Section A-Research paper

RECENT DEVELOPMENTS IN NANOSPONGES FOR DRUG DELIVERY AND CANCER TREATMENT

Poushali Boral [a#], Soumik Ray [a#], Mrinmoy Ghosh[a], Mayukh Jana[a]*, Tania Chowdhury[b], Bratati Bandyopadhyay[a], Poulami Ghosh[c] , Biplab Debnath [d]*

[a] Department of Pharmaceutics, Bharat Technology, Uluberia, WB, India

[b] Department of Pharmacology, Bharat Technology, Uluberia, Howrah, WB, India

[c] Department of Pharmacognosy, Bharat Technology, Uluberia, Howrah, WB, India

[d,] Department of Pharmaceutical Chemistry, Bharat Technology, Uluberia, WB, India

# These authors contributed equally to this work

***Corresponding authors:**

Mr. Mayukh Jana

Associate Professor,

Head, Department of Pharmaceutics,

Bharat Technology,

Banitabla, Uluberia, Howrah, West Bengal- 711316.

E-mail :mayukhjana@gmail.com

Ph No-+917003730170

or

Dr. Biplab Debnath,

Professor & Principal,

Department of Pharmaceutical Chemistry, , India

E-mail: biplab.d86@gmail.com

Ph No-+919471304160

ABSTRACT

The creation of a targeted drug delivery system has been made possible by the most current creative advances in nanotechnology. Use of specialised drug delivery systems is necessary to effectively target a molecule to a specific site with the aid of a drug delivery system. The invention of the nanosponge solves issues such as drug toxicity, poor bioavailability, and predictable drug release. Nanosponges are tiny sponges that can move through the body to a particular spot and adhere to the surface, releasing medication in a regulated and predictable way. It is common practice to build nanosponges with three-dimensional (3D) porous architectures, narrow size distributions, and high entrapment efficiencies for cancer therapy and drug delivery. The porous shape that characterizes nanosponges in nature makes them uniquely able to entrap drug molecules. Cyclodextrins and carbonyl or di-carboxylate

(Crosslinkers) are used to crosslink the ingredients in the formulation of nanosponges. High specificity, biocompatibility, degradability, and prolonged release behavior have all been utilized in nanosponge-based delivery systems for cancer therapy. In addition to the currently used processes, which include melting techniques, solvent techniques, ultrasound-assisted preparation, and emulsion solvent diffusion methods, eco-friendly approaches for the production of nanosponges still need to be discovered. The nanosponges utilized as anticancer agents are the major subject of this review. In-depth discussion is regarding the various factors and formulation process for the nanosponges.

KEYWORDS: Targeted drug delivery system, Crosslinker, Cyclodextrin-based nanosponges, Cancer therapy, Bioavailability.

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INTRODUCTION

Contrasted to traditional drug distribution methods, the cost of the healthcare system has increased due to an increase in the research and development of new drugs over the past few decades. Due to advances in carcinogensis, cancer cell biology, and tumour microenvironment, the way that cancer is treated has undergone significant changes. Many clinical and pre-clinical studies have been conducted, however malignant tumours are still lethal. Thus, to increase the survival of cancer patients, nanocarriers for anticancer medications were created[11].

Nanotechnology and nanomedicine are developing quickly. The goals in developing nanodrugs are improved pharmacokinetic qualities, higher safety and biocompatibility, and both targeted and nonspecific targeting and administration. Here, Nanosponges create a controlled release of active substances at the predetermined place due to their reduced size and effective carrier qualities. The term “Nanosponges” means small sponges which have porous structures. Nanosponges are nanoparticles with an average diameter of less than 1µm and the size of a virus. The nanosponges are three-dimensional scaffold(backbone) or network of polyester that can break down naturally (fig:1). To create nanosponges, these polyesters are dissolved in a solution together with a cross-linker. Here, the polyester degrades in the body moderately because it is normally biodegradable. When the scaffold of nanosponges disintegrates, it releases the drug molecules that are loaded in an unfavourable way[1]. Containing small molecules called cross-linkers that have an affinity for specific polyester segments. These cross-linkers “cross-link” polyester segments to form a spherical shape with several pockets where pharmaceuticals can be kept[4]. The first type is based on nanosponges and nanocapsules. Nanocapsules such as poly (epsilon-caprolactone) are also encapsulating nanoparticles. They have an aqueous core where drug molecules can be trapped.

The second type is complexing nanoparticles, which draw molecules with electrostatic charges. The third type is conjugating nanoparticles, which have covalent connections with drugs. In contrast to other nanoparticles, they are porous, non-toxic, and insoluble in both water and organic solvents. They are also stable at high temperatures up to 300°C.[4] These

tiny sponges can travel throughout the body the body until they reach the intended target spot, where they adhere to the surface and start to release the drug in a regulated and predictable manner. It will be more effective for a specified dosage because the drug can be released at the designated target place rather than circulating throughout the body[7]. The nanosponges can bind to the target site more strongly because of the chemical linkers. The nanosponges may be paracrystalline or crystalline in nature. There are various loading capacities for paracrystaline nanosponges.[4]

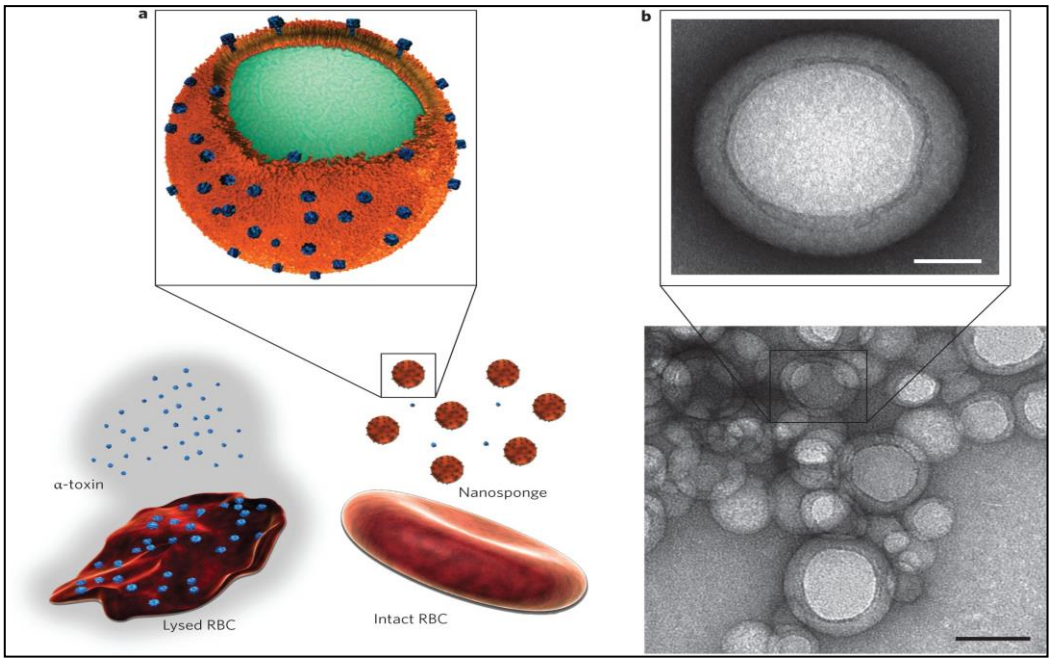


Fig. 1 . Nanosponges[14]

Nanotherapeutics may use nanoporous and mesoporous systems (based on organic or inorganic nanosponges). Organic systems have been given more research attention since inorganic systems are hazardous. Cancer therapy involves the use of Nanosponges based on cyclodextrin(CD). The creation of cyclodextrin nanosponges involves the employment of a variety of organic or inorganic components, including silicon particles, titanium or metal oxide, and carbon-coated metallic nanosponges. The anticancer medication Lapatinib has been developed into nanosponges to increase its solubility and bioavailability and to lower its oral dosage. For cell-based cancer therapy, peptide nanosponges (~80 nm) were developed.

ADVANTAGES

- This technology offers entrapment of ingredients and reduces side effects.
- These formulations are stable over range of pH 1 to 11.
- Poorly soluble drugs become more soluble because of nanosponges.
- They improve the drug's bioavailability.

- It has a prolonged release that offers continuous action for up to 12 hours.

DISADVANTAGES

- The main disadvantage of these nanosponges is their ability to contain only tiny molecules.
- Depend only upon the loading capacities.

MATERIALS AND METHODS FOR THE PREPARATION OF NANOSPONGES

Materials:

Polymers	Copolymers	Crosslinkers
Hyper cross linked Polystyrenes, Cyclodextrines an derivatives like Methyl β-Cyclodextrine, 2-Hydroxy Propyl β-Cyclodextrines.	Ethyl Cellulose, Poly(valerolactone-allylvalerolactoneoxepanedione), Polyvinyl Alcohol(PVA).	Glutarldehyde, Diphenyl Carbonate, Epichloridine, Carboxylic Acid Dianhydrides,Dichloromethane and Diarylcarbonates.

Methods of Preparation of Nanosponge :

Emulsion solvent diffusion method

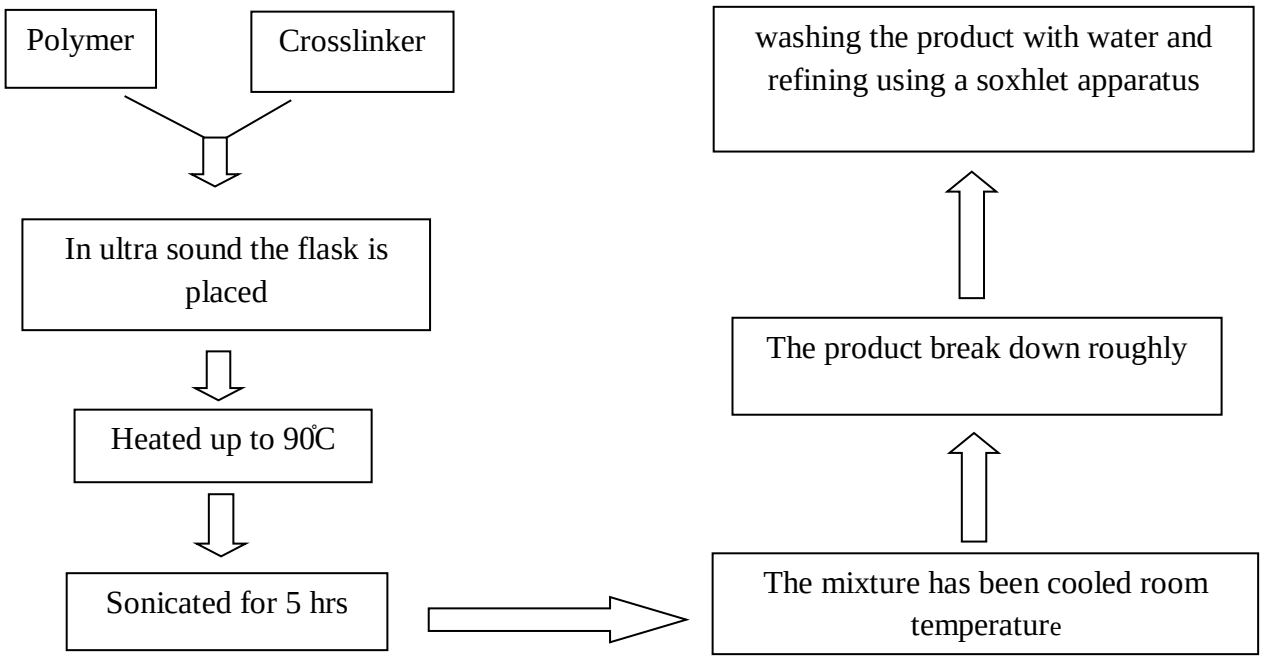
Ethyl Cellulose and Polyvinyl Alcohol were used to create varied ratios of Nanosponges. Following the dissolution of the drug and Ethyl Cellulose dispersion phase in 20 ml of Dichloromethane , a specific volume of Polyvinyl Alcohol was slowly added to 150 ml of aqueous continuous phase. For 2 hrs, the reaction mixture was stirred at 1000 rpm. The formed nanosponges were collected by filtration and dried in an oven for 24 hrs at 400°C. To assure the removal of any remaining solvent, the dried nanosponges were kept in vacuum desiccators.[4]

Solvent method

Bycombining polar aprotic solvents like Dimethyl Sulfoxide, Dimethyl formamide, Nanosponges are made using the solvent method. Then, in a 1:4 ratio, a crosslinker is added to this mixture. Over a period of time between 1 to 48 hrs, the reaction should be carried out at a temperature of 10℃ to reflux the solvent's temperature. After the reaction is finished, the mixture is cooled to room temperature, and the resultant product is then added to bi-distilled water. Under vaccum, the product is filtered, refined by soxhlet extraction with Ethanol, and then dried to recover the product.[1]

Ultra-sound assisted synthesis

Without the use of a solvent, crosslinkers and polymers are made to react in a flask. The combination is sonicated for 5 hrs while the flask is submerged in an ultrasound bath that is filled with water and heated to 90℃. The product is next broken into rough bits when the mixture has been cooled room temperature. In order to produce nanosponges, the non-reacting polymer is finally eliminated by washing the product with water and refining using a soxhlet apparatus(ethanol).[1]



Flow chart of Ultra-sound assisted synthesis

FACTORS AFFECTING IN THE FORMULATION OF NANOSPONGES

Types of polymer

The polymer used to prepare nanosponges can have an impact on how they formulated as well as how they are pre-formulated. The nanosponge'scavity or pore size should be able to fit a drug molecule of the appropriate size.[2]

Drug types

The following features of the drug molecules should be present for them to be complex with nanosponges:

- There shouldn't be more than five condensed rings in the drug's structure.
- There should be fewer than 10 mg/ml of solubility in water.
- The drug's molecular weight should fall between 100 to 400 Daltons.

- The drug's melting point must be lower than 250°C.[1]

Method of preparation

The process used to load the drug into the nanosponges may modify how the drug and the nanosponges are complexed. However, the type or properties of the drug and polymer are ultimately determined if a procedure is successful. In some cases, freeze drying has frequently been proven to be a more efficient method of drug complexation.[1]

Degree of substitution

The type, quantity, and placement of substituents on the parent molecule can have a significant impact on the formulation of the nanosponge.[2]

Temperature

The appearance of drugs or nanosponges can be impacted by the changes in the temperature. The stability constant of the drug or nanosponge complex typically decreases as the temperature rises, which may be because the drug and nanosponges interact less forcefully as the temperature rises. [1]

RATIONALITY OF NANOSPONGES FOR CANCER TREATMENT

After arriving at the site of action, nanoparticles instantly release the medicine they have been loaded with, causing a "burst." Because nanoparticles are comprised of biodegradable polymers and release their medications in a delayed, controlled manner after coming into contact with a tumour, effective dosage cannot be accurately calculated.[29] Both aqueous and organic solvents can be used to dissolve nanosponges. These carriers are heat-stable and non-toxic. Due to their water solubility, nanosponges can be used to dissolve insoluble medicines after being loaded with them.[30] In comparison to other nanoparticles, loading of nanosponges is quite simple. The functional groups poking out of the nanosponge surface can be utilised for post-modification techniques like functionalization.[31] Many nanoparticles have complicated chemical compositions, making it difficult to easily scale them up for large-scale manufacture. On the other hand, it is simple to scale up nanosponges for commercial manufacturing as they are merely made of polymers and crosslinkers. In contrast to other nanoparticles, which are difficult to recreate if they lose their structure, nanosponges can be easily recreated using techniques including cleaning with environmentally friendly solvents, moderate heating, or altering pH or ionic strength.[32]

For cancer therapy and drug administration, nanosponges with three-dimensional (3D) porous architectures, narrow size distributions, and high entrapment efficiencies are frequently produced. In addition to being magnetised to achieve the right magnetic properties, they aid to improve the solubility of lipophilic medicinal agents and pharmaceuticals with alternatives for targeted distribution. They have demonstrated desirable qualities that make them appropriate for biological applications, including good biocompatibility, biodegradability, and low cytotoxicity. For instance, cyclodextrin-based nanosponges show high potential for producing inclusion and non-inclusion complexes with a variety of medications and active

molecules, providing a useful therapeutic vehicle for transferring medications with low bioavailability. The medication and cyclodextrin molecule join forces to generate inclusion complex nanosponges.[33]

Nanosponges are excellent candidates for the encapsulation of various compounds because of their mesh-like/colloidal structures, including drugs, phytochemicals, volatile oils, antineoplastic agents, genetic materials, proteins/peptides, and others. One illustration is the development of peptide nanosponges (80 nm) for cell-based cancer therapy. [34]

APPLICATION OF NANOSPONGES

1. Nanosponges as Anti-Cancer Agents

Nanosponges may be used to deliver anticancer drugs to tumours. Researchers claim that this approach is 3-5 times more effective at suppressing versus direct drug administration, tumour development.

a) Cyclodextrin-based nanosponges drug delivery

Cyclodextrin nanosponges have been developed as secure drug delivery systems for the treatment of a variety of disorders (especially cancer/tumors) because of their special qualities, including biocompatibility, porous architectures, controlled-release behaviour, and enhanced oral bioavailability[11]. The solubility of pharmaceuticals and therapeutic agents and stability of compounds (e.g., volatile compounds) can be increased by using cyclodextrin nanosponges, which have variable lipophilic cavities and a hydrophilic network based on the properties of cross-linkers (fig :2).[19] Notably, the amount of cross-linkers used can influence the porosity and surface area of nanosponges; typically, using more cross-linkers results in nanosponges with smaller diameters and greater porosity. These nanosystems are capable of good thermal stability (up to 300 °C) and resistance to organic solvents, which makes them interesting candidates for a range of nanoformulations.[20] For instance, kynurenic acid, an antioxidant with medicinal properties, has been made more soluble in water by the development of nanosponges based on cyclodextrin. In turn, this antioxidant's solubility was greatly improved, and drug loading was increased. They could also achieve proficiency in (19.06%) and encapsulation (95.31%) [28].

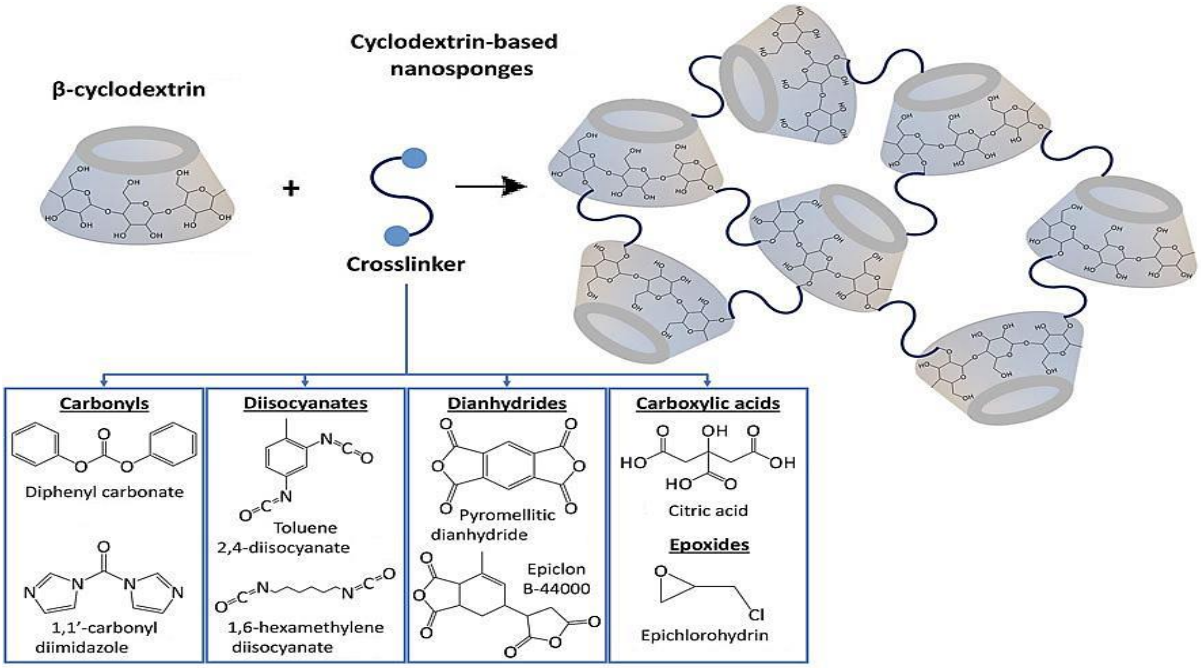


Fig : 2 various cross-linkers used to create cyclodextrin nanosponge-based system[20]

Paclitaxel

Chemotherapy is a challenging procedure. It can occasionally result in toxicity; the fundamental cause of the high toxicity of the majority of very successful anti-neoplastic medications is their non-specificity. The negative effects caused by anticancer compounds are substantially more common because of their limited water solubility. Small and non-small-cell lung cancer , bladder cancer, neck cancer and head cancer are all treated with paclitaxel. It exhibits a wide range of adverse effects and has a low water solubility of 0.5 mg/l.

Paclitaxel has been subject to numerous studies to alter it using a variety of techniques, including emulsification, micellization, liposome formulation, non-liposomal lipid transport, and many more. For chemotherapy in the treatment of recurrent metastatic breast cancer, albumin-bound paclitaxel, a novel formulation was created. Paclitaxel was encapsulated in the nanosponge by mixing cyclo-dextrins with diphenyl carbonate as a cross-linker following extensive study and development of nanosponges. Nanosponge, adiameter of roughly 350 nm was attained. Paclitaxel nanosponge was administerded orally to ratsto assess its pharmacokinetic characteristics. When compared to commercial taxol, it demonstrated a threefold improvement in bioavailability.[12,15]

Temozolomide

Temozolomide was proposed as a possible medication for the treatment of giloma when it was discovered to generate in-vitro toxicity in phenyl carbonate-based β-CD nanosponges . When gilomas have been surgically removed, it has been used as the first line of treatment. Since thet have a 1.8 hour half-life and a 15 % protein binding rate, intermittent dosage is

necessary. Hence, Temozolomide has achieved success in the field of nanotechnology [21] (Fig. 3).

Magnetic resonance spectroscopy can be used to infer the structure of nanosponges. The pharmacological interaction was calculated based on a tiny change in the molecule's wavelength that indicated contact with hydrophobic groups. The embodiment and complexion inside the Nanosponge were conducted using Fourier-transformation infrared radiation (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD). After Nanosponge formulation, the acquired peaks either disappeared or were relocated. Temozolomide formulation based on Nanosponge demonstrated prolonged in-vitro release. It displayed the same level of toxicity as a free drug. Following treatment, the morphology of a malignant human glioblastoma tumour deteriorated. A more advanced version of this formulation was created to potentially produce distribution to the target brain spot. [12,22]

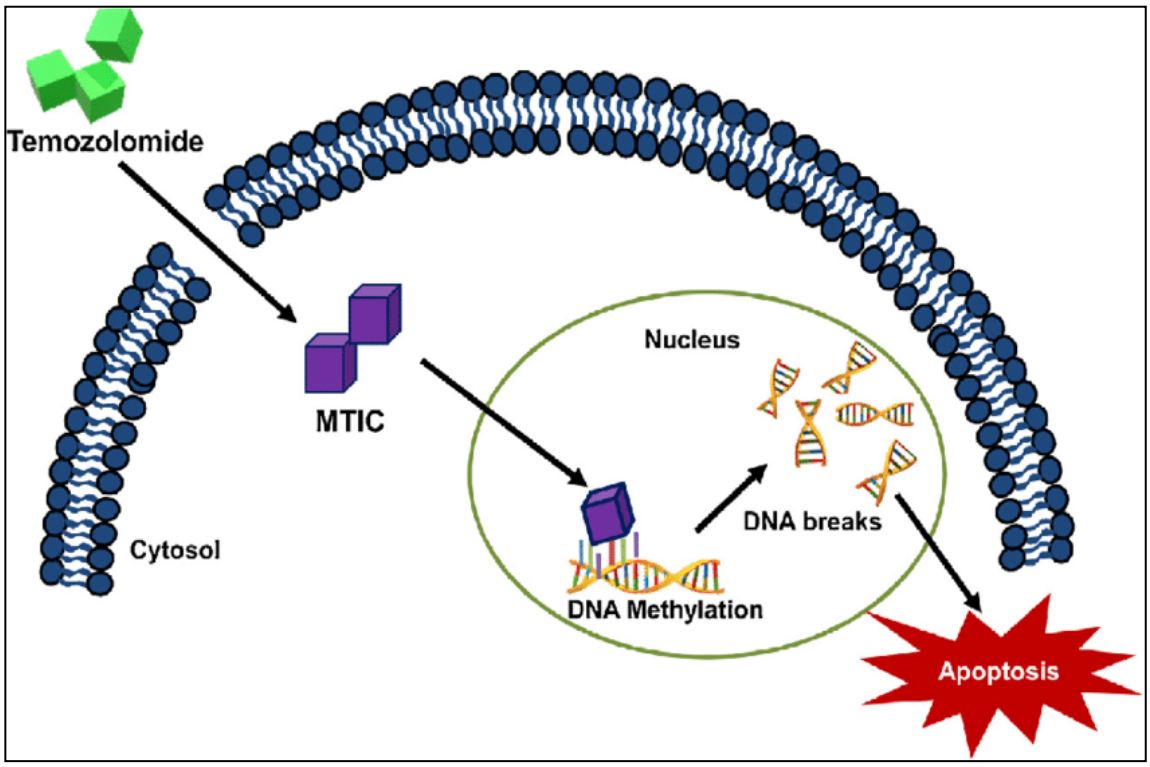


Fig. 3 : Mechanism of action of Temozolomide[16]

Resveratrol

An organic stilibenoid phenol is Resveratrol. It can be derived through foods like grapes, groundnuts, pistachios and blueberries. It is an antioxidant and has anti-oncogenic qualities. It has ashort half-life and is rapidly digested before being excreted. When used orally, it has a

negligible absorption and may have fatal consequences. It's usage is therefore limited to ongoing clinical studies. Nanotechnology has been created to get around these restrictions.

Resveratrol's solubility, soundness and skin permeability were all improved by the nanosponges. The molar premise of CD:CDI was used to determine the cross-linker concentrations (1:2 and 1:4 respectively). When compared to commercially available medications, the solubility was 33 to 48 times higher in the F1:2 and F1:4 formulations. The interaction of resveratrol with nanosponge resulted in notable modification to the FTIR peaks. In comparison to F1:2, the release of the F1:4 formulation was far more uniform. Also, the photographs were enhanced. When compared to skin penetration by hydroalcoholic mixtures, the skin permeability of resvertrol by nanosponge formulation was much higher in pigs. Resvertrol F1:4 caused a rabbit to acquire mucosa on both sides.[12,23]

Curcumin

One of the best anti-cancer agents is curcumin. It is a hydrophobic polyphenolic phytochemical that dissolves poorly in liquid at acidic pH but very well at basic pH (fig. 4).[14] It is a crucial component of turmeric. In addition to being an anticancer agent. Additionally, it functions as a cardioprotective, neuroprotective, and antiathescleritis agent. It is used to treat a variety of tumour types, including prostate cancer, hepatic cellular carcinoma, leukaemia, and colon tumours. The action of curcumin on atomic nuclear factor –κB, tumor necrosis factor-α, interferon-Y, interleukins, C-Jun N-terminal kinase, cyclo-oxygenases, protein kinase-C nitrogen activated protein kinase, and many other reactors inhibits cell proliferation and metastasis and simultaneously induces apoptosis.Curcumin was thought to be more effective than a single pathway therapy based on the pleiotropic qualities. Curcumin has a wide range of applications, but it also has significant drawbacks.It has considerable metabolism, low solubility, and low gastro intestinal absorption rate in addition to low bioavailability. At a physiological pH, degradation takes place.[24]

In order to address the aforementioned formulational issues, Kurien et al. created the β-CD NSs curcumin formulation, which was successful as an antineoplastic medication. Compared to ordinary curcumin, the solubility of curcumin was increased significantly. This resulted from curcumin's complexation with NSs. A performance index (PI) of 0.476 was attained with a unimodal molecular size distribution within a narrow range, and the molecular size was approximately 487 nm. Zeta potential was approximately -27mV, which was high enough to allow for the development of a steady suspension. The medication can easily diffuse into the polymeric matrix of NSs in an amorphous state, resulting in a controlled release.At 176°C, the DSC was shown to be ineffective in producing a peak suggesting the formation of an inclusion complex. After being created, curcumin maintains its original subatomic structure. The formulation was found to be non- haemolytic upto a concentration of 2mg/ml.[25]

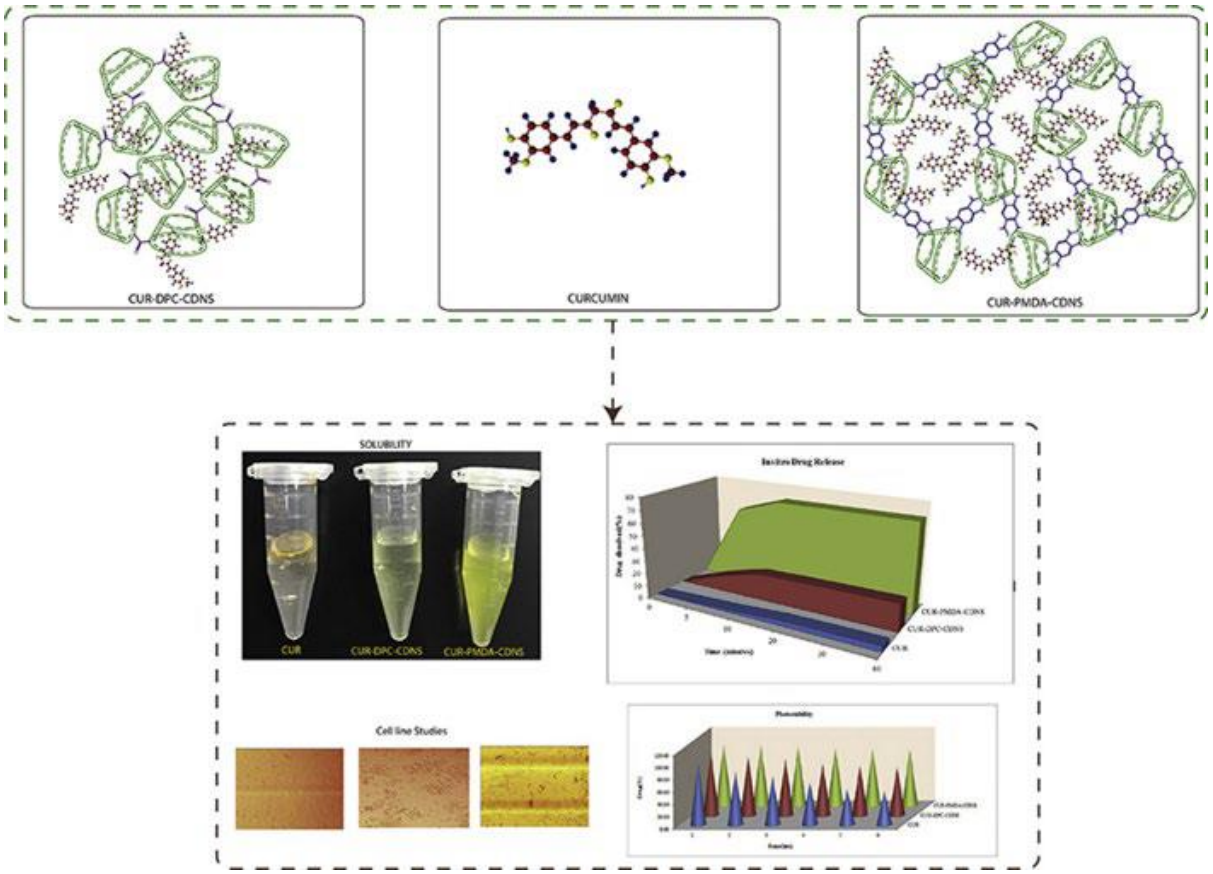


Fig. 4 . Curcumin as an anticancer agent[14]

b) Delivery of Oxygen by Nanosponge Formulation used in Cancer Therapy

Hypoxia is caused by a lack of oxygen. Patients with cervical malignant tumours that are hypoxic have a poor prognosis.The ability to store gases like oxygen and the use of 1-methylcyclopropene in CD-based NSs, which were created using alpha, beta, or gamma carbonyl di-imidazole, suggest that they may have promising applications in cosmetics, drugs, and biotechnology.In order to supply oxygen, three distinct CDI-based nanosponges—alpha, beta, and gamma—were coupled with the NS formulation. High shear rates were used to homogenise the suspension for two to three minutes.Also, it was sealed, filled with oxygen, and kept at 25°C to show the stability of NS. The toxicity investigations were conducted using Vero cells.On the NS surface, a range of between 40 and 50m^2/g was achieved. The circular NS's molecular size was limited to 400–500 nm. Zeta potential was recorded as negative (-30mV). The toxicity of this oxygen mixture was undetectable.Even after 15 days of storage at 25°C, there was no aggregation or deterioration. Under the impact of ultrasound, which revealed an underlying oxygen surge, oxygen penetration in -CD NS was increased to above 192%.[17,18]

A hydrogel arrangement based on Pluronic® was employed to create a uniform release of oxygen in order to eliminate the oxygen spike. By combining sodium chloride, PEG 400, and

deca-fluoropentane, Trotta et al. created the O2 stacked NSs. These substances were combined with NSs and water to improve distribution, stockpiling, and stacking. The two formulations, -CD NSs and -CD NSs, were created. Ultrasound had a beneficial effect on O2 discharge; a 30% rise in the rate of O2 penetration from the formulation of -CD NSs was attained. [12]

(c) Water- Soluble and Sparingly Soluble Anti-Cancer Molecule

Flurouracil (5-FU)

The preferred medication for treating colorectal cancer, stomach malignant tumours, and cervical malignant development is 5-FU.Its limited solubility caused it to be poorly absorbed when given orally. When supplied parentally, it has a short terminal half-life (8–20 mins). When taken intravenously, the side effects were quite severe.As a result, gamma CD-based NSs were employed to enhance the drug's characteristics. A direct compression technique was used to make the 5-FU nanosponge. The excipients were well mixed before being compressed into 8mm-diameter tablets. To 96.66%, the drug's invitro release was increased. It was possible to achieve better solubility profiles.[12]

Doxorubicin

Doxorubicin hydrochloride infusion was the first anticancer medication in liposomal form to receive administrative approval. Cancers of the delicate tissues and main organs can both be treated with doxorubicin.Nanotechnology was recommended in order to lessen its negative effects, which included cardiotoxicity and doxorubicin's sharp action. Following incorporation into the nanosponges, it was noticed that doxorubicin released in a mild and consistent manner.Doxorubicin released at a pH-dependent average rate of 1% in an acidic pH over the course of two hours and 29% in a basic pH over the course of three hours. Therefore, it can be inferred that doxorubicin was protected by the NS in the stomach's acidic environment before being transported to the gut and duodenum's basic environment.[26,27]

2. Other applications of Nanosponges

a) Solubility Enhancement

The main problem, which can impact how well the formulation works, is with the badly water-soluble medications. Nanosponge is the carrier device, traps the drug in its pore and raises the formulation’s solubility and bioavailability. It is common practise to use inclusion complex of cyclodextrin nanosponge method to increase drug solubility and bioavailability.[13]

b) Nanosponges in Drug Delivery

Drug nanospongecomplexes’s solubility and permeability play key roles in accelerating rate of disintegration. It has been reported that cyclodextrin-based nanosponges are three to five times more effective at delivering the drug to the desired location. The solid structure of nanosponges allows for the production of them in a range of dose forms, including oral, parenteral, topical, and inhalation. For the production of tablets, capsules or oral

administration, the complexes of the nanosponges are distributed in an appropriate additive such as lubricant, fillers and anti- cracking agents. [14]

c) Protein Delivery

Using bovine serum albumin(BSA) as a model protein, the enclosing ability of cyclodextrin-based nanosponges was examinated, Protein solutions of bovin serum albumin are stored in lyophilized state due to their brittle nature. Using a nanosponge made of cyclodextrin, inclusion compoundes containing 1-methyl cyclopropane, oxygen, and carbon dioxide were produced. The uptake of proteins delivered via cyclodextrin, such as bovine serum albumin, can be improved by nanosponges. Nanosponges have also been used to encapsulate proteins, regulate and stabilize distribution, and immobilize enzymes.[12, 14]

d) Photo Degradation Protective Agent

Gamma-oryzanol can be contained in a nanosponge, which offers superior photoprotection. Food and pharmaceutical raw materials are stabilised using the ferulic acid combination known as gamma oryzanol. The antioxidant is natural. Using it is confined because to its extremely high level of instability and photodegradation.[14]

FUTURE ASPECTS

Thankfully, the field of nanosponges continues to pique the curiosity of the chemical research community thanks to significant discoveries and fresh scientific problems. It is necessary to conduct more studies on the kinematics and biochemical interactions of nanosponges within animals. It is unclear how nanosponges affect the lymphatic and immune systems as well as a variety of organs. For instance, it is known that nanosponges influence the immune system's response to a variety of diseases; however, additional study is required to fully comprehend how and to what extent this occurs, as well as the consequences of risk groups (age, genotype).To better understand the potential function of nanosponges in diseases that have recently been linked to them (such as Crohn's disease, neurodegenerative diseases, autoimmune diseases, and cancer), nanoscale characterization techniques should be used more frequently to locate nanosponges at disease sites in affected organs or tissues and to establish relevant interaction mechanisms.

CONCLUSION

Nanosponges have applications in a number of industries, including agrochemistry, biomedicine, cosmetics, and bioremediation.[14] Nanosponges are available in liquid, powder, and topical forms like creams, lotions, and ointments. They ar also capable of carrying both lipophilic and hydrophilic drug molecules.As prospective alternatives to targeted drug delivery and cancer therapy, nanosponge-based systems with amazing porosity, straightforward functionalization methods, distinctive topologies, and cost-effectiveness have been investigated. Cyclodextrin nanosponges stand out among the others due to their distinctive qualities, excellent biocompatibility, low toxicity, and simplicity of surface

modification, making them the most frequently tested nanosponges in bio and nanomedicine.[11] Drugs that are targeted to a particular location have fewer side effects, are more stable, have more formulation flexibility, and have higher patient compliance. They are able to controllably deliver the medication to the desired location.

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