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Nanosponges: Novel Drug Delivery for Treatment of cancer

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ABSTRACT

The problems faced due to the conventional drug delivery system have been defeated after the invention of nanosponges (NS). NSs drug delivery system is considered as the novel drug delivery system which has emerged as one of the most successful fields in life sciences. Nanosponges have been proved to be a boon in the treatment of cancer. Conventional drug delivery system, used in the treatment of cancer is generally insoluble and produces serious side effects. Thus, nanosponges are used in which the active drug is entrapped in a complex of polymers such as cyclodextrins. The drug is released from these nanoparticles to the specific targeted tumor sites and produce optimum therapeutic effect and minimal side effects. The nanosponges are generally biodegradable in nature. The solubility of the drug is increased due to which hydrophobic drugs can be incorporated within the NSs. The patient compliance is also improved due to this type of drug delivery system. Various factors which influence the drug delivery of NSs are the type of polymer used, type of drug incorporated, temperature, method of preparation and degree of substitution. The NSs are formulated by maintaining the above factors. The methods used are solvent method, melt technique, ultra-sound assisted synthesis, emulsion solvent diffusion method and loading the drug into the NSs. NSs are either crystalline or paracrystalline which have different loading capacities. This review mainly focuses on the nanosponges used as anticancer agents. The factors, method of formulation of the nanosponges are discussed in detail.

Keywords: Nanosponge, biodegradable, polymers, minimal side effects, targeted tumor sites.

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INTRODUCTION:

Over the past few decades, there has been a rise in research of new drugs which has made health-care system expensive when compared to conventional drug delivery systems. Cancer treatment encountered major modifications due to the improved process of carcinogensis, cancer cell biology and tumor micro-environment. Despite of various clinical and pre-clinical researches, malignant tumors still remain fatal. Therefore, nanocarriers for anticancer drugs were developed to improve the survival of cancer patients.

Most anticancer drugs are less water soluble and hence it results in multistep synthetic routes, which requires high specificity and selectivity. This can result in difficulty in development of formulations. Conventional techniques are not efficiently used in the delivery of atineoplastic agents, as it releases active ingredients inconveniently for a long period of time with short duration of action. It also induces acute adverse effects with toxic effects on active tissues. [1-3]

Nanomedicines and nanotechnology is emerging in a rapid pace. The objectives in development of nanodrugs are both specific and nonspecific in targeting and delivery, better safety and biocompatibility with improved pharmacokinetic properties. Nanosponges produce controlled release of active ingredients to the predestined site, due to its smaller size and efficacious carrier characteristics. The nanoparticles release drug in a predictable fashion by adhereing to the surface of the tumor cells. Targeting the particle size of the system is the primary need in the tumor with large pore size, as tissue accumulation by enhanced permeability and retention (EPR) depends on extravasation of pores on highly permeable tumor vasculture. [4-7]

Nanosponges (NSs) are prepared by using nanotechnology. These are made up of tiny particles with a narrow cavity measuring few nanometers. These tiny particles have the capability of carrying both hydrophillic and lipophillic drug substances and hence, it can increase the stability of poorly-soluble drugs[8]. Nanosponges are three-dimensional scaffold with a network of polyester that is capable of degrading naturally. These are made of polyesters which are generally biodegradable, are mixed with a solution of cross-linkers. The polyester breaks down in the body. Once the scaffold is broken down, it releases the loaded drug molecule in a

derogatory fashion. As a result of this type of drug delivery, there is a reduce in side effects[9].

Nanoporous and mesoporous systems (organic or inorganic based NSs) have potential application in nanotherapeutics. Research prominence has been laid on organic systems, as inorganic systems leads to toxicity[10]. Cyclodextrin (CD) based NSs are used in cancer therapy[11]. An illustration of development and application of CD- based NSs is presented in this review.

Various organic or inorganic materials such as silicon particle, titanium or other metal oxide and carbon coated metallic NSs are used in the formation of CD NSs. Initially CD NSs were used in water purification, as it can strongly bind to organic molecules in water and removes them at low concentrations. In the field of pharmaceuticals and biomedical sciences they are being used to increase solubility, bioavailability and stability, regulation of drug release, cosmetic conveyers and diagnostics.[12]

Nanosponges have a nanosized cavity which belongs to hyper crosslinked polymer based colloidal solid nanoparticles. The average diameter of the NSs ranges upto 1µm and fractions below 500nm can also be selected. They may be present in the form of crystalline or paracrystalline configuration depending on the loading capacities. Due to the presence of these unique properties NSs is considered as a drug of choice in delivery system for cancer therapy.

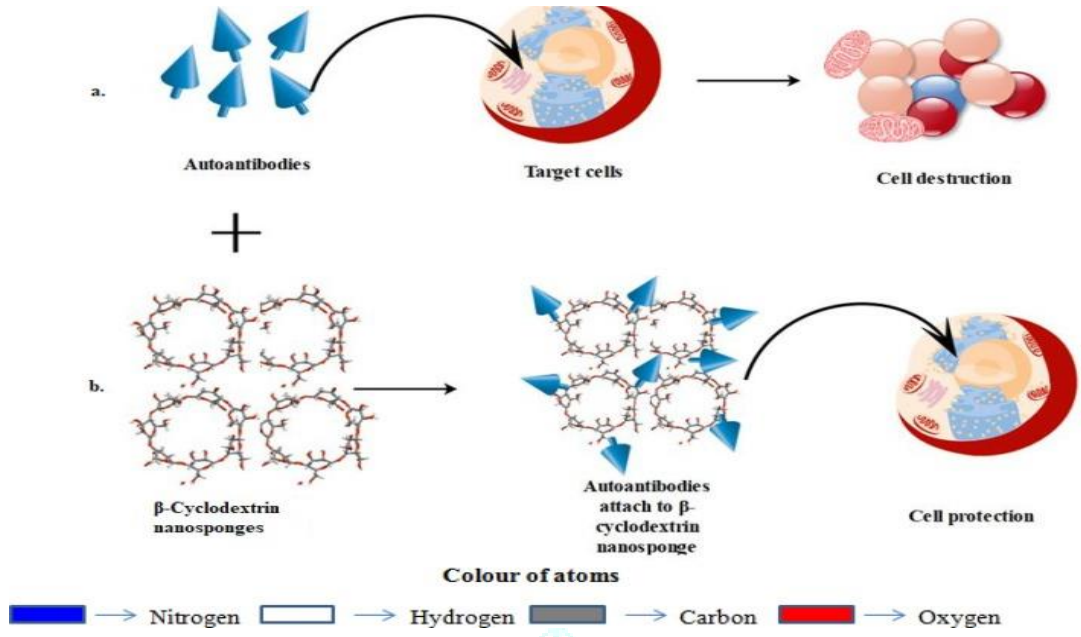

FIG.1: Action of cyclodextrin based nanosponge.

ADVANTAGES OF NANOSPONGES:

- Drug is released in a predictable fashion using nanosponges.
- Relentless action up to 24hrs can be achieved.
- The drug is encapsulated in the polymeric cage which provides sustained release and can withstand a temperature up to 300°C.
- Provides enhanced stability and flexibility in formulation.
- It has better solubility; hence, hydrophobic drugs can be entrapped within the NSs, after mixing with an adjuvant reagent.
- NSs act as a self sterilizer as bacteria cannot penetrate into them because of their tiny pore size.
- Side effects are minimized.
- NS complexes are stable over a wide range of pH (1-11) and temperatures upto 130°C.
- Converts liquids to powders, therefore, it offers higher degree of material processing.
- Provides better patient compliance.
- Used in masking the unpleasant flavour of the drug.
- It has better stability, bioavailability and is also biodegradable.
- Also used in topical delivery system.
- Acts as a carrier for gases like oxygen and carbon dioxide, it carries oxygen to the hypoxic tissues.
- The materials used provide barriers from premature destruction of the drug within the body.
- It has the ability to link with the functional groups and hence enables drug delivery to the targeted site, it can be further enhanced by means of chemical linkers.
- External magnetic field can also be applied for drug delivery to the targeted site by in-cooperating magnetic properties into NSs.
- A milky colloidal suspension is produced in aqueous media, which is easy to regenerate by means of solvent extraction and thermal desorption using ultrasound.

DISADANTAGES OF NANOSPONGES:

- Not suitable for larger molecules, as NSs have the capacity to encapsulate only small molecules.
- Dose dumping may occur occasionally.
- May retard the release of drug.

FACTORS INFLUENCING DRUG DELIVERY BY NANOSPONGES:

Type of Polymers Used:

The performance of NSs depends on the polymer employed. The cavity size of NSs should be as such that it can accommodate the drug of a particular size.[13]

Polymers	Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly (valerolactone – allylvalerolactone) & Poly (valerolactone-oxepanedione) and Ethyl Cellulose & Poly vinyl acetate(PVA).
Cross linkers	DiphenylCarbonate,Di-arylcarbonates, Di-Isocyanates, Pyromellitic anhydride,Carbonyldi-imidazoles, Epi-chloridrine, Glutraldehyde, Carboxylic acid di-anhydrides, 2, 2- bis (acrylamidos), Acetic acid and Dichloromethane

FIG.2: Types of polymer used

Type of Drugs:

Drug molecules to be in-corporated with NSs should have the following characteristics:

- Molecular weight should be in between 100 to 400 Daltons.
- Not more than five condensed rings should be present in the structure of the drug molecule.
- Water solubility of the drug should be less than 10 mg/ml
- Melting point should not be more than 250°c [13].

Temperature:

Changes in the temperature can affect the drug or the NS complexation. Generally , the magnitude of the apparent stability constant of the drug or NS decreases with increase in temperature, as a result of which there is possibility in reduction of drugs or NSs' interaction forces such as Van-der waal forces and hydrophobic forces.[14]

Method of Preparation:

The drug/ nanosponge complexation can be affected depending on the method of preparation. However, effectiveness of a method depends on the nature of drug and polymer. Freeze drying was found to be most effective method for drug complexes in many cases.[14]

Degree of Substitution:

The type, number and position of the substituent on the parent molecules affects the complexation ability of the nanosponges.[14]

METHODS OF PREPARATION:

The methods used in the preparation of nanosponges are as follows:

- Solvent method
- Melt technique
- Ultra-sound assisted synthesis
- Emulsion solvent diffusion method
- Loading of drug into nanosponges.

1) Solvent Method:

In this method, NSs can be obtained by mixing polymer with a suitable solvent like Dimethylformide (DMF), Dimethylsulfoxide (DMSO). Thereafter, the above mixture is added to the cross-linker in a molar ratio of 1:4. A temperature of 10°C to the reflux temperature of solution is maintained. The solution is then cooled to room temperature and transferred to bi-distilled water. Finally, the solution was filtered under vaccum with subsequent purification by prolonged soxhlet extraction with ethanol. The final product is obtained by drying under vaccum. The obtained size of nanosponges can be reduced by applying high-pressure homogenization at 4°C to avoid degradation.[12]

2) Melt Technique:

In this method, cyclo-dextrin is reacted with a cross-linker like dimetyl carbonate, di phenyl carbonate, di-isocyanates, di-aryl carbonates, carbonyl di-imidazole, carboxylic acid anhydrides and 2,2-bis (acrylamido) acetic acid. The above ingredients are homogenized and placed in a 250ml flask. It is then heated at 100°C and stirred using magnetic stirrer for 5hours. The mixture was then allowed to cool and the product was broken down. The final product was washed with suitable solvents to remove additional excipients and the by-products formed.[12]

3) Ultra-Sound Assisted Synthesis:

Nanosponges can be prepared by treating polymers with cross-linkers under sonication in the absence of solvent. In the above process, β-CD and diphenyl carbonate are combined together in a particular molar ratio, in a flask. This flask is then placed in an ultrasound bath filled with water and heated upto 90°C. It is sonicated for 5 hours. It is then allowed to cool down and the product is broken down abruptly. The final product was purified with water by soxhlet extraction with ethanol to remove the unreacted polymer. The obtained product was dried an stored at 25°C.[15]

4) **Emulsion Solvent Diffusion Method**:

Different proportions of ethyl cellulose and polyvinyl alcohol are used. There are two phases; dispersed phase and continuous phase. In dispersed phase, ethyl cellulose and the drug is dissolved in 20ml of dichloromethane with addition of polyvinyl alcohol (PVA) to 150ml of continuous phase (aqueous). The mixture is then stirred at 1000 rpm for 2 hours. The mixture is filtered to collect the product. Eventually, the product is dried in an oven at a temperature of 400°C.[16]

5) Loading Of Drug into Nanosponges:

A nanosponge for drug delivery is pre-treated to a significant particle size below 500nm. Therefore, NSs are suspended in water and sonicated to avoid aggregates. The suspended solution undergoes centrifugation and the colloidal fraction is obtained. The resilient obtained is separated and the sample is freeze dried. The NS obtained is in aqueous suspension form which is dispersed in the excess amount of the drug and is stirred constantly until a complexation is formed. The uncomplexed drug form is separated by centrifugation. Further, the NSs are obtained in the form of solid crystals by solvent evapouration or by freeze drying.

Crystal structure of NSs is much favoured in complexation with drug as the paracrystalline NSs show different loading capacities. The loading capacity for crystalline NSs is greater when compared to the paracrystalline NSs.[17]

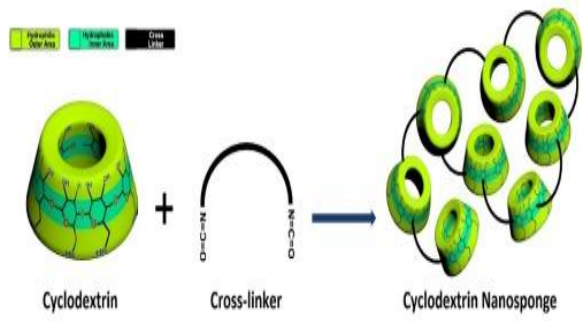

FIG.3: Loading of drug into NSs.

Nanosponges for Cancer Therapy:

Anticancer drugs have low solubility; hence, it has become one of the most challenging works in the field of pharmaceutics. Nanosponges claim to be three times more effective in the reduction of growth of the tumor cells. The complexation of NS is loaded with a drug which is then exposed to the targeted peptide which is induced by a radiation, binds to the tumor receptor. The NS, bound to the tumor receptor starts releasing the drug molecules. This provides enhanced therapeutic effects with minimized adverse effects within the same dose.

Nanosponges as Anti-Cancer Agents:

1) CD- BASED NSs DRUG DELIVERY:

Temozolomide:

Phenyl carbonate based β-CD nanosponges was found to produce in-vitro toxicity which claimed Temozolomide to be a potential drug for the treatment of Glioma. It has been utilized as the 1st line therapy in the treatment o Gliomas after surgical resection. It requires intermittent dosing because of their short half-life of 1.8h and 15%of protein binding. Hence, Temozolomide has become successful in nanotechnology.[18]

The structure of NSs can be estimated by using magnetic resonance spectroscopy. A slight shift in wavelength of the molecule showed interaction with hydrophobic groups; hence, the drug interaction was estimated. Fourier-tranformation infrared radiation (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD), was used in the embodiment and complexation inside the NS. The peaks obtained were either concealed or moved after NS formulation. NS based formulation of temozolomide showed sustained *in-vitro* release. It showed equivalent toxicity as that of free drug. The morphology of human giloblstoma astrocytoma of malignant tumor was deteriorated after the therapy. This formulation was further developed to produce potential delivery to the target site of the brain.[19]

Paclitaxel:

Chemotherapy is a complicated process. At times it may lead to toxicity; the non-specificity of anti-neoplastic drugs is the main reason for most of the effective drug being highly toxic. Due to the anticancer molecules, the occurrence of the side effects is much higher due to the poor water solubility of anticancer molecule. Paclitaxel is used in the treatment of small and non-small cell lung cancer, bladder cancer, neck and head cancer. It has low water solubility of 0.5mg/l and shows wide range of side effects. Various researches have been performed to modify paclitaxel by various methods such as emulsification, micellization, liposome formation, non- liposomal lipid carries and many others. A new formulation, albumin bound paclitaxel was developed for chemotherapy in the treatment of recurrent metastatic breast cancer.

After many researches and development of nanosponges, paclitaxel was encapsulated in the nanosponge by combining cyclo-dextrins with diphenyl carbonate as cross-linker. A diameter of about 350nm with a drug payload of 500mg of paclitaxel/g of nanosponge was obtained. The evaluation of pharmacokinetic properties of paclitaxel NS was done via oral administration in rats. It showed a three-fold increase in bioavailability when compared to commercial taxol.[20]

Resveratrol:

Resveratrol is a natural, stilibenoid phenol. It is obtained from dietary sources like grapes, groundnuts, pistachios and blue-berries. It is an anti-oxidant and also has anti-oncogenic property. It has restricted half life and is digested at a faster rate followed by excretion. It has insignificant bioavailability when taken orally and may cause death blow. Therefore, its use is restricted for further use in clinical research. To overcome these limitations, nanotechnology has been developed. The NSs were used to enhance solubility, soundness and skin permeability of resveratrol. Different concentrations of cross-linkers (1:2 and 1:4; the molar premise of CD:CDI) were used. The solubility was increased by 33 to 48 times in F1:2 and F1:4 formulations when compared to the marketed drugs. Significant changes are the FTIR peaks were achieved by the action of resveratrol with NS. Release of the F1:4 formulations was much more uniform s compared to F1:2. The photostabiliy was aso improved. The skin permeation of resveratrol by NS formulation was much higher in pigs when compared to the skin permeation by hydroalcoholic mixtures. A two-fold mucosa acquisition in rabbit by resvertrol F1:4 was observed.[12]

Curcumin:

Curcumin is one of the most favourable anti-cancer agents. It is a hydrophobic polyphenolic phytochemical with low liquid solubility at acidic pH, whereas at basic pH it is highly soluble. It is a major constituent of turmeric. Apart from being a anticancer agent. It also acts as a neuroprotective, cardioprotective and antiathescleroti agent. It is used in the treatment of various types of tumors such as colon tumors, leukaemia, hepatic cellular carcinoma and prostate cancer. The cell proliferation and metastatis is inhibited and apoptosis is induced simultaneously by 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 reactos. Based on the pleiotropic properties, it was estimated that curcumin was more powerful than a solitary pathway therapy. Despite of its wide range of uses, curcumin has many disadvantages. It has low solubility, lower gastro intestinal absorption rate as well as lower bioavailability with significant metabolism. Degradation occurs at a physiological pH.[21]

To overcome the above challenges in the formulation, Kurien et al. Developed β-CD NSs curcumin formulation; this proved to be an effective antineoplastic drug. Solubility of curcumin was enhanced to multiple times when compared to plain curcumin. This was because of the complexation of curcumin with NSs. Molecular size was around 487nm and performance index (PI) of 0.476 was achieved with a unimodal molecular size distribution within a narrow range. Zeta potential was about -27mV, this was sufficiently high for developing steady suspension. In an amorphous state, the drug can easily diffuse through the polymeric matrix of NSs producing a controlled release. The DSC was demonstrated

at 176°C, did not produce peak indicating the formation of inclusion complex. The sub-atomic structure of curcumin stays unaltered after its formulation. The formulation was found to be non- haemolytic upto a concentration of 2mg/ml.[22]

ETB Glutathione:

One of the main causes for the cause for the cancer- related deaths is lung cancer, where chemotherapy is the only option for the treatment. Lung cancer is of two types; small cell lung cancer (SCLC) which comprises 15% of the cases and about 85% of total cases comprises Non small cell lung cancer (NSCLC). Though chemotherapy is the only option, yet it produces undesired side-effects. Researches worked out and developed new targets for the treatment of various cancers by targeting epidermal growth factor receptor (EGFR). Erlotinib hydrochloric acid (ETB) was approved by USFDA for the treatment of NSCLC. Chemically, ETB is [6, 7-bis (2-methoxy-ethoxy)-quinazolin-4-yl]-(-3-ethynylphenyl) amine hydrochloride which binds to human epidermal growth factor receptor by inhibiting tyrosine kinase. It inhibits angiogenisis by promoting cell cycle arrest and apoptosis. The cell is invaded by binding to the intracellular tyrosine kinase of EGFR, thus the receptor auto-phosphorylation is inhibited and downstream signal transduction is blocked. ETB glutathione is also used in the treatment of glioma, head and neck cancer and also ovarian cancer.

There are some challenges which obstruct proper formulation of TB glutathione. Poor bioavailability due to its poor solubility is one of the reasons for the poor formulation of the drug. It is also unstable in gastro-intestinal environment. It produces toxic effects like severe skin rash, diarrhoeas and other haematological side effects. Therefore, to overcome these side effects, the therapeutic efficacy of the drug molecules is improved by encapsulating them within the internal cavity of nano-carriers. This process enhances the solubility, targeting efficacy and also the biocompatibility rate. Sustained release of the drug has also been achieved.

ETB glutathione was incorporated into NSs by a single step reaction at room temperature. In-vitro release was evaluated by using high pressure liquid chromatography (HPLC). The NSs were a sphere shaped with a diameter of 212±245 nm and the loading capacity was around 92.34% ± 5.31% ($p < 0.001$). In- vitro release of drug was much higher around 76.89% ± 0.1% for duration of 168 hours; this was proportional to the concentration of ETB glutathione. 97.5% blockade in tumor cells was achieved by ETB glutathione NS when compared to plain ETB (48%). This proves that NSs directly targets the tumor site, thus preventing the drug exposure to other cells.[23]

2) Delivery of Oxygen By NS Formulation Used In Cancer Therapy*:*

Oxygen deficiency leads to hypoxia. The survival rate of the patients with hypoxic cervical malignant tumors is low. CD-based NSs which were synthesised using alpha, beta or gamma carbonyl di-imidazole, has the capacity to store gases like oxygen and 1- methyl cyclopropene claims to play a promising role in cosmeceuticals, pharmaceuticals and biotechnology. The NS formulation to deliver oxygen, was combined with three different CDI based nanosponges i.e., alpha, beta and gamma. The suspension formed was homogenised using high shear rate for about 2-3 mins. Further, it was saturated with oxygen, sealed and stored at 25°C to demonstrate the stability of NS. Vero cells were used to carry out the toxicity studies. A range between 40 and $50m^2/g$ was attained on the surface region of the NS. The molecular size of the circular NS was restricted to 400-500nm. Negative zeta potential (-30mV) was obtained. This oxygen formulation did not show any toxicity. Agglomeration or degradation was not seen even at 25°C when stored for 15 days. Oxygen penetration in β-CD NS was improved to above 192% under the influence of ultra-sound which showed underlying oxygen spike.

To eliminate the oxygen spike, a Pluronic® based hydrogel arrangement was used to produce a uniform release of oxygen. Trotta *et al.* Developed the O_2 stacked NSs by including sodium chloride, PEG 400 and deca- fluoropentane. These compounds were blended along with NSs and water to enhance the stacking, stockpiling and delivery. Two formulations were developed; β-CD NSs and α-CD NSs. O_2 discharge was positively affected by ultrasound; 30% increase in the penetration rate of O_2 from β-CD NSs formulation was achieved.[24,25]

3) Water- Soluble and Sparingly Soluble Anti-Cancer Molecules:

Doxorubicin:

The first liposomal anticancer drug to get administrative approval was doxorubicin hydrochloride infusion. Doxorubicin is functional in the treatment of major organ tumors and delicate tissue cancers. It had certain disadvantages like cardiotoxicity and sharp action of doxorubicin, hence, nano-technology was proposed o decrease these effects. It was observed that doxorubicin was discharged in a moderate and uniform way after the incorporation into the nanosponges. The release of doxorubicin was pH dependent at an average rate of 1% in acidic pH over duration of 2 hours and about 29% release was observed in basic pH in 3 hours. Therefore, it can be estimated that doxorubicin was shielded by the NS in acidic media i.e., the stomach and then carried to the basic media, intestine and duodenum.[26,27]

Flurouracil (5-FU):

5-FU is the drug of choice in the treatment of colorectal cancer, stomach malignant tumors, and cervical malignant growth. When administered orally, it was poorly absorbed due to low solubility. It has low terminal half-life (8-20 mins) when administered parentally. The side effects produced were highly photosensitive when given intravenously. Thus, to improve the properties of this drug, gamma CD-based NSs were used. Direct compression method ws utilized in the preparation of 5-FU nanosponge. The excipients were combined homogenously and then commpressed into tablets of about 8mm. The invitro release of the drug was improved to 96.66%. Better solubility profiles were achieved.

CONCLUSION:

The nanosponge is a boon in cancer treatment and an effective drug delivery system for hydrophobic and lipophillic drugs. The efficacy in the formulation, maintaining stability of the drug has been increased due to the nanosponges. Thus, nanosponges is one of the most favoured drug delivery system and is a rising trend in pharmaceutical sciences for oral, topical and parenteral drug administration.

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