied.(4)
- These are harmless, porous particles that are unsolvable in most polar solvents and can withstand temperatures reaching up to 300 degrees Celsius.. (5)
- Their three-dimensional structure makes it possible to collect, transfer, and precisely release a huge variety of compounds. Because of their potential to be connected with several functional groups, they can be targeted to various environments. Chemical linkers allow nanosponges to preferentially attach to specific locations.With various medications, they produce inclusion and non-inclusion complexes.(6)

Advantages & Disadvantages of Nanosponges

Table: 1 Advantages & Disadvantages of Nanosponges

Sr. No.	Advantages	Disadvantages
1.	Drug administration at specified locations	The capability of nanosponges to include only tiny molecules
2.	This technology offers minimized adverseeffects and the ability to entrap a wide range of substances.	Nanosponges could be paracrystalline orcrystalline in nature.
3.	Greater elegance, better formulationflexibility, and good stability.	The degree of crystallisation has has aconsiderable impact on the load-bearing capacity of nano-sponges.
4.	Nano-sponge systems don't cause allergies,irritation, mutagenesis, or damage.	The loading capabilities of paracrystallinenanosponges can vary.

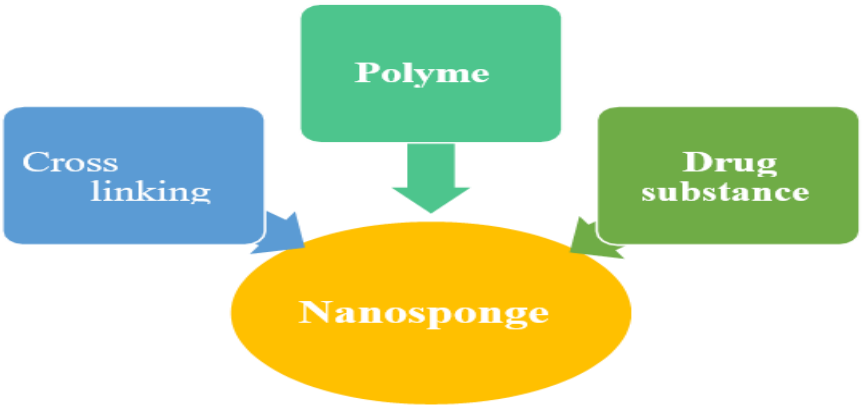


Figure: 2 Compositions of Nanosponges

Polymer

The polymer selected can have effect on the manufacture and performance of nano-sponges. The cavity must be large enough to accommodate the drug molecule. The polymer is selected based on the desired release and medicine which is encapsulated. The polymer of choice must be able to bind to the selected ligands.[9]

Agent for cross-linking

These cross-linking agents can be chosen on the basis of the polymer structure and the medicament to be prepared. Diaryl carbonates, dichloromethane, diphenyl carbonates & Di isocyanates are some examples.[7,8]

Drug component

- Between 100 and 400 Daltons are the ranges of molar mass.
- A pharmacological molecule is made up of no more than five compacted rings.
- Lower than 10 mg/ml of solubility is required in water.
- The substance's melting point is less than 250 °C.
- Procedure for the Preparation of Nano-sponges
- Procedure for the Preparation of Nano-sponges

Procedure for the Preparation of Nano-sponges

Diffusion Method for Emulsion Solvent

Different quantities of ethyl cellulose (EC) and polyvinyl alcohol (PVA) can be used to make nanosponges. A specific quantity of polyvinyl alcohol was introduced gradually to a dispersed phase made up of ethyl cellulose and the medication in 150ml of an aqueous continuous phase after being dissolved in 20ml of dichloromethane.

For two hours, the reaction mixture was agitated at a speed of 1000 rpm. The formed nanosponges were obtained by filtering and drying in an oven at 400 °C for 24 hours. To ensure that all remaining solvents were eliminated, the dried Nanosponges were kept in vacuum desiccators.

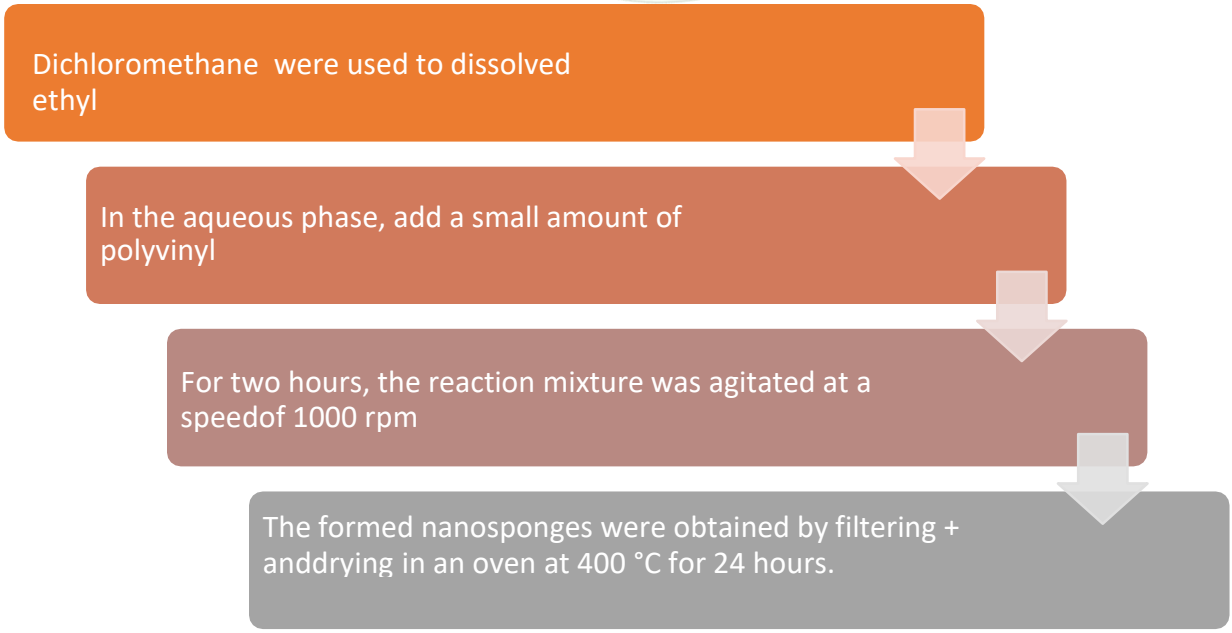


Figure: 3 Diffusion method for Emulsion solvent

Solvent Method

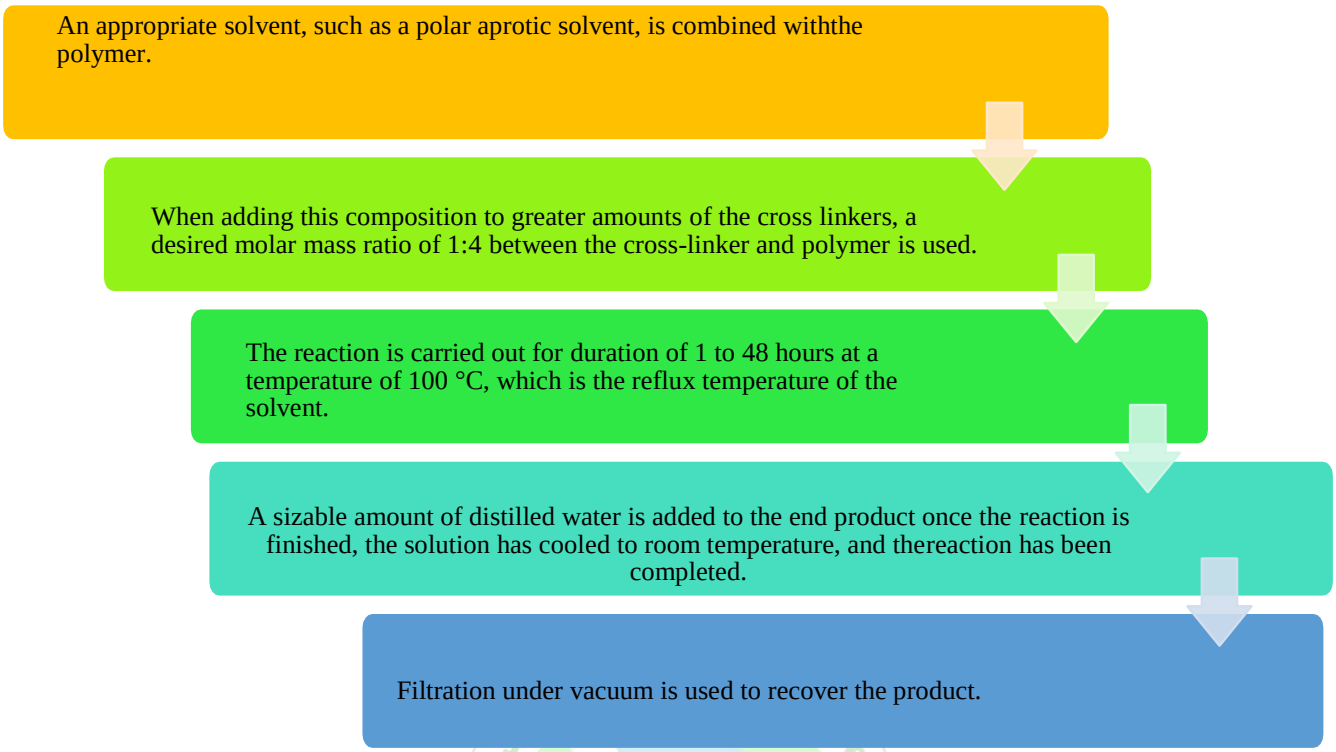


Figure: 4 process of solvent evaporation method

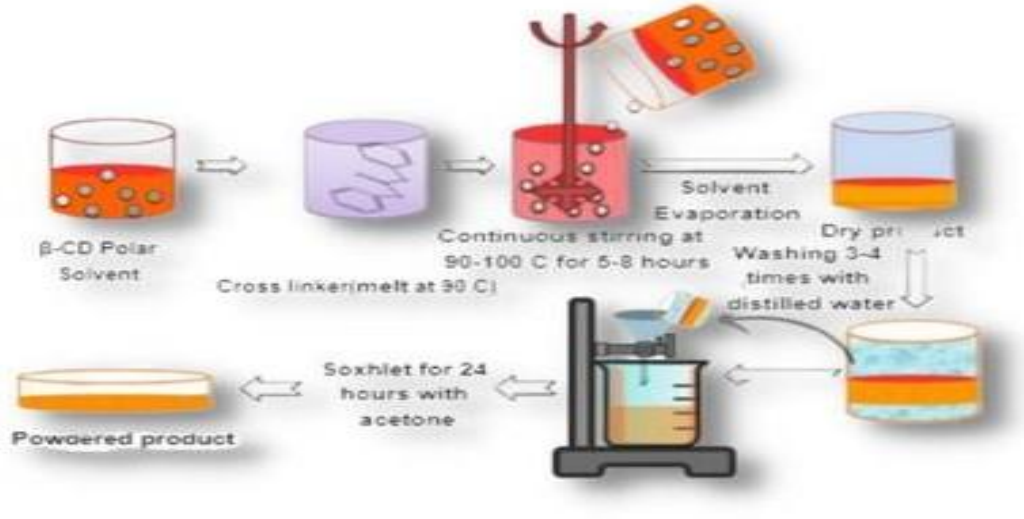


Figure 5: Solvent method procedure

Synthesis using Assisted Ultrasound

By combining polymers and cross-linkers in this process without the use of a solvent and while using sonication, nanosponges can be produced. This process will produce spherical, uniform-sized nanosponges

Figure: 6 Process of Ultrasound-Assisted Synthesis

Loading of Drug into Nanosponges [14,15,16]

Pre-treatment of nanosponges is required to achieve mean particle sizes below 500 nm for drug delivery. To avoid the formation of aggregates, sonicate the nanosponges in water before centrifuging the solution to extract the colloidal fraction. Freeze-dry the supernatant after separating it from the sample. Make an aqueous suspension of Nanosponge, distribute the excess medication, and keep the suspension constantly stirring for the duration of the complexation process. After complexation, separate the insoluble (undissolved) drug from the complexed drug using centrifugation. Solvent evaporation or freeze-drying can then be used to generate solid crystals of nanosponges. The nanosponges crystal structure is necessary for drug complexation. One study found that paracrystalline nanosponges and crystalline nanosponges have distinct loading capacities. In comparison to paracrystalline nanosponges, crystalline nanosponges have a higher drug loading. Instead of an inclusion complex, drug loading happens mechanically in weakly crystalline nanosponges.

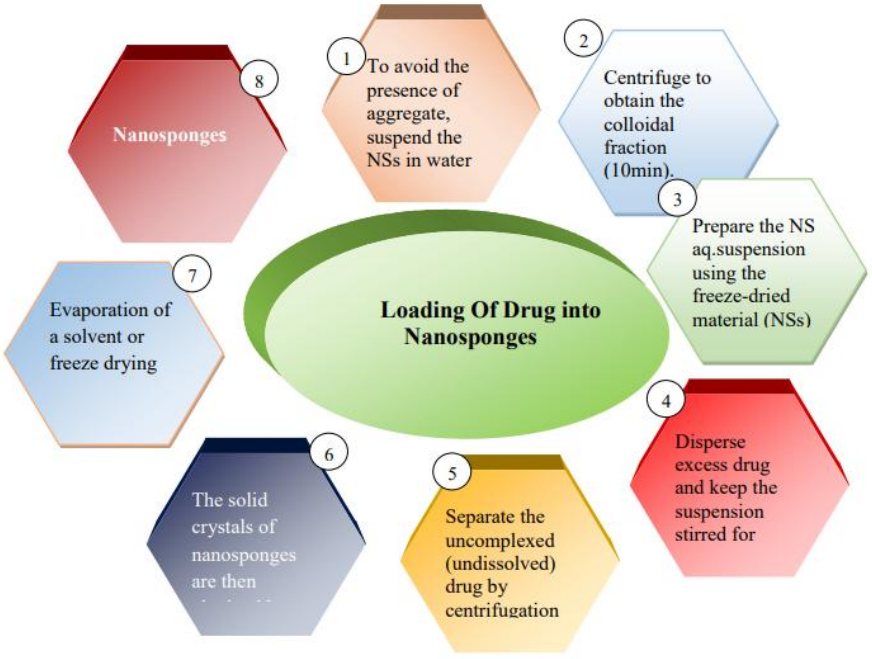


Figure 7: Loading Of Drug into Nanosponges

NANOSPONGE

1
- The nanosponges have a porous surface and an open structure.
- The active ingredient is incorporated into the vehicle in an encapsulatedform because there isn't an uninterrupted membrane around the nanosponges.

2
- Until the vehicle is saturated and equilibrium has been reached, the encapsulated active component can freely travel from the particles intothe vehicle.
- The vehicle carrying the active ingredient becomes unsaturated when the product is put on the skin, causing upsetting the balance.

3
- As a result, an active flow will start from the sponge particle into the vehicle, then onto the skin, where it will remain until the vehicle is eitherdried as well as absorbed.
- The release of active ingredients continues for a considerable amount of time even when the nanosponges particles are removed from the stratumcorneum of the skin.

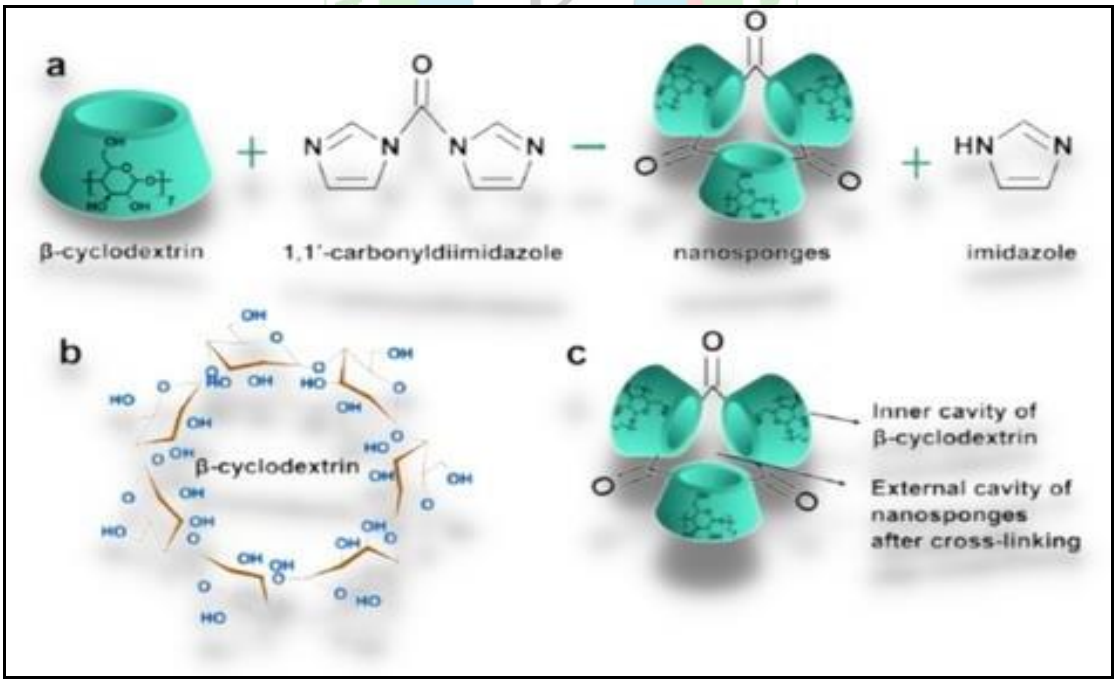


Figure 8: Cross Linking Process

Formulations of some drugs using Nanosponges

Drug	Nanosponges vehicle/Polymer	Study	Indication	In -vitro / in -vivo / Mathematicalmodel	Bcs Class	Reference
Temozolamide	Poly(valerolactone allyl valerolactone) And poly (valerolactone allyl valerolactoneo xepanedione)	release of drug	Brain tumors	In -vitro & In-vivo	Class I	18
Camptothecin	β-Cyclodextrin	Hemolytic activity Cyto-toxicty	Cancer	Diluted blood HT-29 cell line		19,20
Antisense oligonucleotides	Sodiumalginate Poly L-lysine	Pharmacokineticstudies	Cancer therapy Viral infections Pathologic disorders	Mice		21
Resveratrol	β-Cyclodextrin	CytotoxictyDrug Accumulation in rabbit buccal mucosa Eg-Vivo Study	Inflammation, Cardiovascular diseases, Dermatitis, Gonorrhea, Fever and Hyperlipide mia	HCPC-I cell line Rabbit Buccal mucosa	Class II	22
Bovine Serum albumin	Cyclodextrin based poly (amino amine)	release of drug and Stability study	Protein supplement	Stability and modification of in vitro release		23
Paclitaxel	β-Cyclodextrin	Bio- availabilityCytotoxicty	Cancer	MCF7 cell line from Sprague-Dawley rats	Class IV	24,25
Dexamethason e	β-Cyclodextrin	Experiment of drug release	Brain tumors	In-vitro dialysis bag technique	Class II	26
Tamoxifen	β-Cyclodextrin	Cytotoxicty	Breastcancer	MCF-7 cell line	Class II	27

Nanosponges used in Formulation of Antifungal Drugs

Antifungal drugs loaded nanosponges	BCS class	Polymers used in the preparation of nanosponges	Cross linkers	Method used	Reference
Pediatric dose formulation of griseofulvin oral liquid nanosponges	BCS class II	B-cyclodextrins	Diphenylcarbonate	Ultrasonication method	28
Terbinafine nanosponges	BCS class II	Ethyl cellulose	Polyvinylalcohol	Solvent emulsion evaporationmethod	28
Voriconazole	BCS class II	Ethyl cellulose	Polymethyl methacrylate	Emulsion solvent evaporation method	29
Fluconazole nanosponges-based hydrogel	BCS class I	Ethyl cellulose	Polyvinylalcohol	Diffusion method emulsion solvent	30
Miconazolenitrate	BCS class II	B-cyclodextrins	Diphenylcarbonate	Solvent evaporationmethod	31
Clotrimazole (shorter half-life)	BCS class II	Hydroxy propyl B-cyclodextrins	Dimethylcarbonate	Solvent evaporation method	32
Itraconazole	BCS class II	B-cyclodextrins	Copolyvinodu	Solid dispersion	33
Ketoconazole gel-based nanosponges	class II	B-Cyclodextrin	Diphenylcarbonate	Condensation polymerization techniques	34
Econazolenitrate	class II	Ethyl cellulose	Polyvinylalcohol	Solvent evaporationmethod	35

3D chemical structures of drugs used in formulation of nanosponges

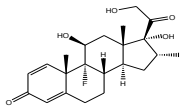
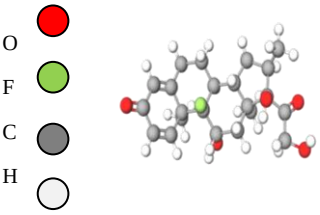
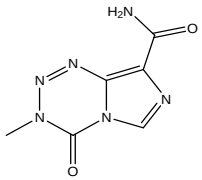
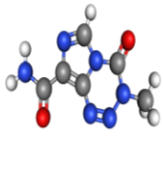
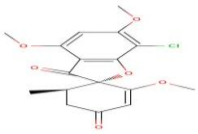
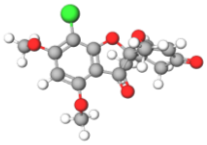
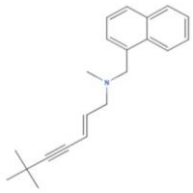
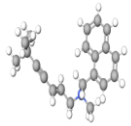
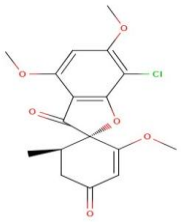
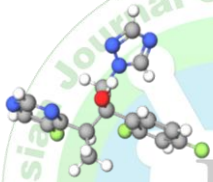
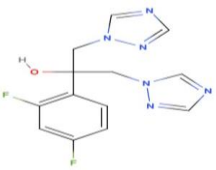
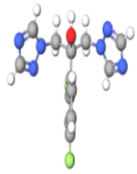
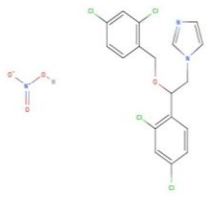
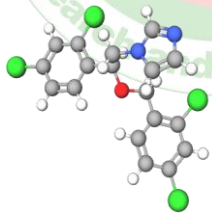
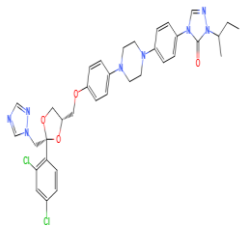
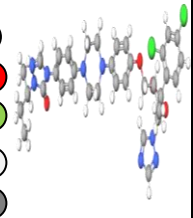
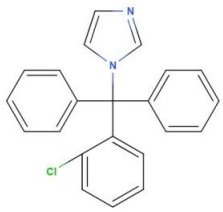
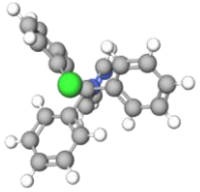
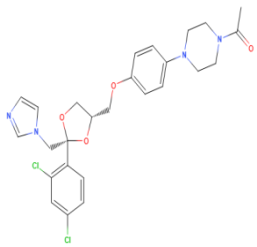
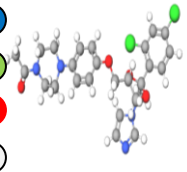
Name	Simple Structure	3D Structure	Name	Simple Structure	3D Structure
Dexamethasone C22H29FO5			Temozolamide C6H6N6O2		
Griseofulvin C17H17ClO6			Terbinafine C21H25N		
Voriconazole C16H14F3N5O			Fluconazole C13H12F2N6O		
Miconazole nitrate $C_{18}H_{14}Cl_4N_2O$			Itraconazole C35H38Cl2N8O4		
Clotrimazole C22H17ClN2			Ketoconazole C26H28Cl2N4O4		

Table 3: The use of antifungal drug-loaded nanosponges and its disadvantages

Antifungal drugs	Applications	Drawbacks	References
Grieseofulvin	• Masks bitter taste	• Bitter taste	36
Nystatin	• Sustained release • Increased topical • activity	• penetration in the skin is Less	37
Itraconazole	• Increased solubility • Increased Bioavailability • Enhanced permeation	• Decrease bioavailability • penetration in the skin is Less	38
Ketoconazole	• Increase in solubility • Increase topical • Activity • Increase • bioavailability	• Less topical activity • Less solubilty	39,40
Terbinafine	• Bitter taste masking • Increase in • Bioavailability • Improved topical • activity	• penetration in the skin is Less • Bitter taste	41
Amphotericin B	• Masking bitter taste • Prevent degradation • Increase in half life	• Short half life • Bitter taste	42
Econazole	• Increase retention • Time • Increased topical • permeation in skin • Sustained release	• Low retention time • Poor solubility	43,44

CHARACTERIZATION OF NANOSPONGE [45-50]

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

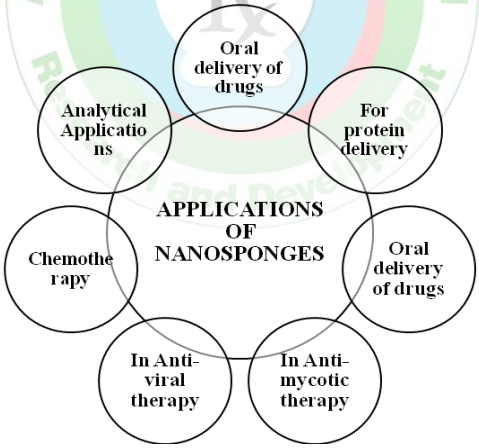
Table 4:

Sr.No.	Characterization	Analytical methods/Instrumentation

Characterization of Nanosponges using Analytical /Instrumentation methods

1.	Morphology and surface Topography	Scanning Electron Microsocopy (SEM) Transmission Electron Microscopy (TEM)
2.	Particle Size and Polydispersity Index	Laser Light Scattering Technique
3.	Surface Charge	Zeta potential measurement
4.	Loading Efficiency	Determined by the quantitative estimation of drug loaded into nanosponges
5.	Drug Release	In vitro diffusion cell,dialysis bag
6.	Interaction between Nanosponges and drug molecules	Infrared spectroscopy
7.	Thermal degradation of the Nanosponges	DSC,DTS,TGA
8.	Inclusion complexation in the solid state.	X-ray diffractometry
9.	Complex formation between the drug and Nanosponges	Thin layer chromatography
10.	Molecular structures	Raman spectroscopy

APPLICATIONS OF NANOSPONGES [51-54]



CONCLUSIONS:

The Nanosponges can deliver the drug to the desired site in a regulated manner. They can also transport both lipophilic and hydrophilic compounds. Because of their small particle size and spherical shape, these can be designed as oral, parenteral, and topical treatments. Nanosponge technology entraps chemicals, resulting in fewer adverse effects, higher stability, increased elegance, and increased formulation flexibility. Nanosponge can be efficiently incorporated into a topical drug delivery system for dosage form retention on skin, as well as used for oral drug delivery using bioerodible polymers, particularly for colon specific delivery and controlled-release drug delivery systems. Thus, Nanosponge technology delivers drugs to particular locations while also extending dosing intervals, improving patient compliance. The formulation of nanosponges may be the greatest approach for resolving different nano-related challenges in the pharmaceutical business.[2]With huge discoveries and new scientific challenges, the topic of nanosponges continues to gain attention. Nanosponges are used in a variety of drug delivery systems, including oral, topical, intravenous, and immunosuppressive. Nanosponge particles can also be used in a targeted medication delivery system that works through the lungs, liver, and spleen. Some approaches can also be used to identify nanosponges at ailment sites such as Crohn's disease, auto-immune disease, and cancer that impact distinct organs or tissues.

Nanosponges are now utilised in gastro-retentive medication delivery devices.

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