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Review Article

CURRENT REVIEW ON NANOSPONGES FOR EFFECTIVE TREATMENT OF IBD

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ABSTRACT

The chronic gastrointestinal tract condition known as inflammatory bowel disease (IBD) is marked by uncontrollably high levels of inflammation in response to dysbiosis of the gut microbiota and disruption of the intestinal epithelial barrier. The limited effectiveness of currently available small-molecule immunosuppressive drugs and anti-cytokine biologics is mostly attributable to the intricate inflammatory network associated with inflammatory bowel disease. Drug delivery devices called nanosponges are made of tiny sponges that have been mixed with medication. This technology has recently improved the treatment of numerous disorders that call for tailored delivery, such as IBD. This review will provide outline about IBD pertaining to its various aspects and further details of nanosponge from its characteristics, classification, preparation, evaluation, application, advantages and some notable works enlisting nanosponge mediated drug delivery.

Keywords: Nanosponge, Colon targeted drug delivery, Inflammatory bowl disease, Ulcerative colitis

INTRODUCTION

The combination of environmental and genetic factors that affect immune responses leads to inflammatory bowel disease (IBD). The two primary categories of inflammatory bowel illnesses are Crohn's disease (CD) and ulcerative colitis (UC). Both Crohn's disease and ulcerative colitis (UC) are considered chronic inflammatory bowel diseases (IBDs) that cause inflammation and digestive problems in the gastrointestinal tract. Weight loss, diarrhea, abdominal pain, and rectal bleeding are a few of the symptoms of CD and UC. Inflammation is the primary characteristic of them. Both diseases affect men and women equally and can strike teenagers as well as adults. There are several distinctions in the symptoms of CD and UC, despite the similarities between the symptoms of these two illnesses (Fakhoury *et al*., 2014; Mulder *et al*., 2014).

IBD is a chronic illness that affects both boys and females at a young age. Over the course of the second half of the 20th century, both the incidence and prevalence of IBD significantly rose. Since the start of the 21st century, IBD has been regarded as one of the most common gastrointestinal disorders, with an increasing frequency in recently industrialized nations (Cai and Wang, 2021).

Although Crohn's disease often affects the colon and ileum, it can attack any part of the intestines, frequently sporadically. The rectum is affected by ulcerative colitis, which can also affect the colon as a whole (pancolitis) or in isolated episodes. with ulcerative colitis, inflammation is usually limited to the mucosa; with Crohn's disease, however, inflammation is frequently transmural. Although intestinal fistulas, strictures, and granulomas are not common in ulcerative colitis, they can be

linked to Crohn's disease (Cho and Abraham, 2007).

Cigarette smoking has distinct effects on these two conditions: nonsmokers and former smokers are more likely to develop ulcerative colitis, while smokers are more likely to get Crohn's disease and tend to have a more severe case. Psoriasis, ankylosing spondylitis, and primary sclerosing cholangitis are among conditions that patients with inflammatory bowel disease may develop (Bernstein *et al*., 2005).

The management of IBD involves multiple steps. For IBD patients, aminosalicylates are the first line of pharmacologic treatment. The second step is to add corticosteroids, which typically cause a significant decrease in inflammation, if the patient does not respond to an appropriate dose of aminosalicylates. The dose can be reduced after the desired outcome is observed (McDowell, 2023).

The immune-modifying agents (eg anti-TNF agents) are the step three drugs. These are used when the patient does not respond to corticosteroids, steroids are required for prolonged periods, or the steroids cannot be tapered down without recurrence of symptoms (Yun and Hanauer, 2009).

Step-down therapy is increasingly preferred these days for patients with severe or high-risk illnesses. This involves starting higher step drugs earlier and quickly de-escalating them when a response is observed, such as anti-TNF medicines. Step-down therapy enhances patient outcomes and guards against problems in patients with severe or high-risk conditions. Clinical trial drugs, which are typically disease-specific that is, some only work for ulcerative colitis and others just for Crohn's disease are included in step four. Thalidomide and interleukin (IL)-11 for Crohn's disease, butyrate enema, nicotine patches, and heparin for ulcerative colitis are a few examples of these experimental drugs (Juillerat, 2014; K Ko and Auyeung, 2014).

With the aim of achieving mucosal repair and long-term remission, the paradigm for care has shifted from being symptom-driven to treat-to-target (Guan, 2019). This approach has been made easier by the development of targeted biologic medications that directly block key inflammatory mediators like interleukin (IL)-12, IL-23, and tumor necrosis factor-alpha (TNF-α). In addition, improved surgical techniques including laparoscopy and minimally invasive procedures have improved the prognosis of patients in need of surgery (Ratajczak *et al*., 2022).

Thanks to advancements in drug delivery, the oral route is the most popular approach for a medicine to enter the systemic circulation since it is the simplest to administer, costs less, encourages patient compliance, and has a more flexible formulation. Oral administration is used to administer about 90% of all medications. Solid oral dose forms are the most often used product category, even if the medications are taken orally. According to Goud and Pandey (2016), tablets are the most often used solid dosage form. They are categorized into two categories: immediate release and modulated release. Among the numerous disadvantages of the quick release pills is their non-site-specific medication release. On the other hand, a lot of medications just need to be released at the precise location where they are absorbed in order to improve absorption.

Drug release from the dosage form, the rate at which pharmaceuticals are absorbed in the gastrointestinal tract, the stomach emptying process, and the site of absorption all influence how differently drugs are absorbed in the GIT. Medications with short half-lives and easy absorption from the GIT are rapidly removed from the systemic circulation. It takes frequent doses to produce the desired therapeutic effect (Prinderre *et al*., 2011). One method to target site-specific medication release in the stomach for local or systemic effects is gastro-retentive drug delivery, which extends the gastric residence period. These dose forms greatly extend the time that the medications are retained in the stomach by staying in the stomach area for extended periods of time. It will gradually release the medication into the stomach, allowing the drug to be continually administered to the stomach, which is the absorption site in the gastrointestinal tract (Patel *et al*., 2012).

The importance of colon drug delivery has grown as well since it may be a place for the systemic injectable distribution of therapeutic proteins and peptides. These delivery systems enable medications to be released from the delivery system once the drug enters the colon when taken orally. In conclusion, the colon exhibits a high degree of receptivity to absorption enhancers due to its extended residency period of up to five days. Other routes for CDDs can be employed, even though the oral route is the most practical and recommended one. Rectal delivery of medication is the most direct route to the colon (Rama Prasad *et al*., 1998).

Colon drug delivery can be achieved through a variety of methods, including the formation of prodrugs, coatings made of pH-sensitive or biodegradable polymers, formulation design using polysaccharides, timed release systems, pressure-controlled drug delivery systems, and osmotic pressure-controlled systems. Because the colon has a high capacity for absorbing water, the contents of the colon are highly viscous, making it difficult for most medications to reach the absorptive membrane (Chien *et al*., 1992; Antonin *et al*., 1996).

Drug delivery via the colon is becoming more and more important. This is not only for treating localized colon diseases like Crohn's disease, ulcerative colitis, irritable bowel syndrome, and constipation, but also for the systemic delivery of therapeutic peptides, proteins, antiasthmatic medications, antihypertensive medications, and antidiabetic agents (Tozaki *et al*., 1997).

Nanosponges: A novel approach for targeted drug delivery

Nanosponges are tiny, mesh-like structures that have the ability to contain a wide range of materials, including drug molecules. They have a spherical colloidal structure and improve the solubilization ability of both lipid- and water-soluble medications. They make medications with delayed drug release more bioavailable. The amphiphilic characteristic of nanosponges allows them to carry hydrophilic and hydrophobic medicinal compounds due to their outside hydrophilic branching and internal hydrophobic chambers. With a foundation of long-chain polyesters in the solution and crosslinkers joining various polymer segments, they resemble a three-dimensional network (Ahire *et al*., 2020; Patel and Oswal, 2012).

Solid by nature, nanosponges can be prepared in dose forms for oral, parentral, topical, or inhalation.

For oral delivery, nanosponges can be prepared into tablets or capsules by dispersing them in a matrix containing lubricants, excipients, dilutes, and anti-cacking agents. Drug irritability can be greatly decreased by nanosponges without compromising their effectiveness (Jagtap *et al*., 2019). The nanosponges have a scaffold structure made of naturally degreadable polyester and are roughly the size of viruses. The long polyester stands are combined with tiny molecules known as cross-linkers, which are specific to specific polyester segments, in a solution.They create a spherical shape with several pockets where pharmaceuticals can be stored by cross-linking segments of polyester. Because the polyester degrades reliably in the body, the medication can be released according to a predetermined schedule (Trotta *et al*., 2009; Ahmed *et al*., 2013).

Advantages of Nanosponge

1. It can be applied as a targeted and controlled drug delivery device.
2. Its consistent drug release makes it a significant edge over other nanoparticle delivery methods currently under development.

It is also applicable to hydrophobic medications.

4. Nanosponge technology can be used to improve the solubility of medications.
5. The preparation method calls for basic chemistry (Singh *et al*., 2016).

Composition of nanosponge

Cross linking agent: Depending on the structure of the polymer and the medicine that has to be synthesized, the cross-linking agent can be chosen. Diphenyl carbonate, dichloromethane, dialyl carbonates, and diisocyanates are a few of the several instances (Suchita *et al*., 2017).

Polymer: The choice of polymer can affect both the creation and functionality of nanosponge materials. The size of the cavity needs to be appropriate to fit the specific medication molecule. The medicine to be encapsulated and the necessary release determine the polymer to use. The chosen polymer ought to possess the ability to bind with particular ligands.

Drug substance

- Molecular mass in the range of 100–400 Daltons.
- The drug molecule has less than five condensed rings in its structure.
- Solubility is less than 10 mg/ml in water.
- The substance's melting point is lower than 250 °C (Modi *et al*., 2023).

Methods of nanosponge preparation

Solvent method

The solvent approach is used to make nano sponges by combining the polymer with polar, aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). Subsequently, a 1:4 crosslinker is added to this combination. To reflux the solvent's temperature for a duration of one to forty-eight hours, the aforementioned reaction should be carried out at a temperature of ten degrees Celsius. After the reaction is finished, the solution is allowed to cool to ambient temperature, and the resulting product is then mixed with bi-distilled water. After the product is filtered under vacuum and refined by soxhlet extraction with ethanol and drying, the product is recovered (Bhowmik *et al*., 2018).

Ultrasound-Assisted Synthesis

In this procedure, cross-linkers and polymers react while being sonicated without the use of a solvent. This is the time to attach the polymer and cross-linker to the flask. After heating the flask for five hours at 900°C in an ultrasonic tub filled with water, sonicate it. Let cool down before washing to get rid of any stubborn polymer. Soak soxhlet in ethanol for an extended period of time to clean. The product should be vacuum-dried and kept at 250°C (Kaivalya, *et al*., 2020).

Emulsion solvent diffusion method

This process makes use of two phases the organic and aqueous phases in varying ratios to create nanosponges. Polyvinyl alcohol is employed in the aqueous phase, whereas a medication and polymer solution is used in the organic phase. After choosing the polymer and dissolving the medication in an appropriate organic solvent, the mixture is gradually introduced to the aqueous phase. The final mixture is agitated at 1000 rpm for over two hours. After formulation, the nanosponges are dried, cleaned, and filtered (Aritomi *et al*., 1996).

Hot Melting Procedure

This method is straightforward, repeatable, and solvent-free. It involves fusing CD together with a carbonyl linker, most often diphenyl carbonate. To guarantee a full crosslinking reaction, homogenization usually takes place at 90–130°C for at least five hours. An extended incubation period is necessary for the combination to undergo further crosslinking. An extremely fine, homogenous powder is produced at the end of the process. The powdered material is frequently cleaned with acetone or water, and usually undergoes a second washing with sodium hydroxide (NaOH) solution after being extracted using ethanol or acetone in a Soxhlet process (Sadjadi, 2019).

Characterization of Nano sponge

Microscopic study

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are used to study the microscopical properties of the drug, product, and nanosponges (drug nanosponges complex). Under an electron microscope, the variations in the crystallization state and product show the production of inclusion complexes (Jyoti *et al*., 2016).

Zeta potential

Using particle size equipment with an extra electrode, surface charge is measured. The nanosponges sample was put in an electrophoretic cell with a 15 v/cm electric field after being diluted with 0.1 mol/L potassium chloride. The polydispersity index and mean hydrodynamic diameter are calculated by averaging the entire measurement (Srinivas and Sreeja, 2013).

Loading efficiency

The ratio of the actual drug content in the nanosponge to the theoretical drug content is called loading efficiency. UV spectrophotometer and HPLC are used to determine it (Penjuri *et al*., 2016).

Solubility studies

As the phase solubility method, an inclusion complexes is the most commonly used methodology for nanosponge analysis. The phase solubility plot displays the degree of completion. The medicine's pH, solubulization, and other parameters influencing drug solubility can all be found out through solubility experiments (Trotta *et al*., 2012).

Particle size and polydispersity index

Ninety plus particle size re-equipped with MAS OPTION particle sizing software of the dynamic light scattering method can be used to calculate the particle size of nanosponges (Rosalba *et al*., 2011).

Infrared spectroscopy

The interaction between the medication in its solid state and the nanosponges was ascertained by IR spectroscopy. The nanosponges band changes as a compound forms (Farooq and Saini, 2013).

Thin layer chromatography (TLC)

When using TLC, a drug's retention factor can be used to determine whether a complex has formed between the drug and nanosponges (Singh *et al*., 2010).

Thermoanalytical method

The process ascertains how the medication substance changes during melting, oxidation, breakdown, and evaporation. These modifications show the complex's genesis. (Solunke *et al*., 2019).

X- Ray diffractometry and the single crystal x-ray structure analysis

By employing x-ray diffractometry, the inclusion complexation in the solid state was discovered. The crystalline nature of the medication and the development of inclusion complexes alter the diffraction patterns (Kurhe *et al*., 2015).

Swelling and water uptake

The produced nanosponges can be soaked in an aqueous solvent to measure the water uptake of swellable polymers such as polyamidoamine nanosponges (Mashaqbeh *et al*., 2021). Equations can be used to calculate swelling and water intake.

% Swelling=Marking of cylinder at aspecified time point/Initial marking before soaking×100 % Water uptake=Mass of hydrogel after 72 hrs/Initial mass of dry polymer×100

Resiliency (Viscoelastic properties)

Sponge resilience can be adjusted to yield beadlets with varying firmness or softness based on the requirements of the finished product. The rate of release is generally slowed down by increased crosslinking. Thus, the release as a function of cross-linking will be taken into consideration when studying and optimizing the resilience of sponges to meet the required standards (Thakre *et al*., 2016).

***In vitro* release studies**

Using a modified basket made of 5 m stainless steel mesh, the dissolution apparatus USP XXIIII can be used to study the dissolution profile of nanosponge. There is a 150 rpm rotational speed. In order to guarantee sink conditions, the dissolution medium is chosen while taking the actives' solubility into account. An appropriate analytical technique can be used to analyze samples from the dissolving medium. investigated using the USP dissolving device and a customized basket made of stainless steel mesh measuring five meters. There is a 150 rpm rotational speed. In order to guarantee sink conditions, the dissolution medium is chosen while taking the actives' solubility into account. An appropriate analytical technique can be used to analyze samples from the dissolving medium (Wester *et al*., 1991).

Permeation studies

To investigate the dissolution release of the manufactured nanosponge across a cellophane membrane, diffusion studies of the nanosponge can be conducted in a Franz diffusion cell. A 0.5g nanosponge sample can

be placed on a cellophane membrane, and diffusion studies were conducted at 37 ± 1° with a dissolution media of 250 ml of phosphate buffer (pH 7.4). Every one to eight hours, 5 milliliters of each sample can be taken out and replaced with an equivalent volume of brand-new dissolving medium. After then, the samples' medication content can be determined by using phosphate buffer as a blank (Renuka *et al*., 2011).

Factors influencing nanosponge

Type of polymer

The production and functionality of Nanosponges might be influenced by the kind of polymer that is utilized. A nanosponge's cavity size should be sufficient to allow the complexation of a drug molecule of a particular size.

Temperature

Variations in temperature affect the drug/nanosponge complexation process. With rising temperatures, the drug/nanosponge complex's apparent stability constant appears to be smaller. This could be because the drug/nanosponge contact forces such as hydrophobic and van der Waal forces are weaker (Khan *et al*., 2016).

Degree of substitution

The ability of the nanosponge to complex may be significantly influenced by the kind, quantity, and location of the substituent on the parent molecule. The degree of crosslinking and the number of substitutions are correlated; the higher the likelihood of higher crosslinking, the more substituents there are. Higher levels of crosslinking will result in very porous nanosponges because of the extra links between the polymers that form a mesh-like network (Shrestha and Bhattacharya, 2020).

Method of preparation

The way a drug is put into a nanosponge can have an impact on the drug/nanosponge complexation. But since a method's effectiveness depends on the characteristics of the drug and polymer, freeze drying has consistently shown to be the most effective strategy for drug complexation (Shivani and Poladi, 2015).

Mechanism of drug release from nanosponges

The active ingredient is given to the vehicle in an encapsulated form since the nanosponges have an open structure, meaning that there is no continuous barrier around them. Up until the vehicle is saturated and equilibrium is reached, the encapsulated active material can freely flow from the particles into the vehicle. The vehicle holding the active ingredient becomes unsaturated as soon as the product is applied to the skin, upsetting the equilibrium. Therefore, until the vehicle is either absorbed or dried, the flow of active chemicals from nanosponge particles into vehicles begins to diminish. Even when the nanosponge particles are retained on the stratum corneum, the skin's surface, the release of the active ingredient (Upadhye *et al*., 2021).

Application of nanosponge

In enzyme immobilization

The usage of nanosponges to stabilize the enzyme is common. When compared to CD, CD-NS exhibits significantly greater inclusion constants, making it a good choice for supporting enzyme immobilization. They support the maintenance of the immobilized enzymes' stability and catalytic efficacy (Deshmukh *et al*., 2016).

In chemotherapy

The drug-filled microscopic sponges reveal a targeting peptide that attaches to a tumor's radiation-induced cell surface receptor. The sponges attach to the surface and release their contents when they come into contact with tumor cells. One significant medication that has been designed as a nanosponge is paclitaxel, which is the main component of the anti-cancer treatment Taxol (Palminteri *et al*., 2021).

Topical agents

Topical agent-containing nanosponges release medication in a sustained and controlled manner. Topical nanosponges comprising lotions, creams, ointments, powders, and liquids can be a convenient way to create local anesthetics, antibiotics, and antifungal medicines (Iriventi *et al*., 2020).

Gases provided by nanosponges carrier

Oxygen is applied topically using a formulation of nanosponges to treat hypoxia. Hypoxia, or not getting enough oxygen in the body, has been connected to a number of illnesses, including cancer and inflammation.

As topical agent

A novel technology known as the Nanosponge delivery system makes it possible to administer topical medications in a controlled manner for long-term drug release and drug form retention on the skin. Among the drugs that can be produced as easily as local nanosponges are antibiotics, antifungals, and local anesthetics. Epidemics typically worsen in young people and during pregnancy. Conversely, this method offers a constant level of relaxation, removing pain without sacrificing effectiveness. A product that is gel, lotion, cream, ointment, liquid, or powder can have a variety of ingredients added to it (Cavalli *et al*., 2010).

Solubility enhancement

Compounds with the lowest water solubility can be made more soluble by using nanosponges. Drugs can be delivered as molecules and molecularly dispersed within the nanosponge structure to avoid the disintegration process. The tree's apparent melting may therefore quicken. By raising the substance's melting point and dissolving, many structural and bioavailability problems can be resolved, and the solubility of medications can be significantly increased using nanosponges (Moin *et al*., 2020).

Antiviral therapy

In order to combat viruses that cause respiratory tract infections (RTIs), such as influenza, rhinovirus, and respiratory syncytial virus, the nano hauler/carrier may be subjected to specific drug discharges into the nasal epithelia and lungs. Among the medications mentioned in the nano discharge classifications are zidovudine, saquinavir, interferon-alpha, acyclovir, Nelfinavir, and others (Vyas and Saraf, 2008).

Nanosponges as protective agent from light or degradation

In addition to being used as sunscreen in the cosmetics sector, gamma-oryzanol [A ferulic acid ester combination] is an antioxidant that is typically administered to balance organic components in food and pharmaceuticals. Due to its high unsteadiness and light deterioration, its utility is limited. Nanosponges have been filled with gamma oryzanol. revealing an image that compromises security. Gamma-oryzanol-medicated nanosponges were categorized

using an o/w emulsion and a gel (Ansari *et al*., 2011).

CONCLUSION

It has been established that hydrophilic and lipophilic drugs can be encapsulated or accumulated using nanosponges as a drug delivery method by creating a complex. They are capable of efficiently and under control delivering the medication to the intended location. Topical preparations in liquid or powder form, such as lotions, creams, ointments, etc., can comprise nanosponges. Targeting the medication to a particular spot has the advantage of reducing side effects, improving stability, improving formulation flexibility, and improving patient compliance. In the widest range of applications, the utilization of nanosponges is still in its infancy. Many of the research that are now being reported in the literature are based on their use in the biomedical and pharmaceutical industries. Nonetheless, pertinent research has recently been released on the application of nanosponges in water and, to a lesser extent, soil remediation.

NS might be applied as a conventional water filter in the future. Reducing manufacturing costs is the primary issue, which calls for the development of new production techniques as well as the investigation of novel polymers and crosslinkers. Due to their special characteristics, they are crucial to downstream production, which calls for in-depth study. There is a lot of potential in understanding how particle size, synthesis, crystallinity, porosity, and crosslinking strength affect drug release. The conventional method and ultrasound-assisted synthesis have been the most frequently documented preparation techniques up to this point, although new techniques such bubble electrospinning and solvent evaporation are currently being updated and created. Increasing yields, repeatability, and cost-effective production are the emerging trends; these will aid in mass production.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

Table 1: Some notable works on encapsulating various categories of drug in nanosponge

Drug	Category of drug Nanosponge vehicle	Nanosponge vehicle	Study Focus	Reference
Miconazole Nitrate	Antifungal	Beracyclodextrin, Di-phenyl carbonate	Drug release	(Kumar *et al*., 2015)
Camptothecin	Antineoplastic	Betacyclodextrin	Stability and solubility	(Cheng *et al*., 2004)
Nifedipine	Calcium channel blocker	Betacyclodextrin	Solubility	(Beig *et al*., 2013)
Temozolamie	Antitumour	Poly(valerolactineallylvalero lactone) and poly (valerolactoneallylvalero lactone oxepanedione)	Drug release	(Lee, 2017)

Ibuprofen	NSAID	Ethyl cellulose and PVA	Drug release	(Priyanka et al., 2018)
Gamma-Oryzanol	Antioxidant	Betacyclodextrin	Stability	(Sapino *et al*., 2013)
Fenofibrate	Fibrate	Maize starch, SDS	Solubility and Bioavailability	(Jadhav and Vavia, 2017)
Dexamethosane	Antitumour	Betacyclodextrin	Drug relase	(Swaminathan et al., 2013)
Paclitaxel	Antineoplastic	Betacyclodextrin	Bioavailability	(Torne *et al*., 2010)
Telmisartan	Antihypertensive	Carbonated crosslinkers	Dissolution rate	(Rao *et al*., 2013)
Itraconazole	Antifungal	Betacyclodextrin, and copolyvidonum	Solubility	(Swaminathan *et al*., 2007)
Glypizide	Sulfonylurea	Betacyclodextrin	Drug relase	(Arvapally *et al*., 2017)

Table 2: Previously evaluated nanosponge for treating colon related disorder

Name of drug	**Method of preparation**	**Reference**
Budenoside	Quasi-emulsion solvent diffusion	(Salunke and Upmanyu,2021)
Resveratrol	3^3 Box–Behnken design	(Gandhi *et al*., 2020)
5-Fluorouracil	Hot melt technique	(Arun Raj and Thomas, 2019)

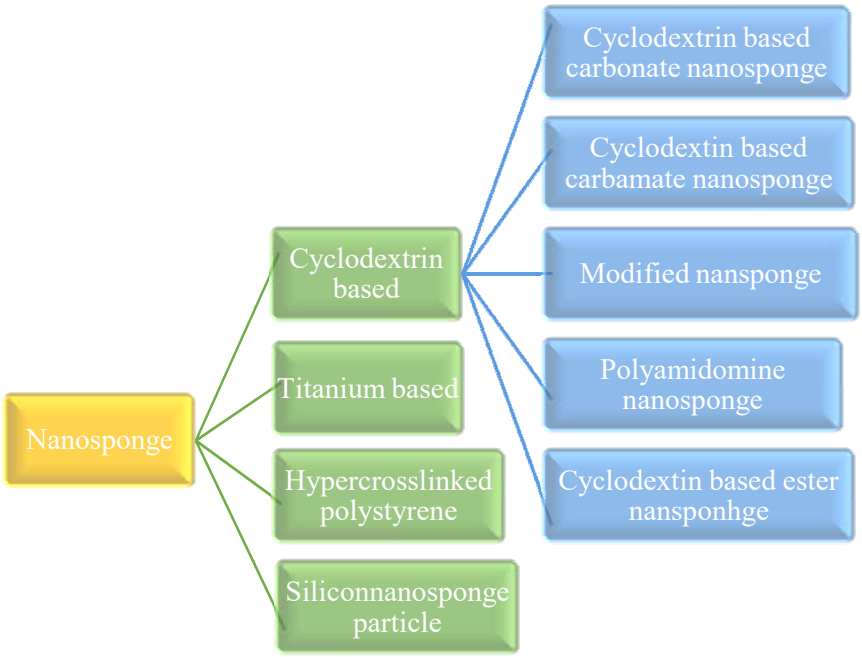

Figure 1: Classification of nanosponge

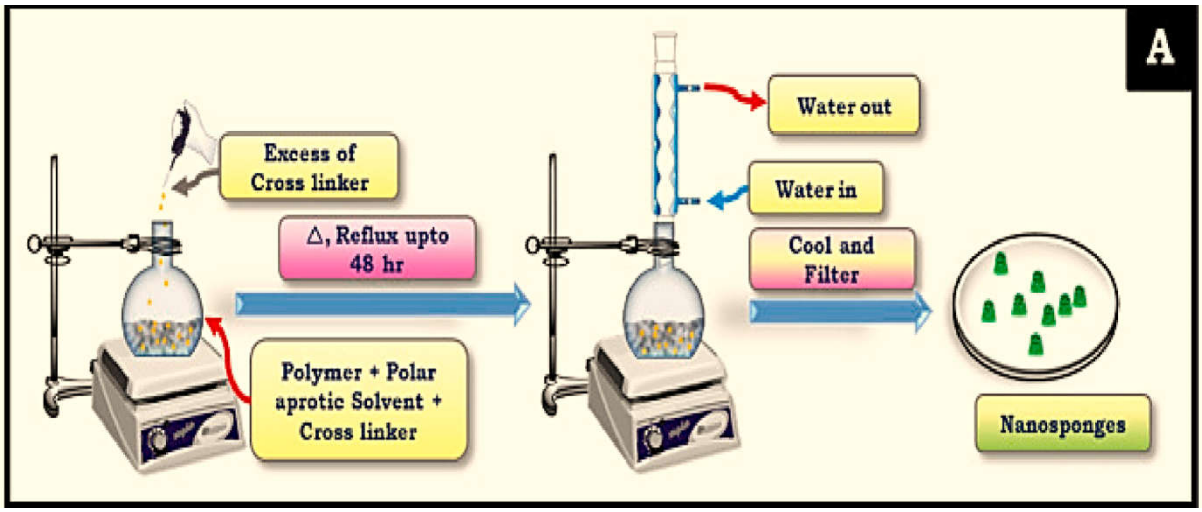

Figure 2: Solvent method for preparing nanosponge

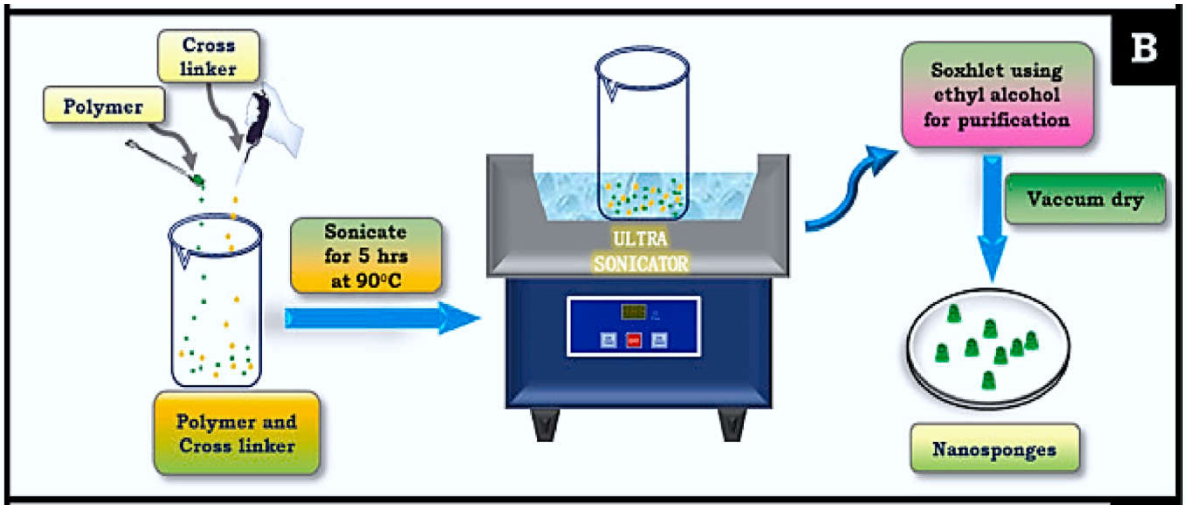

Figure 3: Ultrssound assisted method for preparing nanosponge

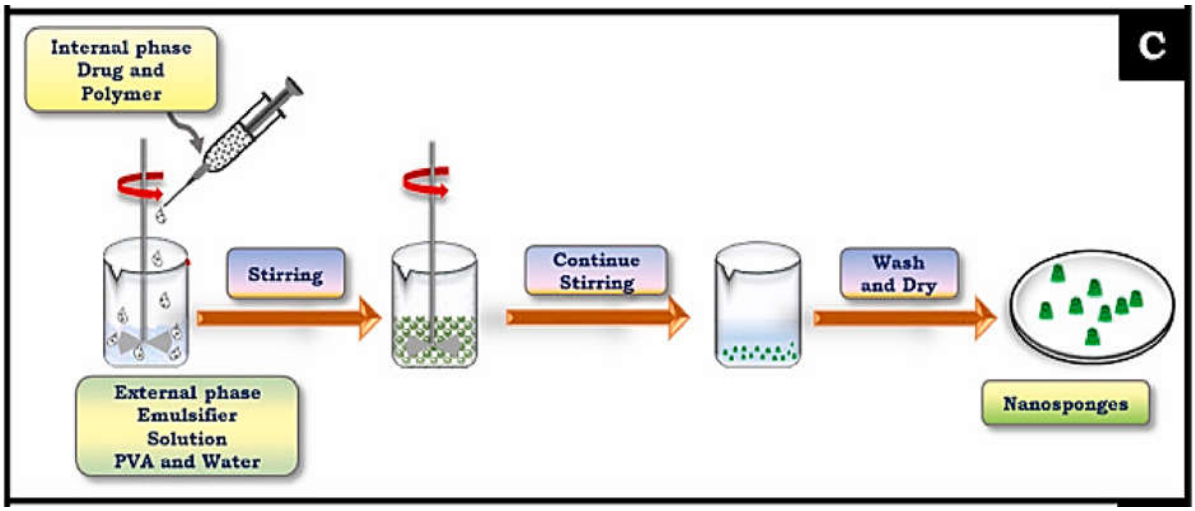

Figure 4: Emulsion solvent diffusion method for preparing naosponge

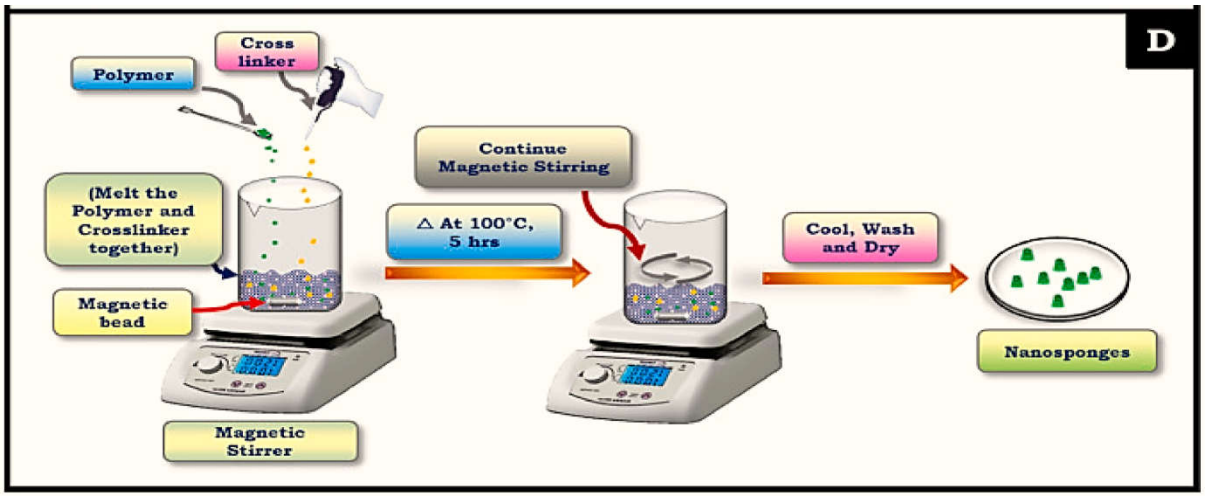

Figure 5: Hot Melting Procedure for preparing nanosponge

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