A REVIEW ON NANOSPONGES: A BOON TO TARGETED DRUG DELIVERY FOR ANTICANCER DRUG

NIKITA SEHGAL*, VISHAL GUPTA N, SANDEEP KANNA
Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysore, Karnataka, India.
Email: sehgal.nikita28@gmail.com

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ABSTRACT
In recent decades, the rise in the investigation of new drugs had made health-care system expensive compared to conventional drug delivery systems and techniques. The present drug delivery systems have become highly productive and are growing fast. Majority of the anticancer agent has low water solubility resulting in multistep synthetic routes that require higher selectivity and specificity that can cause difficulty in the development of the formulation. Nanospones (NSs) are branched cyclodextrin (CD) polymeric systems which have proven to be a boon in the pharmaceutical and biomedical fields. Different kinds of NSs based on different types of CDs and crosslinkers are used for developing of new drug formulations from the past few years for various applications in health care. Nanotechnology has overcome the issues regarding the drug solubility, stability, and other parameters and has attained success in achieving of sustained release, increased activity, improved permeability, delivery of nucleoprotein, the stimuli-responsive release of the drug, and improved drug bioavailability. There is a huge eruption of research on NSs for cancer treatment. Multiple anticancer moieties have been developed, taking into account the pharmacological and physicochemical perspective of the drug to develop a NS formulation. Our target in this review is to catch an efficient and far-reaching NSs for malignancy cancer treatment announced until now. This survey will give a perfect stage for providing details for researchers taking a shot at using new polymers for improving the treatment of the disease using nanotechnology. The present article provides details regarding antineoplastic molecules and provides ideas on CD-based NSs specifically using curcumin, tamoxifen, resveratrol, quercetin, oxygen-Ns, lemozoikide, doxorubicin, and 5-fluourouracil (5-FU), and erlotinib (ETB) glutathione.

Keywords: Nanospones, Cyclodextrin, Antineoplastic molecules.

INTRODUCTION
In recent decades, the rise in the investigation of new drugs had made health-care system expensive compared to conventional drug delivery systems and techniques. The present drug delivery systems have become highly productive and are growing fast. Majority of the anticancer agent has low water solubility resulting in multistep synthetic routes that require higher selectivity and specificity, that can cause difficulty in the development of the formulation. For the optimization of therapy and cost-effective treatment, huge research is carried on drug delivery systems. Delivery of these antineoplastic agents is tough using conventional techniques as it causes the inconvenient release of active ingredient for an extended period of time and shorter duration of action which led to acute side effects and produced a toxic effect on healthy tissues. Moreover, the development of drug resistance can further reduce the efficacy of conventional drugs and most molecules are affected by degradation in the gastrointestinal tract. Due to this, the advanced targeted drug delivery systems have gained prime importance in these days [1-5].

Nanomedicine and nanotechnology landscape is evolving post haste. Nanotechnology allows control and sustained release of the drug, refinement of the physical and chemical properties of drugs producing ameliorate pharmacokinetics and biodistribution profiles without affecting the efficacy and with reduced side effects thus provides promising nanoparticle as flexible drug delivery vehicle. This technology ameliorates the therapeutic index of many compounds, extensively in case anticancer drugs, where insufficient concentration in tumor site and high toxicity of drug are the prime reason for narrow efficacy of the drug [6-9].

Nanoparticles have potential to penetrate the cells that enable intracellular accumulation of their load, which was shown for the first time by Couvreur, either by active or passive targeting, even it allows drug delivery to the specific site and tissue [10-13]. Cancerous tissue offer enhanced permeability and retention (EPR) effect as they do not belong to the reticuloendothelial system [14,15]. By the EPR, passive targeting of the nanoparticles had evaded through tumor vessel leading to flawed architecture. Tumor is said to have a larger pore size (380–780) compared to healthy organs. Hence, in this type of targeting, the particle size of the system is of prime concern as tumor tissue accumulation by EPR relies on extravasation through pores on hyperpermeable tumor vasculature [13,16].

In the case of active targeting, modification of nanoparticles surface using specific ligands such as sugar, antibiotics, and peptides helps to recognize and bind with specific cell receptor [17]. Due to this, research is focused on using nanotechnology for the use of a different chemotherapeutic agent. Nanocarriers include liposomes, dendrimers, gold nanoparticle, and a magnetic nanoparticle [4]. At present, Doxil, Abraxane, and Daunoxome are the nanoparticle medicines available in market approved by the Food and Drug Administration for treating cancer [19].

Another procedure that specialists have found against the tumor is focusing on its lower pH and increment the temperature of the tumor due to an explicit moiety in the polymer structure which acts as a receptive for the outside improvements, for example, separation of the carboxylic assembly and the redox-responsive group may encourage confined drug delivery. This method of conveying boosts the drug delivery utilizing nanoparticle helps in focusing on the tumor [20].

Thus, to conquer incapability of present and forthcoming antineoplastic agents and also to the delivery drug with optimum efficacy and minimal side effects, there is a need for novel nanostructured molecules and nano techniques consisting of carrier systems.
Modern search focuses on the development of novel drug delivery systems such as nanoporous and mesoporous (organic or inorganic based NSs) that have potential application in drug delivery and nanotherapeutics. Due to the toxicity caused by inorganic systems, research prominence has been laid on organic systems [21]. About decades ago, researchers have developed CD-based NSs to overcome the limitation of drug delivery and cancer therapeutics [5]. The goal of the present review article is to illustrate the development and application of CD-based NSs for cancer therapy.

CD NSs are formed from various organic or inorganic materials such as titanium or another metal oxide, silicon particle, and carbon coated metallic NSs. CD-based NSs were initially used for purification of water, because at low concentration also it can strongly bind to organic molecules and removes them from the water. However, now they have been used and explored in the field of pharmaceuticals and biomedical sciences such as to increase solubility, stability, bioavailability, modulation of drug release, delivery of protein, cosmetics carrier, and diagnostic.

NSs belongs to hyper crosslinked polymer based colloidal solid nanoparticles with a nanosized cavity. The crosslinkers, i.e. small molecules in a mixture of polymer solution act like tiny grappling hooks which leads to the formation of sphere-shaped particles with cavities in which drug molecules are incorporated. As it is biodegradable polyester, breaks down gradually in the body. Due to this NSs, delivery of the drug in a predictable manner with reduced side effects. They provide succors in case of hydrophobic drug exceedingly for an anticancer drug, as NSs are water soluble. Another unique property that makes NSs a choice of the delivery system is by varying the proportion of crosslinker to the polymer; any size of NSs can be formulated.

The advantage of NS based delivery
1. It provides relentless action up to 24 h.
2. A drug that is entrapped in the polymeric cage provides sustained release with lesser side effects and can withstand temperature up to 30°C.
3. Better solubility, stability, bioavailability, flexibility, and gracefulness.
4. As it converts liquids to powders, it offers a higher degree of material processing.
5. Provides protection from light or degradation, also used in the topical delivery system.
6. It can be used as a carrier for gases like oxygen and carbon dioxide, and in the case for many diseases, it provides oxygen to hypoxic tissues.
7. Used as unpleasant taste masking.
8. NSs formulation is stable up to 130°C and in the pH range of 1–11.
9. It enables target drug delivery as it has the ability to link with a various functional group, which can be further enhanced by means of chemical linkers, even the external magnetic field can be also be applied for target drug delivery, by incorporating magnetic properties into NSs.
10. NSs give clear to milky colloidal suspension in aqueous media, and its easy to regenerate by means of solvent extraction, thermal desorption using ultrasound.

METHOD OF PREPARATION OF CD-BASED NSS

Techniques used in synthesis to prepare CD-based NSs
1. Solvent technique
2. Melt technique
3. Ultrasound-assisted synthesis
4. Microwave-assisted synthesis.

Solvent method
In this procedure, crosslinkers are solubilized in solvents such as dimethylsulfoxide or dimethylformamide and on another side, the polar aprotic solvent is used to treat the polymer, and this solution is transferred to the above-prepared solution cross. The temperature was kept in the range of 10°C to the reflux temperature of solvent for 1–48 h.

To the obtained product, the cooled solution is added and transferred to large double distilled water. Filtration is done to obtain the final product under vacuum. It is also possible to reduce the size of the obtained NSs by providing high-pressure homogenization. To avoid degradation and aggregation of the product, it is stored in the refrigerator at 4°C.

Melt technique
In this technique, crosslinkers are allowed to melt with CDs and all other ingredients are homogenized at a temperature up to 100°C and magnetic stirring is done for 5 h. This above solution is allowed to cool and continuously washed to remove unreacted excipients and byproduct that is formed during the reaction.

Ultrasound-assisted synthesis
At initial stages, under sonication, the polymer is treated with crosslinkers without adding solvent. In this procedure, β-CD and diphenyl carbonate are blended in a suitable container, and this container is then transferred to previously filled with water in an ultrasound bath at 90°C for 5 h, which is further crystallized and purified as mentioned in solvent method and melt method. This method can be put back by a process involving like high energy input using probe sonication. This method does not require the use of organic solvents, which makes it a method of choice for the individual.

Microwave-assisted synthesis
This is the easiest method for NS preparation, which offers a greater advantage over another method by having a higher degree of crystallinity and also provides four folds reduction in reaction time and uniform particle size distribution. By applying all these techniques above, NSs can be synthesized, crystallized, and purified. Out of which purification of NSs in the most crucial thing as the by-products that are formed can cause toxicity. By-products are of various natures, chemical structure and are formed depending on various crosslinkers used.

NSs as anticancer agent

Delivery of CD-based NSs
Tamoxifen
Tamoxifen comes under the class of drugs called selective estrogen receptor modulators, which have both estrogenic and antiestrogenic effect and is used to treat breast cancer in pre- and post-menopausal women [22]. However, it has several side effect, which is also life-threatening such as endometrial carcinoma, metastatic tumor, venous thrombosis, and pulmonary emboli, which are suspected to be dose dependent to necessitate the development of prolonged release formulation of tamoxifen to reduce side effects [23,24]. Apart from this, it has very low aqueous solubility, which limits its therapeutic action that again becomes a challenge in the process of developing the formulation [25-29]. Broad research has been completed on tamoxifen delivery utilizing novel nano carriers to overcome the limitation related to the delivery of tamoxifen to the site [33,34]. Torne et al. developed β-CD-based NSs for oral delivery of tamoxifen using different cross-linking densities (F1, F2, and F3). Out of which, formulation F2 showed a tremendous increase in solubility as compared to the other marketed products of tamoxifen [38,25].

Temozolomide
Author investigated phenyl carbonate based β-CD NS for in vitro toxicity appraisal of temozolomide to become a potential drug for the treatment of glioma [40]. For the treatment of gliomas, this has been utilized as first-line therapy after its surgical resection [41]. They depict significant difficulties among which is the short half-life of 1.8 h and protein binding of 15%, due to which it requires intermittent dosing [41,37]. Site targeting of temozolomide has become successful by utilizing nanotechnology [38,41-48]. Using magnetic resonance spectroscopy, researches affirmed the structure of NSs. They assessed the drug interaction, wherein a slight shift in the stated wavelength of the molecule prompt interaction of water-hating groups. The complexation and embodiment inside NSs were done using Fourier-transform infrared (FTIR), differential scanning calorimetry...
Curcumín
Curcumín is a hydrophobic polyphenolic phytochemical which has poor liquid solubility at acidic and unbuffered pH, yet is dissolvable at basic pH [49]. It is a critical constituent of turmeric powder. Other than being a solid cancer preventive agent, it also acts as a cardioprotective, neuroprotective, calming, and antiatherosclerotic specialist (a nonexclusive rundown). Curcumín has been comprehensively declared as a propitious anticancer agent [44,50]. A few examinations suggest that curcumín may be a propitious medicine for the treatment of different sorts of tumors such as a bosom disease, colon threatening development, kidney harm, leukemia, hepatocellular carcinoma, and prostate dangerous development [46]. Curcumín applies its antiplastic properties through its consequences on atomic nuclear factor-kB, tumor necrosis factor-α, interleukins, interferon γ, ephrin receptor A5, tyrosine kinases, cyclin dependent kinases, mammalian focal point of atomic dimension. Further, utilizing Raman spectroscopy, the creators found interactions at the β-CD region of quercetin after forming NSs recommended interactions at the β-CD complexation of the molecule with NSs. Particular crests in XRD spectra were either moved or concealed after formulation with NS. The slow (DSC), and X-ray diffraction (XRD), as the drug peaks were either moved compared to the marketed drug. With about 40–50% w/w concentration of CD and diphenyl carbonate 1:2–1:10, molar distinct sorts of quercetin NSs (using NSs with a various crosslinking nature). Resveratrol release was more uniform and complete from the F1.4 formulations compared to F1.2. Proposing improved photostability of resveratrol in formulation with NSs. Formulation F1.4 showed a higher level of cytotoxicity when compared with the drug in HCP/C4 cells, which is both dose and time-dependent. A two-fold higher in vitro rat liver microsoma acquisition of resveratrol from F1.4 was seen by the researchers when contrasted with the drug dispersed in a hydroalcoholic blend (1:1 v/v). They also perceived higher permeation of resveratrol across pig skin through the NSs formulation as compared to the drug dispersed in a hydroalcoholic mixture [68].

Quercetin
Quercetin is flavonoid that is found in vegetables, organic products, leaves, grains, and seeds, which possess a great advantage as an anticancerous agent [74]. The dynamic type of quercetin is an aglycone frame displaying exceptionally poor oral bioavailability (~2% in people), which indicates low solubility and possess difficulty in disintegration in the gastrointestinal tract [69,70]. Moreover, it additionally experiences broad first-pass metabolism, which moreover limits its oral delivery [71]. Quercetin belongs to BCS Class II, i.e. have low solubility (7.7 μg/mL), which was accounted to be upgraded using nanoparticles but failed to produce remarkable results by increasing solubility to just about 0.4 mg/mL [71,72]. Hence, there is a requirement for further enhancing the physicochemical properties of quercetin [71]. Few novel advancements used by specialists to defeat the issues related to quercetin delivery are SNEDDS, biodegradable nanoparticles, polymeric microparticulate frameworks, nanocrystals, lipid nanoemulsions, etc. [73].

Anandam and Selvamuthukumar investigated NSs with diphenyl carbonate for enhancing the quercetin delivery [74]. They arranged five distinct sorts of quercetin NSs (using NSs with a various crosslinking concentration of CD and diphenyl carbonate 1:2–1:10, molar proportions for their examinations. Solvency of quercetin was upgraded by about 20 overlays compared to the drug. With about 40–50% w/w stacking, F1.4 and F1.6 emerged as the ideal formulae. Peak moves and peak expanding in the FTIR spectra showed a unique finger impression region of quercetin after forming NSs recommended interactions at atomic dimensions. Further, utilizing Raman spectroscopy, the creators saw that essential markers of quercetin have significantly concealed or moved after formulation with NSs, which straightforwardly validated their FTIR findings. Further DSC and XRD discoveries support complexation of the moleculer with NSs. Particular crests in XRD spectra were covered after forming of NSs, proposing the amorphization of the drug post complexation with NS. As the examination showed a particular particle size of NSs pretreated (mean size of NSs <100 nm), the molecule size was additionally observed to be in the scope of 41–94 nm which is less than the past reports by Trota et al. [74-77,81,85]. The particles were round, consistently scattered, and confirmed a tight survey information accessible and wide scope of medical importance, the clinical utilization of resveratrol is restricted by its short half-life [55] and immense and fast digestion pursued by excretion [54,56].
Further, *in vitro* release for quercetin NS and marketed formulation are performed to differentiate the release. The radical [2,2-diphenyl-1-picrylhydrazyl] action which is the main parameter depicting cancer as a preventive agent potentially demonstrated that all NFs of quercetin showed around 500–850% release after 3 h in simulated intestinal fluid and 100% drug degraded in NSs. Both the examinations showed better physicochemical properties and photostability of quercetin in forming NSs [75,99].

**NS Formulations to deliver oxygen**

NSs have capabilities of storing certain gases such as carbon dioxide, oxygen, and 1-methylcyclopropene which have a promising role in cosmeceuticals, pharmaceuticals, and biotechnology. Certain CD-based NSs have been synthesized using alpha, beta, or gamma with carbonyldiimidazole as oxygen delivering formulation. For the first time, Researchers explained the gas storing capacity and delivery of NSs as a potential apparatus in hypoxia-related to cancer. Deficiency of oxygen causes hypoxia with certain limits for the treatment. Patients with hypoxic cervical malignant growths survival rate have been poor [86]. Thinking about the capability of NSs in drug epitome and controlled discharge, Cavalli et al. orchestrated three distinct kinds of CDI-based NSs, i.e., alpha, beta, and gamma NS utilizing the particular CD particles. NS suspension was homogenized at the high shear rate for about 2–3 min. Later it was sealed and was saturated with oxygen. This was stored at 25°C to evaluate the stability of NSs. A toxicity study was carried out using Vero cells. About 3 mg/mL NS fluid scattering was infused with saline in vials in hypoxic conditions at a steady temperature to study the *in vitro* O₂ discharge design with an in-line oximeter. An in-house modified gadget was utilized to check the concentrate penetration of O₂ wherein two compartments were isolated using a thin silicon membrane. The surface region estems for NS were in the scope of 40 and 50 m²/g. NS were circular with molecule sizes of 400 and 550 nm with restricted dissemination. Zeta potential was toward the negative side (−30 mV). The O₂ formation did not show toxicity to Vero cells. The suspension did not show any agglomeration or degradation at 25°C when stored for 15 days. It was observed that ultrasound enhanced the O₂ discharge by about 58% from NS formulation. Researchers compared two formulation one with oxygenated NSs and another with plain oxygen. Oxygen saturation NSs demonstrated that the β-CD NS detailing displayed a higher pervasion compared to their α- and γ-CD partners. Oxygen penetration from the β-CD NS detailing enhanced by about 192% with the utilization of ultrasound showed underlying O₂ spike.

The creators at that point investigated a Pluronic®-based hydrogel arrangement of the β-CD NS, which gave a uniform, continued arrival of O₂ without the spike (with or without ultrasound) [77]. Proceeding with the examination further, Trotta et al. used an adjusted philosophy for designing the O₂-stacked NSs. They included sodium chloride, PEG 400, and decafluoropentane in the blend alongside NSs and water to additionally enhance the O₂ stacking, stockpiling, and delivery. They built two formulations of β-CD NSs and one of α-CD NSs. The physical attributes acquired were like the past examination. These details were nonhemolytic and safe to be infused in vivo as assessed by *in vitro* hemolytic action. Supported O₂ discharge for up to 60 min was gotten by NS details. Ultrasound positively affected O₂ discharge. A Pluronic®-based hydrogel prompted the bring down of O₂ discharge. Ultrasound achieved a 30% increase in the penetration rate of O₂ from the β-CD NSs formulation [79].

**ETB glutathione**

ETB glutathione is used to treat lung cancer, ovarian, head, and neck as well. However, due to the several limitations which include poor bioavailability, unstable at the acidic environment and first-pass metabolism making it difficult to deliver the drug to the targeted site. Furthermore, it possesses several side effects such as skin rashes, anemia, Stevens-Johnson syndrome. "Momina et al. explored the efficacy of ETB glutathione that has increased by incorporating it into the nanocarrier systems. Among which the most useful technology for site target drug delivery system was NSs without showing any cytotoxicity on several cancer cell lines. They incorporated glutathione into NSs for a single step reaction at room temperature. Evaluation of in vitro release was carried out using high-performance liquid chromatography technique. Cytotoxicity was evaluated on human lung cancer (A549) cell lines and *in vivo* studies were carried out in BALB mice. The obtained NSs were sphere sized (212 ± 245 nm) with drug entrapment efficiency of 92.34% ± 5.31% (p<0.001). Highest *in vitro* drug release was 76.89% ± 0.1% release at 168 h, which was proportional to the concentration of ETB glutathione demonstrating tumor targeting. It showed 97.5% hindrance in tumor development on regulating NSs when compared with plain ETB (49% restraint) depicting that NSs directly targets the tumors site preventing unnecessary drug exposure to other cells [97].

**Delivery of water-soluble and sparingly solvent anticancer molecules**

Trotta, Cavalli, and collaborators assessed the properties of NSs to enhance water solubility and sparingly solvent anticancer particles, for example, doxorubicin, 5-FU [90,91]. Doxorubicin is a standout among the most usually utilized particles for treating tumors of the major organ and delicate tissues [82]. Doxorubicin hydrochloride infusion was the first liposomal anticancer item to get regulatory approval. In a long time, a great part of the examination endeavors have been engaged toward investigating nanotechnology devices for decreasing the cardiotoxicity and expanding the explicitness of doxorubicin [77-90]. Cavalli et al. used NSs out of the blue for regulating the arrival of doxorubicin [90,91]. Doxorubicin was stacked in NSs (stacking of 20% w/w) as demonstrated by previously mentioned methods. The creators discovered that doxorubicin was discharged in a moderate and controlled way after consolidation in NSs. In vitro, release contemplates recommended that doxorubicin was released in a pH-dependent manner at a moderate rate of about 1% at acidic pH after 2 h. At basic pH, doxorubicin discharge was about 29% after 3 h. This indicates that NS protects doxorubicin from acidic environment, especially in the stomach. It shields the drug and releases it into basic condition, i.e., intestine and duodenum. Top to bottom examinations is expected to approve this specific discharge conduct conclusively [87,88]. Further, Researchers, enhanced the properties of 5-FU by utilizing gamma CD-based NSs. 5-FU is the most favored drug in the treatment of colorectal disease, stomach malignancy, and cervical malignant growth. It is a very polar drug with pka estimations of 8.0–13.0 [91]. It has low solubility when taken orally. It displays low terminal half-life (8–20 min) by means of the parenteral route [91]. It causes serious side effects and is highly photosensitive when infused intravenously [91]. Research to relieve these issues of 5-FU delivery has used as imaginative methodologies, for example, gelan gum microbeads, chitosan polycarbophil inter polyelectrolyte complex, mastic gum-based frameworks, egg whites nanoparticles, strong lipid nanoparticles, and other traditional polymeric nanoparticles [83,95-96].

**CONCLUSION**

CD-based NSs have shown promising results in cancer therapy. In spite of that few structural modifications required to enhance the efficacy of NSs, which can also function through external or internal stimuli. New research
has been carried out on cigastplastine and doxorubicin. NS offers an extra favorable position of different associating destinations for medicating stacking. The crosslinking thickness and the blend can be tuned to tweak the drug discharge in light of the upgrades. In our underlying investigations, we gave promising outcomes a progression of disulfide-containing NS (with fluctuating measures of the delicate disulfide NS) nanosized by high weight homogenization (normal size ~200 nm). The research will likely additionally proceed toward investigating different courses of the organization, for example, intraocular, intratumoral, topical, parenteral, buccal, what’s more, nasal-to-cerebrum.

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AUTHORS’ CONTRIBUTIONS

All the authors have contributed equally in the design, development, review and finalization of the contents of the manuscript.

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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