REVIEW ON NANOSPONGES IN CANCER THERAPY

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ABSTRACT:

The development of recent colloidal, porous, microscopic mesh-like delivery systems, or nanosponges, with a size range of 1 m, provides regulated drug delivery at a specific spot in the majority of cancer treatments. Nanosponges have a crucial role to play in the controlled shipping of drugs. Numerous medications, both lipophilic and hydrophilic, may be placed into nanosponges for targeted drug administration and to increase the solubility and bioavailability of the same medication. Nanosponge are able to move freely across the entire frame until they interact with a specific target point, cling to the floor, and begin a controlled drug release. After the development of Nanosponges, issues caused by conventional drug delivery systems were solved. Nanosponges are multifunctional drug delivery systems that both increase treatment efficacy and lessen undesirable side effects. A breakthrough in the treatment of cancer has been made possible by the development of nanosponges (NSs), which are polymeric structures made of branching cyclodextrin (CD). The traditional medication delivery mechanism, which is employed in the treatment of most malignancies, is frequently insoluble and has negative side effects. Thus, energetic drugs that are trapped in complex polymers made of cyclodextrins are employed in nanosponges. Because of the drug's increased solubility, hydrophobic tablets may incorporate into NSs. In this review, we concentrated on providing a fundamental introduction to nanosponges. We also concluded their preparation techniques, polymers used, and characterization.

Keywords: Nanosponge, cancer, cyclodextrin, solubility enhancement, Nanosponges in cancer.

1.INTRODUCTION

With its healing targets for cancer treatment, tailored drug delivery technology has undoubtedly given pharmaceuticals a new lease on life. It is also working to deliver drugs to the proper locations in the body and to regulate their release to prevent overdose. The key advancements inside the site of therapies include the administration of drugs by target-oriented in cancer treatment that enhances healing efficacy, reduction in side effects, and optimal dosage routine [1]. These issues can be resolved by the development of new, complex molecules known as Nanosponges, which selectively and effectively localize pharmacologically active molecules at a pre-diagnosed goal in healing awareness and prescribing access to the non-target ordinary cell lining and thereby decrease toxic effects and increase the therapeutic index of the anti-cancer drug [2]. Nanosponges are microscopic sponges with porous structures that can bind poorly soluble pharmaceuticals to a matrix and increase their bioavailability by altering the drug molecules' pharmacokinetic characteristics. These nanosponges represent a special elegance of nanoparticles that are often generated by employing plant compounds. In contrast to other nanoparticles, they may be porous, dependable, and strong at high temperatures up to 300°C [3, 4]. They may also be insoluble in both water and natural solvents. Due to its 3D structure, which includes chambers with tunable polarity and nonmetric size, they can catch, ship, and launch a wide range of chemicals. NSs are colloidal, solid nanoparticles made of hypercross-linked polymers that have a man-sized cavity. In a combination of polymer solution, the small molecules known as crosslinkers function as tiny

grappling hooks that cause sphere-shaped particles with cavities for drug molecules to develop. Polyester that is biodegradable degrades gradually in the body. This NSs allows for reliable drug administration with less side effects [5, 6].

Nanosponges are nanoparticles with an average diameter of less than 1 m and a length comparable to a contagious disease. They can improve the bioavailability of poorly soluble medications by binding them within the matrix due to their small size and porous nature. This is done by altering the drug molecules' pharmacokinetic characteristics. A revolutionary method called nanosponge provides regulated drug delivery for the treatment of cancer [7]. An developing method for the delivery of cancer drugs is nanosponge. For the development of overall effectiveness of orally, parenterally, and topically delivered medications in cancer treatment, nanosponge drug delivery device is utilised. The medicine can be released at a chosen place in a controlled manner via a nanosponge that can circulate throughout the entire body. Numerous diseases can be treated with nanosponges, and this technology is more effective than the traditional approach at distributing breast cancer medications [8]. The core of nanosponges, which are nanoparticles, may contain several different therapeutic ingredients. These tiny particles can transport both hydrophilic and lipophilic compounds, and they can also increase the solubility of medicinal molecules [9]. Nanosponges' diminutive size and spherical shape have allowed them to evolve into a variety of dosage forms, including parenteral, aerosol, topical, tablets, and capsules [10].

Because of their smaller size and more effective service features, nanosponges create a controlled release of energetic components at the predetermined spot. The nanoparticles use attaching to the surface of the tumour cells to release the medicine in a predictable manner. As tissue accumulation through more ideal permeability and retention (EPR) depends on extravasations of pores on extremely permeable tumour vasculature, targeting the device's particle size is the top priority inside the tumor's large pore size [11, 12]. Due to its organic structure and smooth texture, it resembles a globe, has a community, and is completely biodegradable. The complex molecule disintegrates in the frame at a predetermined rate. As the name suggests, nanosponges are tiny particles that contain pharmaceuticals. As the sponge starts to dissolve, the pharmaceuticals are gradually released. NSs are three-dimensional scaffolds made of a community of polyester that can naturally degrade. When the scaffold breaks, the loaded medicine molecule is released, which lessens the negative effects. This technology is five times more effective than conventional methods at producing breast cancer drugs. Most NSs with a cyclodextrin base are utilised in the treatment of cancer. Nanosponges are porous, risk-free, and robust at high temperatures up to 300°C compared to other nanoparticles [13, 14].

Porous nanosponges are mostly utilised to encapsulate medications that aren't easily soluble. These nanosponges may wear both lipophilic and hydrophilic medicines and have a high-water solubility. The formulations of Nanosponge are stable at temperatures up to 300°C and a pH range of one to eleven [15].

2.NANOSPONGES STRUCTURE

The core of nanosponges is a polymeric nanoparticle, and pink blood cell membranes are used to round it (as shown in figure 1). In the creation of nanosponges, cross-linkers, co-polymers, and polymers are employed as materials. The nanomaterial (polyester) has a three-dimensional community and is biodegradable, allowing it to break down inside the body gradually and release the medicine. The middlelets are involved in the absorption of toxins and can include a variety of medications, including enzymes, proteins, vaccinations, and antibodies. The ability of both hydrophilic and lipophilic pharmaceuticals to be transported through the body is a significant benefit, and nanosponges have been shown to enhance the solubility, stability, and bioavailability of medications [16, 17].

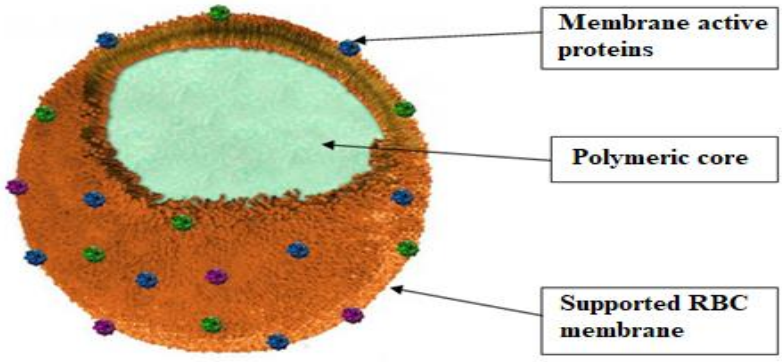

Figure 1: Structure of Nanosponge (Self-created by using Microsoft Windows Paints Version 21H1)

2.1 Polymer

The development and overall effectiveness of Nanosponges can be impacted by the polymer choice. The medicine to be encapsulated and the planned launch serve as the sole determinants of the polymer choice. The chosen polymer must have the ability to bond with particular ligands. Hypercrosslinked polystyrene, cyclodextrines and its derivatives, such as methyl cyclodextrin, and copolymers such ethyl cellulose and PVA are a few examples [18].

2.2 Cross linking agent

Depending on the polymer's shape and the medicine being developed, the choice of the cross-linking agent may be made. Diphenyl carbonate, dichloromethane, dialyl carbonates, and diisocyanates are some unique examples [19].

2.3 Drug substance:

a. Molecular weight among100 and 400 Daltons.

b. Drug molecule includesmuch less than five condensed rings.

c. Solubility in water is much less than 10 mg/ml.

d. Melting factor of substance is beneath 250°C.

3.TYPES OF NANOSPONGES

a. Cyclodextrin based nanosponges.
    - Cyclodextrin based carbamate nanosponges.
    - Cyclodextrin based carbonate nanosponges.
    - Cyclodextrin based ester nanosponges.
    - Polyamidoamine Nano sponges.
    - Modified nanosponges

b. Titanium based nanosponges.

c. Silicon nanosponge particles.

d. Hyper cross-linked polystyrene Nano sponges.

4.LOADING OF DRUG IN NANOSPONGES

Pre-treatment is used to reduce a nanosponge's major particle size to below 500 nm. To prevent aggregates, NSs are sonicated while suspended in water. The suspended solution is centrifuged to separate the colloidal fraction. The sample is then freeze dried after the resilient has been separated. The NS is acquired in the form of an aqueous suspension, which is dissolved in additional medication and agitated continuously until a complexation forms. Centrifugation is used to isolate the simple drug form. Furthermore, via solvent evaporation or freeze drying, the NSs are produced as solid crystals. Because paracrystalline NSs exhibit a range of loading capabilities, their crystal shape is greatly advantageous in complexation with drugs. Loading of Nanosponges as shown in figure 2. When compared to paracrystalline NSs, crystalline NSs have a higher loading capacity [20, 21]. In table 1 list of drugs formulated as Nanosponges shown.

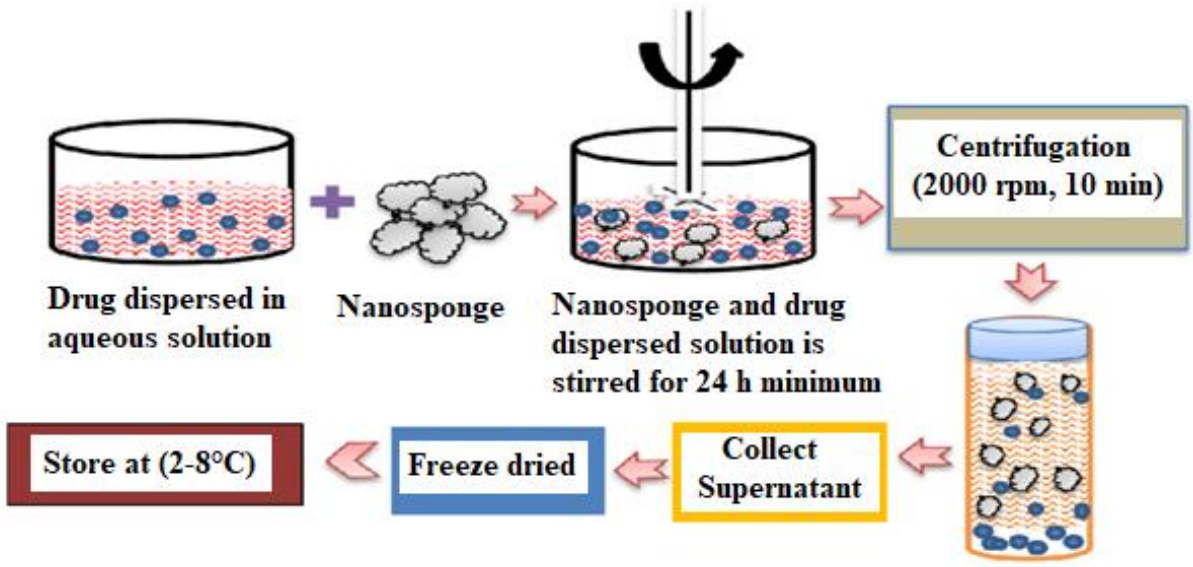

Figure 2: Loading of Nanosponges (Self created by using Microsoft Windows Paints Version21H1).

List of Drugs Formulated as Nanosponges

Table 1: Drugs formulated as Nanosponges

Drug	Nanosponge vehicle	Category of drug
Tamoxifen	β – Cyclodextrin	Breast cancer
Paclitaxel	β – Cyclodextrin	Cancer
Campothecin	β – Cyclodextrin	Cancer
Resveratrol	β – Cyclodextrin	Cancer, Inflammation
Temozolamide	Poly(valerolacto-allylvalerolactone)	Brain tumor

5.FORMULATION OF DOXORUBICIN LOADED NANOSPONGES

By using the method of emulsion solvent evaporation, doxorubicin nanosponges were created. The formulation uses two distinct polymers. Ten batches of Nanosponges (F1 F10) were taken, each of which had different ratios of the polymers ethylene cellulose (EC) and polymethyl methacrylate (PMMA). The aqueous phase is made up of distilled water and polyvinyl alcohol. The polymers were dissolved in dichloromethane, and the drug was dissolved in the necessary solvent (dimethyl sulphoxide). After adding the drug solution to the polymer solution, the aggregate was thoroughly shook. Then, using a high-speed homogenizer, the drug polymer combination was added to the aqueous phase and homogenised for two hours at 35°C at 1500 revolutions per minute (rpm). High-speed cooling centrifuges were used to separate the produced Nanosponges, and the residue was then freeze dried [23, 24]. Formulation of nanosponges as shown in table 2.

Table 2: Formulation of Nanosponge

Sr. No.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Drug (mg)	100	100	100	100	100	100	100	100	100	100
2	EC (mg)	100	200	300	400	500	-	-	-	-	-
3	PMMA (mg)	-	-	-	-	-	100	200	300	400	500
4	PVA (g)	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3

5	DCM (ml)	20	20	20	20	20	20	20	20	20	20
6	Distilled water (ml)	100	100	100	100	100	100	100	100	100	100

EC- Ethyl cellulose, PMMA- Poly methacrylate, DCM- Dichloro methane, PVA- Polyvinyl Alcohol.

6.MECHANISM OF DRUG RELEASE FROM NANOSPONGES

Nanosponges have the capacity to replicate how tablets are injected into the body, increasing their effectiveness and minimising negative effects. Due to its smooth texture and organic nature, it is completely biodegradable. Nanosponges, as the name suggests, are nanoparticles that may contain medicine. This medicine is progressively released over time because the sponge has started to degrade. Because these Nanosponges can cross the tough BBB, according to some recent studies, we can employ them to carry cancer medications and attach linkers that will exclusively connect to cancer cells [25]. The community of polyester in nanosponges, a third-dimensional scaffold, allows for spontaneous degradation. These are formed of polyesters, some of which may be normally biodegradable, mixed with a cross-linker solution. The polyester disintegrates inside the body. Once the scaffold has been compromised, those small sponges can move through the body until they reach the precise target area and begin to distribute the medication in a predictable and regulated manner. A nanosponge reduces the negative effects on other tissues by delivering the anti-cancer agent to the cancerous tissues right away. This also increases the effectiveness of the medicine by giving the tumour cells a better understanding of the drug right away. This method of medicine delivery could result in fewer side effects. NSs with a cyclodextrin basis are typically used in the treatment of cancer [26, 27]. The nanosponge based drug delivery as shown in figure 3.

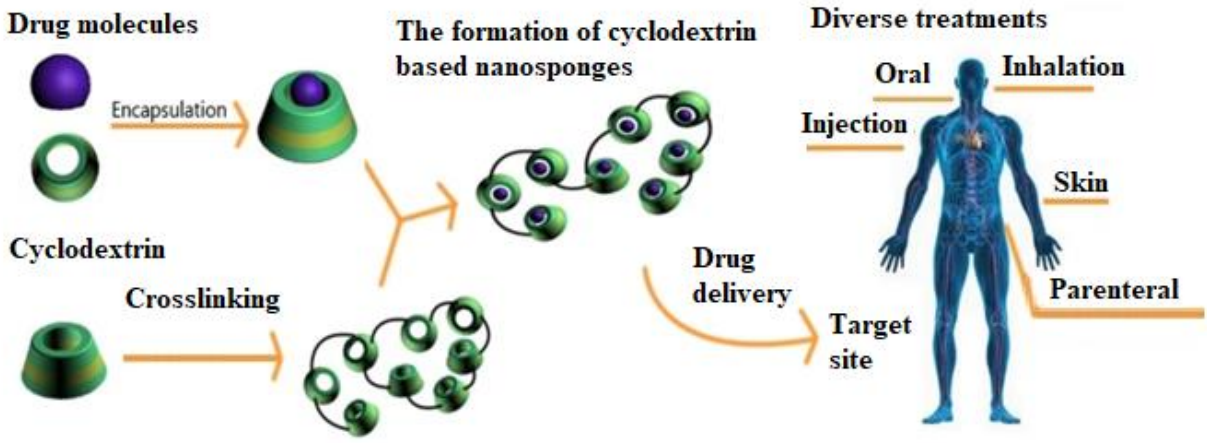

Figure 3: Nanosponge based drug delivery (Self created by using Microsoft Windows Paints Version21H1)

7.IMPACT OF NANOSPONGES ON CANCER

Complex molecules called nanosponges can be employed to deliver anti-cancer medications to specific bodily locations. Although the technology is still in development, it has been demonstrated to be up to five times more effective than conventional methods for dispensing breast cancer medications. Nanosponges have the power to change how tablets are ingested into the body, increasing their effectiveness and reducing negative effects. In the organism, the complex molecule disintegrates in a predictable way [28]. When the name suggests, nanosponges are tiny particles that contain medicine that are gradually released over time as the sponge starts to dissolve. These gadgets can be linked to a chemical transporter, which carries molecules across biological barriers and into specific intracellular niches that are difficult for most tablets to access. These nanosponges may be able to cross the challenging blood-brain barrier, according to several recent research [29]. Therefore, we may attach a linker that will only attach to cancer cells to nanosponges that are holding a cancer drug. A nanosponge reduces the negative effects on other tissues by delivering the anti-cancer agent immediately to the malignant tissues. It will also boost its effectiveness by delivering a better concentration of the drug immediately to the tumour cells. These nanosponges are extremely innovative and adaptable, and they may be designed to deliver proteins, peptides, DNA, and other tiny chemical compounds such as potent medications. These nanosponges can be made magnetic by arranging them around substances that have magnetic qualities. They can

also be attached to a fluorescent tag to indicate where they are supposed to go. Nanosponges can be transported through the lungs and veins thanks to their small size. Instead of the medicine widely circulating throughout the body, nanosponges deliver it directly to the tumour site [30]. Because less of the drug comes into contact with healthy tissue, it is therefore more effective for a given dosage and will also have fewer harmful side effects. They do so in a predictable way when releasing the medication. In contrast to many other nanoparticle delivery designs, once they reach their target, they rapidly and uncontrollably unleash the full amount of their medicine. This is known as the burst impact, and it makes choosing the right dosage levels for strong drugs challenging. Because nanosponges dissolve in water, it is possible to use hydrophobic anticancer tablets that are difficult to dissolve in water. Currently, such tablets must be mixed with every other substance, known as an adjuvant reagent, which decreases the drug's effectiveness and may have negative side effects. Because the nanosponges have a variety of side groups that are accessible, it is simple to bind medications to the particles [31].

8.NANOSPONGES AS ANTI-CANCER AGENTS:

i. CD- Based NSs Drug Delivery

Temozolomide

It has been used as the first line treatment alongside surgical excision of gliomas. Because of their brief half-life of 1.8 hours and 15% of protein binding, it necessitates occasional dosage. Temozolomide has so achieved success in the field of nanotechnology. Magnetic resonance spectroscopy can be used to estimate the structure of NSs. The pharmacological interaction was calculated based on a tiny shift in the molecule's wavelength, which indicated interaction with hydrophobic groups. Temozolomide formulation based on NS demonstrated prolonged in-vitro release. After treatment, the morphology of the malignant human glioblastoma tumour worsened. This formula was improved upon to potentially generate distribution to the target area of the brain [32, 33].

Tamoxifen

Tamoxifen is a drug used to treat breast cancer in pre- and post-menopausal women that falls under the class of drugs known as selective oestrogen receptor modulators, which have both an estrogenic and an antiestrogenic effect. However, it has several side effects, some of which are also life-threatening, including endometrial carcinoma, metastatic tumour, venous thrombosis, and pulmonary emboli. It is therefore necessary to produce a tamoxifen formulation with a sustained release in order to lessen these side effects. In addition, it has a very poor water solubility, which restricts its therapeutic action and, once more, makes it a challenge to develop the formulation. To solve the problem of tamoxifen delivery to the site, extensive research has been conducted [34, 35] on tamoxifen delivery via new Nano suppliers.

Paclitaxel

Chemotherapy involves a difficult process. It can occasionally result in toxicity; the non-specificity of anti-neoplastic medications is the main cause of the majority of highly effective medications becoming harmful. Due to the anticancer compounds' weak water solubility, the likelihood of adverse effects is significantly higher as a result of their use. Small and non-small cell lung cancer, bladder cancer, neck, 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. Numerous studies have been conducted to modify paclitaxel using a variety of techniques, including micellization, emulsification, liposome formation, non-liposomal lipid transport, and many more. The treatment of recurrent metastatic breast cancer with chemotherapy includes the development of a novel formulation called albumin-bound paclitaxel. Paclitaxel was enclosed in the Nanosponge by mixing cyclodextrins with diphenyl carbonate as a cross-linker after extensive study and development of Nano sponges. 500mg of paclitaxel/g of nano sponge with a diameter of around 350 nm was developed as the drug payload. Rats were given oral dose of paclitaxel NS to test its pharmacokinetic characteristics. When compared to commercial taxol, it demonstrated a three-fold increase in bioavailability [36, 37].

Resveratrol

A natural stilibenoid phenol, resveratrol is. It can be derived through foods like blueberries, pistachios, grapes, and groundnuts. It is an antioxidant with anti-oncogenic qualities. It has a short half-life and is rapidly digested before being excreted. When administered orally, it has a negligible bioavailability and may be fatal. Its usage is therefore limited to ongoing clinical studies. Nanotechnology has been created in order to get around these restrictions [38].

Curcumin

One of the best anti-cancer substances is curcumin. It is a hydrophobic polyphenolic phytochemical that dissolves poorly in liquids at acidic pH levels but very well at basic pH levels. It is a key ingredient in turmeric.

In addition to having anticancer properties, it also has neuroprotective, cardioprotective, and antiatherosclerotic properties. It is used to treat a variety of tumour types, including prostate cancer, hepatic cellular carcinoma, leukaemia, and colon cancers [39].

Curcumin has a lot of 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. The -CD NSs curcumin formulation was created to address the aforementioned formulational difficulties and was successful in treating cancer. Compared to ordinary curcumin, the solubility of curcumin was increased significantly. This resulted from curcumin's complexation with NSs [40].

ETB Glutathione

ETB is a chemical compound called [6, 7-bis (2-methoxy-ethoxy)-quinazolin-4-yl]-(-3-ethynylphenyl) amine hydrochloride, which binds to the human epidermal growth factor receptor through suppressing tyrosine kinase. By encouraging cell cycle arrest and death, it prevents angiogenesis. By binding to the EGFR's intracellular tyrosine kinase, the cell is invaded, which inhibits the receptor's autophosphorylation and prevents downstream signal transmission. In addition to treating ovarian cancer, head and neck cancer, and gliomas, ETB glutathione is also employed in this treatment. A few obstacles prevent the appropriate formation of TB glutathione. due to its weak solubility, it has a poor bioavailability. Is one of the causes of the drug's subpar formulation. Additionally, it is unstable in an intestinal environment. In addition to diarrhoea and other haematological side effects, it causes toxic consequences such a severe skin rash. The therapeutic effectiveness of the drug molecules is therefore increased by encasing them inside the interior cavity of nano-carriers in order to avoid unwanted negative effects. The solubility, targeting effectiveness, and biocompatibility rate are all improved by this method. Additionally, the medicine has successfully launched throughout time. In an one step procedure carried out at room temperature, ETB glutathione was integrated into NSs. Using high pressure liquid chromatography (HPLC), in-vitro release was assessed [41, 42].

Delivery of Oxygen by NS Formulation Used in Cancer Therapy

Hypoxia is brought on by a lack of oxygen. Patients with cervical malignant tumours that are hypoxic have a low chance of survival. CD-based NSs, which can store gases like oxygen and were produced using alpha, beta, or gamma carbonyl di-imidazole, have the potential to be useful in the fields of 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. To further show the stability of NS, it was sealed, filled with oxygen, and stored at 25°C [43].

ii. Water- Soluble and Sparingly Soluble Anti-Cancer Molecules

Doxorubicin

Doxorubicin hydrochloride infusion was the first liposomal anticancer medication to receive administrative approval. Major organ tumours and cancer of the soft tissues can be treated with doxorubicin. It had some drawbacks, including as cardiotoxicity and doxorubicin's sharp action, thus nanotechnology was suggested to lessen these effects. After being incorporated into the nanosponges, it was discovered that doxorubicin was released in a consistent and moderate 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 [44, 45].

Flurouracil (5-FU)

The medicine of choice for the treatment of cervical cancer, stomach cancer, and colorectal cancer is 5-FU. Due to its limited solubility, it was poorly absorbed when given orally. When given to children, it has a short terminal half-life (8–20 minutes). When administered intravenously, the negative effects produced were extremely photosensitive. Thus, gamma CD-based NSs were employed to enhance the drug's characteristics. The 5-FU nanosponge was created using the direct compression approach. The excipients were well mixed before being compacted into tablets measuring approximately 8mm. The drug's in-vitro release was enhanced to 96.66%. Achieved were better solubility profiles [46, 47].

CONCLUSION

According to the aforementioned review, nanosponges contain hydrophilic and lipophilic medications and release them at the target spot in a regulated manner. The ratio of cross linkers and polymers can be balanced, and the release charge can be adjusted. Nanosponges enable insoluble tablets while preventing controlled release and physiochemical deterioration of active ingredients.

The nanosponge is a godsend for the treatment of cancer and works well for the delivery of hydrophobic and lipophilic medicines. The use of nanosponges has boosted the efficacy of therapeutic formulation and drug stability maintenance. As a conclusion, nanosponges are one of the preferred drug delivery systems and a growing trend in pharmaceutical sciences for the administration of oral, topical, and parenteral drugs.

ABBREVIATIONS

CD: Cyclodextrin, NSs: Nanosponges, EPR: Enhanced permeability and retention, EC: Ethyl cellulose, PMMA: Polymethyl methacrylate, EC - Ethyl cellulose, PMMA - Poly methacrylate, DCM: Dichloro methane, PVA - Polyvinyl Alcohol.

CONFLICT OF INTEREST

No

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