IJBPAS, November, 2023, 12(11): 5102-5116

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

OVERVIEW OF NANOSPONGES

MANEESHA M[*1], RAJESWARI A.V.S[2], PRANEETH S.T[3] AND ARAVIND. G.M[4]

1: Student, Department of Pharmacy, Joginpally B.R Pharmacy College of Pharmacy, JNTUH, Bhaskar Nagar, Yenkapally, Moinabad, Telangana, India

2: Department of Pharmaceutics, Joginpally B.R Pharmacy College, Faculty of Pharmacy, JNTUH, Bhaskar Nagar, Yenkapally, Moinabad, Telangana, India

3: Student, Department of Pharmacy, Joginpally B.R Pharmacy College of Pharmacy, JNTUH, Bhaskar Nagar, Yenkapally, Moinabad, Telangana, India

4: Student, Department of Pharmacy, Joginpally B.R Pharmacy College of Pharmacy, JNTUH, Bhaskar Nagar, Yenkapally, Moinabad, Telangana, India

[*]**Corresponding Author: Mr. Maneesha M: E Mail: rajeswariavs9@gmail.com**

Received 19th Sept. 2022; Revised 16th Oct. 2022; Accepted 27th Feb. 2023; Available online 1st Nov. 2023

https://doi.org/10.31032/IJBPAS/2023/12.11.7551

ABSTRACT

The delivery of drugs has long been a challenge for medical experts. It was accomplished using nanotechnology. The science of nanotechnology deals with incredibly small particles. We are able to observe and manipulate the individual atoms and molecules thanks to nanotechnology. Studying materials in the nanoscale enables scientists to comprehend and make use of the distinctive chemical, physical, mechanical, and optical features of the materials that occur there. Drug delivery issues may be resolved through the creation of novel, intricate molecules known as nanosponges. Nanosponges are a brand-new, cutting-edge technology that is essential for the targeted, controlled release of drugs. The primary goal of the nanosponges is to increase the drug solubility, provide an effective dosage form, for sustained release nanosponges' travel throughout the body until they come into contact with the target spot. This review aims to expound on the intriguing characteristics of nanosponges as well as their benefits, drawbacks, formulation, technique of manufacturing, and applications.

Keywords: nanotechnology, nanosponges, targeted drug delivery, drug, controlled release

INTRODUCTION:

NANOTECHNOLOGY:

With the ever-increasing demand for scientific advances nanotechnology is forefront of people's minds. The multidisciplinary field has experienced explosion, development and exposure over the last few years. Nanotechnology is a platform that includes biology, electronics, chemistry, physics, material science and engineering. Nanotechnology is working on nanostructured materials for health, energy and environmental applications. Nanotechnology is having several advantages when compared to conventional drug delivery systems.

CLASSIFICATION OF NANOMATERIALS: **[1]**

Based upon the nature of drug nanomaterials are associated with nanomaterials are classified as follows:

1. Encapsulating nanomaterials like nano capsules and nano sponges
2. Conjugating nanomaterials
3. Complexing nanomaterials

In this review we mainly focus on the nanosponges.

NANOSPONGES:

The field nanotechnology promises revolutionary advances across medicine communications one such advance is nanosponges. These nanosponges work to protect the body from viruses, toxins, bacteria and venom and currently being researched as a drug delivery system that can target specific sites in the body before releasing a drug in a predictable and controlled manner. The main application of nanosponges in medicine would be bio detoxification this offers a way to cleanse the body of virtual injuries, infections and biological weaponry its due to the ability to cleanse. that nanosponges can also be applied to other clinical conditions. While as drug delivery system the nanosponges can also be used as chemical sensors, carriers for biocatalysts and release enzymes, proteins, vaccines and antibiotics and potentially even the treatment of cancers.

Nanospones are tiny sponges that are approximate to the size of the viruses [250nm-1micrometer] which consists of cavities which can be loaded with variety of substances. Nanosponges provide solution for many formulations related problems. Nanosponges carries both hydrophilic and hydrophobic drugs. They also increase the solubility of poorly water-soluble drugs.

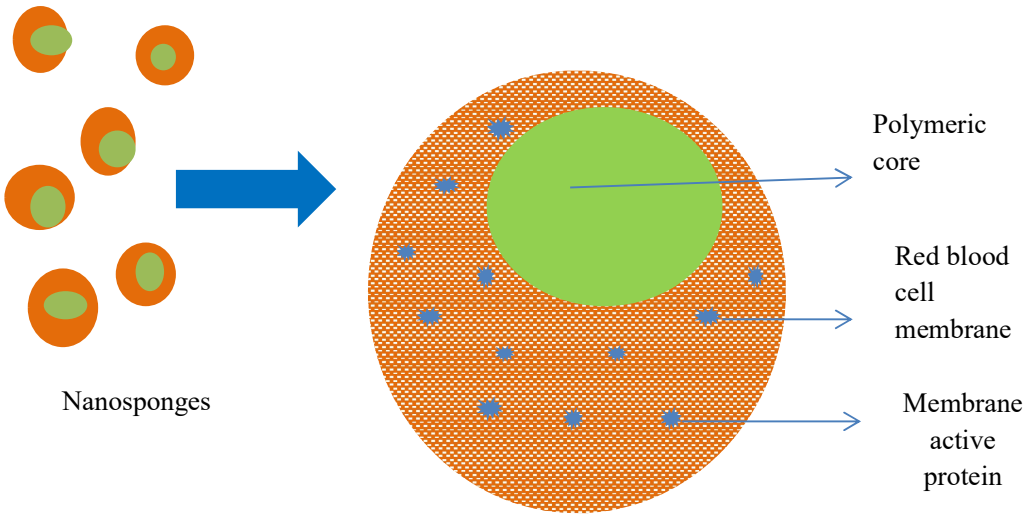

Figure 1: Structure of Nanosponges

BENEFITS OF NANOSPONGES: [2]

- They protect the drug from degradation.
- They are non-toxic, non-mutagenic, non-irritating.
- They increase the aqueous solubility of hydrophobic drugs.
- Apart from oral route we can formulate the drugs in various rooutes for targeted drug delivery.
- By using simple chemicals like polymers and crosslinkers we can reduce many problems related to the formulation.
- Nanosponges reduce the dosing frequency because of its targeted drug delivery.
- They improve formulation flexibility and stability.
- They are used as carriers for gases in many diseases ex: nanosponges provide oxygen to hypoxic -tissues.
- They act as self-sterilizers because of its tiny pore size bacteria cannot penetrate it.
- Nanosponges are used to mask the unpleasant flavours
- Nanosponges are biodegradable.
- It improves the patient compliance.
- It provides therapeutic onset of action.
- Formulations are economical.
- Provide extended-release conditions.
- Drug profile varies from fast, slow and medium.

DRAWBACKS OF NANOSPONGES: [3]

- A nanosponge depends on loading capacities.

- It includes only small particles not suitable for large particles.
- Sometimes dose dumping may occur.

FORMULATION OF NANOSPONGES:

Nanosponges are solids in nature. They can be formulated as oral, topical, or inhalations. When it is formulated as paraenteral dosage form it is simply mixed with sterile water / saline / aqueous solution and administered.

When it is formulated as oral dosage form it may be dispersed in a matrix of suitable excipient for the preparation of tablets and capsules and administered.

When it is formulated as topical dosage form it is effectively incorporated into topical hydrogels.

FACTORS EFFECTING THE FORMULATION OF NANOSPONGES: [1]

- Types of polymers and crosslinkers' used.
- Nature of drug
- Method of preparation
- Loading efficiency
- Types of drugs and medium uses.
- Environmental factors like melting point, temperature, degree of substitution.

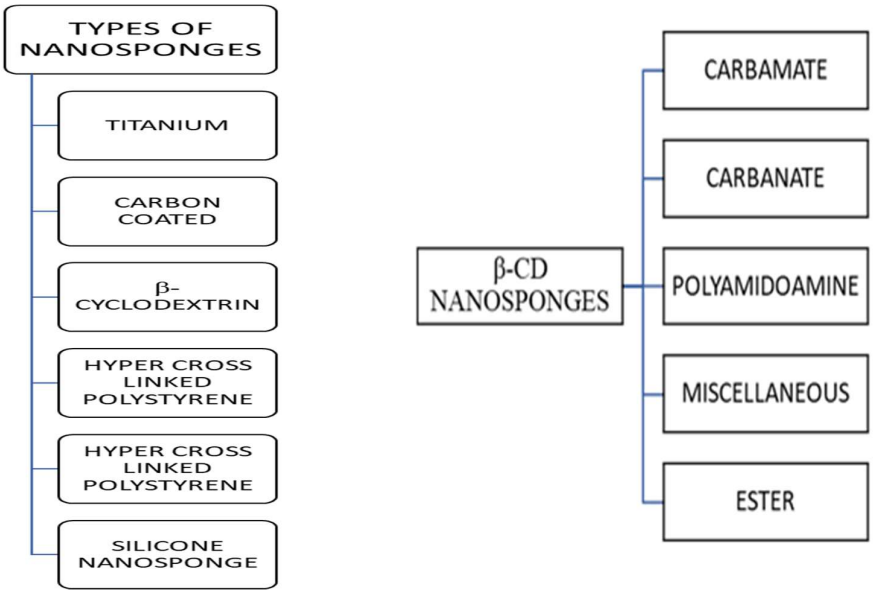

Figure 2: Types of Nanosponges [4]

MATERIALS USED IN THE PREPARATION OF NANOSPONGES

Nanosponges consists 4 components

- Polymers
- Copolymers
- Croosslinkers
- Drug moiety

In nanosponges drugs are encapsulated in the polymers and crosslinkers

POLYMERS:

Polymers are the group of monomeric units. Biodegradable polymers are used in the nanosponges. Biodegradable polymers are non-toxic and completely eliminated from the body by metabolic pathways. Biodegradable polymers influence the pharmacokinetics properties of drug **[5]**.

POLYMERS THAT ARE USED IN NANOSPONGES [6]

Polymers are used in the nanosponges to increase the solubility. Most of the common polymers that are used in the nanosponges are

- Hyper cross-linked polymers- like polystyrenes, cyclodextrines and their derivatives
  Ex: methyl beta cyclodextrins.
- Alkyloxycarbonyl cyclodextrins, copolymers like PVA, ethyl cellulose, valerolactone-allylvalerolactone.
- Methyl beta cyclodextrin
- Hydroxyl propyl beta cyclodextrin
- Eudragit RS 100
- Acrylic acid

COPOLYMERS USED IN NANOSPONGES

- Poly [valerolactone allyl valerolactone]
- Poly [valerolactone allyl valerolactone oxypanedione]
- Ethyl cellulose polyvinyl alcohol

CROSSLINKERS THAT ARE USED IN NANOSPONGES [6]

Crosslinkers are used to form the nonporous structure and nanochannels. The amount of crosslinker influences the surface area and porosity. With the increase in proportion in relation to CD, the smaller the pore diameter more will be the porosity. e.g., acetic acid, dichloromethane, diphenyl carbonate, carbonyldiimidazole, carboxylic acid dianhydride, diarylcarbonates, disocyanates, gluataradehyde, pyromelitic anhydride, 2,2bis [acrylamide acetic acid].

POLAR SOLVENTS

Ex: ethanol, dimethylacetamide, dimethylformamide.

METHODS OF PREPARATION OF NANOSPONGES

Nanosponges are prepared by following methods:

- Solvent method
- Ultrasound assisted synthesis
- Emulsion solvent diffusion method
- Quasi emulsion solvent diffusion method
- Melt technique

SOLVENT METHOD:

In this method nanosponges are prepared by using aprotic solvents like dimethylformamide, dimethyl sulfoxide with polymer. To this mixture excess amount of crosslinkers are added in 1:4 ratio and the reaction is carried out at 10°C

temperatures to the reflux temperature of the solvent, for the time ranging 1-48 hours. After completion of the reaction the mixture is cooled to the room temperature and the obtained mixture is added to the excess amount of bi-distilled water. The product is recovered by filtration under vacuum. The pure form of the product is obtained by prolonged soxhlet extraction with ethanol followed by drying **[7]**.

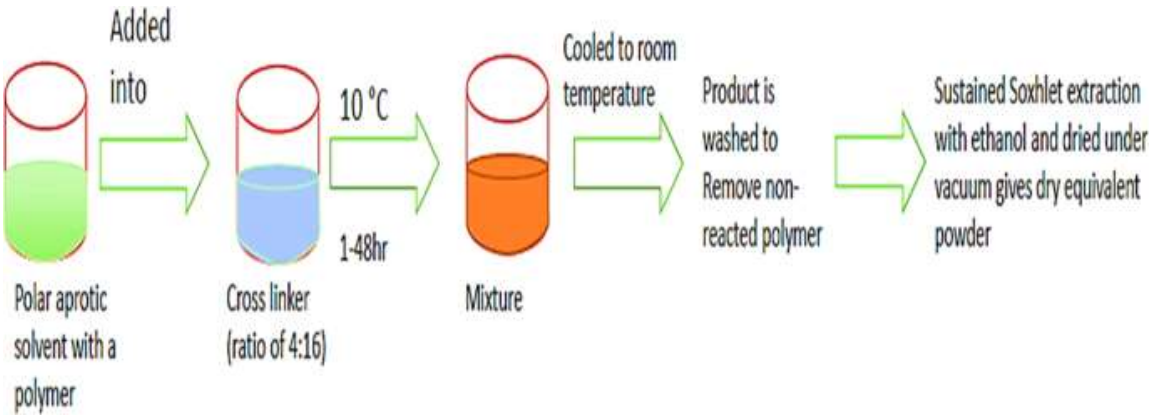

Figure 3: Solvent method of preparation of nanosponges [4]

ULTRASOUND ASSISTED SYNTHESIS:

Unlike solvent method solvent is not used in this method. In this method in flask polymers are mixed with crosslinkers in a particular molar ratio. Flak is then placed in the ultrasound bath that is filled with water and heated up to 90°C. The mixture is sonicated for 5 hours. After sonication the mixture is cooled to the room temperature and product is broken into rough pieces. Then the product is washed with water to remove the unreacted polymer. The pure form of the product is obtained by prolonged soxhlet extraction with ethanol followed by drying under vacuum and stored at 25°C for further use **[8]**.

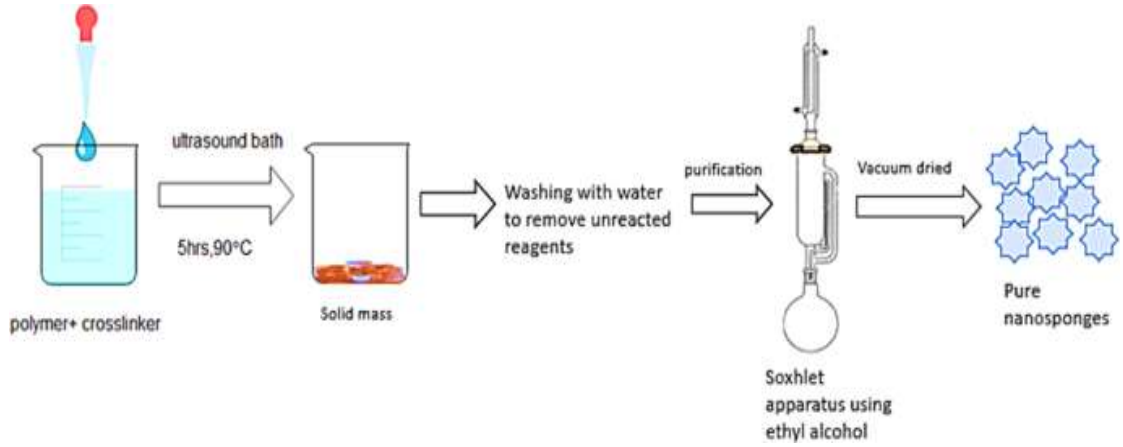

Figure 4: ultrasound assisted synthesis of nanosponges [4]

EMULSION SOLVENT DIFFUSION METHOD:

In this method two phases are used that is organic and aqueous phase. The components of organic phase are dichloromethane in which ethyl cellulose and drug is added. The components of aqueous phase are polyvinyl alcohol in distilled water. By adding drop wise both organic and aqueous phases are emulsified. For proper mixing the mixture is stirred at 1000 RPM for 5 hrs. The final product is collected by filtration followed by drying in oven at 40°C for 24 hours and stored in desiccators **[9]**.

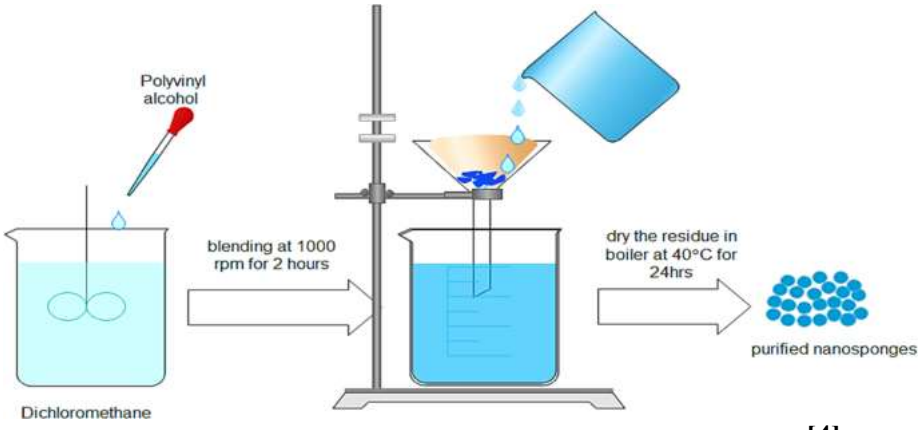

Figure 5: emulsion solvent diffusion method of preparation of nanosponges [4]

QUASI EMULSION SOLVENT DIFFUSION METHOD:

In this method polymers are used in different proportions. In this method we have two phases inner and outer phase. Inner organic phase is prepared by using Eudragit RS 100 dissolved in ethyl alcohol. Outer aqueous phase prepared by dissolving drug in a solution of polyvinyl alcohol under ultra-sonication at 35°C. The inner phase is added to the external phase and the mixture is stirred at 1000-2000RPM for 3 hours. And cooled at room temperature, filtered and dried in an air heated oven at 40 °C for 12 hours **[10]**.

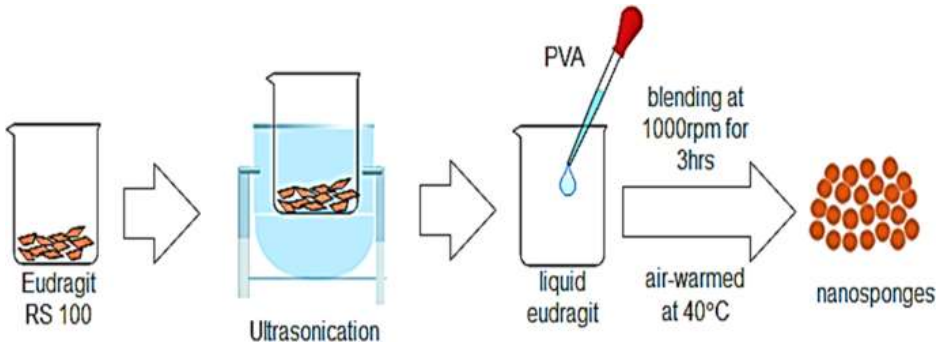

Figure 6: quasi emulsion solvent diffusion method of preparation of nanosponges [4]

MELT TECHNIQUE

In this method cross-linked polymers are melted with polymers and other ingredients and homogenized up to 100°C temperature and stirred with magnetic stirrer for 5 hours. The product is cooled to the room temperature and washed continuously to remove unreacted ingredients **[11]**.

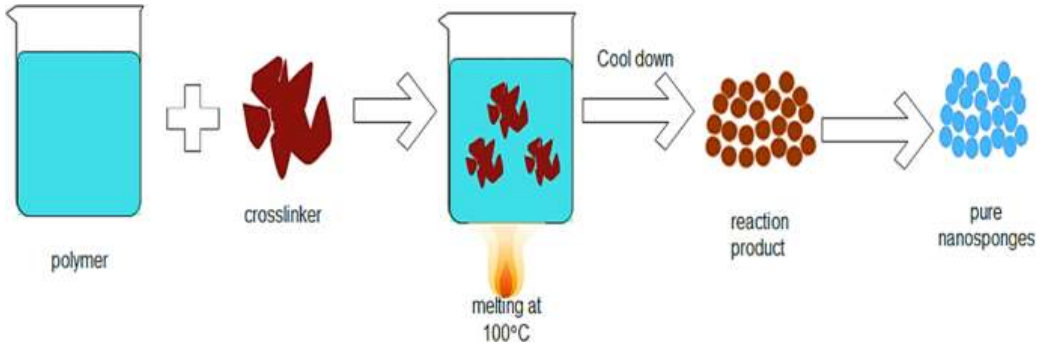

Figure 7: Melt technique for the preparation of nanosponges [4]

METHOD OF LOADING

Nanosponges need to be pre-treated in order to produce particles smaller than 500 nm. The nanosponges are dissolved or suspended in water to attain this range. The suspended nanosponges are sonicated to avoid the formation of aggregates after which the suspension is centrifuged to obtain the colloidal fraction. The supernatant fluid is separated and the sample is dried by freeze drying. An excess amount of the drug is added to the aqueous suspension that is prepared by nanosponges and stirred constantly until the complex is formed. Remove the uncomplexed drug by centrifugation. By freeze drying or by evaporating the solvent solid crystals of nanosponges are obtained **[12]**.

MECHANISM OF DRUG RELEASE FROM NANOSPONGES

Nanosponges ae porous in nature and drugs are encapsulated in vehicle due to its porous structure they have an open structure. The encapsulated forms can easily travel and freely travel into the vehicle until they reach saturated levels and reach equilibrium. When we apply the product topically the vehicle gets unsaturated that causes equilibrium disturbance. the active product from the vehicle releases and get absorbed **[13]**.

EVALUATION OF NANOSPONGES

- Particle size determination
- Morphology and surface topography (SEM and DSC)
- Determination of loading efficiency and production yield
- Determination of true density
- Resiliency
- Dissolution tests.

The evaluation tests for the nanosponges formulation into anti-fungal gel are:

1. Comparative study of the antifungal nanogel formulation with the marketed formulation.
2. *Invitro* antifungal studies
3. pH
4. viscosity
5. spreadability
6. drug content
7. partition coefficient
8. drug diffusion and release kinetics
9. drug permeation studies
10. Irritation studies

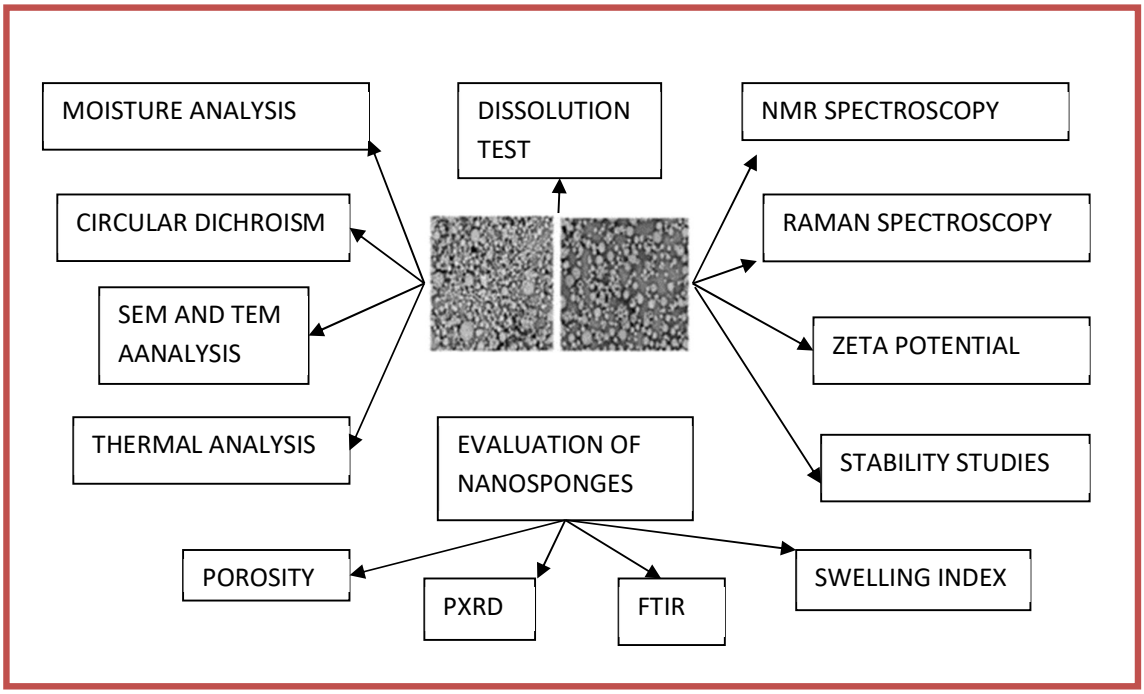

Figure 8: Evaluation of Nanosponges

PAIRTICLE SIZE DETERMINATION [14, 15]

In order to create free-following powders with fine aesthetic qualities, the size of the particles is maintained during polymerization. Using a Malvern zeta sizer or laser light diffractometry, the particle sizes of loaded and unloaded nanosponges were analysed. Particle size against time is plotted based on the cumulative graph we can study the impact of particle size on drug release. Particles larger than 30 m in size give off a grittier impression, and in the final opiate formulation, sizes between 10 and 25 m are favoured and employed.

MORPHOLOGY AND SURFACE TOPOGRAPHY [16]

In terms of morphology, nanosponges are coated with gold-palladium the process is carried at room temperature, and scanning electron microscopy is used to examine the surface structure.

DETERMINATION OF LOADING EFFICIENCY [17]

Loading efficiency can be calculated by following formula

$$\text{Loading efficiency} = \frac{actual\ content\ of\ drug\ nanosponge}{theoretical\ drug\ content} 100$$

DETERMINATION OF PRODUCT YIELD [17]

Product yield can be determined by the following formula

$$\text{Product yield} = \frac{practical\ mass\ of\ nanosponge}{theoretical\ mass} 100$$

DETERMINATION OF TRUE DENSITY [18]

The real density of nanoparticles and benzoyl peroxide can be determined using an ultra-pycnometer and helium gas by employing the repeated mean determination.

RESILENCY [19]

For the final formulation, the viscoelastic characteristics of sponges are adjusted to produce beadles that are harder and softer. When cross linking increased, the rate of release tended to slow down. By releasing the cross-linking over time, resiliency study is conducted in accordance with requirements.

DISSOLUTION TEST [20]

Utilizing a dissolving apparatus USP with a modified basket made of 5 ml stainless steel mesh and rotating at a speed of around 150 rpm, the dissolution profile of nanosponges is examined. To achieve sink conditions, the appropriate dissolution medium is chosen, and the solubility of the active ingredients is taken into account. The sample form dissolution medium is employed with the proper analytical methodology.

Table 1: Drugs that are Formulated as Nanosponges [21-28]

CATEGORY	NANOSPONGES VEHICLE	DRUGS
Anticancer	Beta-cyclodextrine	Paclitaxel, camptothecin, Oxyresveratrol,
Inflammation	Beta- cyclodextrine	Resveratrol
Antifungal	Ethyl cellulose polyvinyl alcohol	Econazole nitrate
Brain tumours	Poly [valerolactone allyl valerolactone]	Temozolamide
Brain tumour	Dexamethasone	Beta cyclodextrin
Cardiovascular diseases	Beta cyclodextrin	Resveratrol
Hyperlipidaemia	Beta-cyclodextrin	Resveratrol
Antifungal	Itraconazole	Copolyvidonum
Viral infections and pathologic disorder	Poly L-lysine	Oligonucleotides
Breast cancer	Tamoxifen	Beta-cyclodextrin
Anticancer	Beta-cyclodextrin	Camptothecin,

Table 2: drug and reason for formulation

S. No.	Drug	Reason for formulation into nanosponges
1.	Irbesartan, sulphamethoxazole	For increase in the solubility
2.	Clobestol propionate, Curcumin, Caffeine	Topical delivery
3.	Thyme essential oils, Limonene	Solubility enhancement and volatility reduction
4.	Sesamol	Photostability enhancement
5.	Paracetamol+Aceclofenac+Caffeine	Combination therapy, solubility enhancement

BCS CLASS-II drugs that are developed as nanosponges [29]

- Anti-anxiety drugs like lorazepam
- Antiarrhythmic agents like azithromycin, ciprofloxacin, erythromycin, ofloxacin, sulfamethoxazole
- Anticoagulants like warfarin
- Anticonvulsants like carbamazepine, clonazepam, felbamate. Oxycarbazepine, primidone
- Antidiabetic and antihyperlipidemic drugs like atorvastatin, fenofibrate, glibenclamide, glipizide, lovastatin, troglitazone
- Antiepileptic drugs like phenytoin
- Antifungal drugs like econazolenitrate, itraconazole, ketoconazole, lansoprazole
- Antihistamines like terfenadine
- antihypertensive drugs like felodipine
- anti-neoplastic drugs like camptothecin, docetaxel, etoposide, exemestane, flutamide, irinotecapaclitaxel, raloxifene, tamoxifen, temozolamide, topotecan
- antioxidants like resvaretrol
- antiulcer drugs like lansoprazole, omeprazole
- NSAIDs like dapsone, diclofenac, diflunisal, etodolac, etoricoxib, flurbiprofen, ibuprofen, indomethacin, ketprofen, mefenamic acid, naproxen, nimesulide, oxaprozin.

APPLICATIONS OF NANOSPONGES [30-34]

Because of their biocompatibility and adaptability, nanosponges have a wide range of applications in the pharmaceutical industry. Nanosponges can be utilised as an excipient in the pharmaceutical industry to create topical dosage forms as well as tablets, capsules, granules, pallets, suspensions, and solid dispersions. Both lipophilic and hydrophilic drug molecules—basically, those chemicals that fall under the biopharmaceutical classification system [BCS-class II] and those that are weakly water-soluble can be accommodated by nanosponges.

1. Nanosponges are used in drug delivery, cancer therapy, delivery of proteins.
2. Nanospones are used as absorbent in blood poisoning.
3. Nanosponges are used to increase the solubility od poorly soluble drug
4. Nansoponges are used in nasal, pulmonary route of administrations in antiviral agents.

5. Nanosponges acts as carrier for biocatalysts
6. A nanosponge acts as carrier for enzymes, proteins, vaccines and antibodies.
7. Nanosponges are used in the treatment of diabetes, fungal infections, inflammation, hyperlipidaemia, etc.
8. For pesticide removal,and removal of their intermediates like Atrazine, Benalaxyl, Fluprifole etc.
9. The dyes like Direct blue, methylene blue, 2-napthol, chloro and nitro anilines are also adsorbed as well as removed by these nanosponges.

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