IJPSR (2020), Volume 11, Issue 7 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 October 2019; received in revised form, 12 January 2020; accepted, 04 March 2020; published 01 July 2020

NANOSPONGES – NOVEL EMERGING DRUG DELIVERY SYSTEM

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Keywords:

Nanosponges, Targeted drug delivery, Solubility enhancement, Polymers, Crosslinkers

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ABSTRACT: The contemporary development in the drug delivery system is a seamless process. Any delivery system targeting a molecule to a particular site is always been appreciated. This requirement can be fulfilled through a specialized drug delivery system that can easily target the drug at the site of action without compromising its efficacy and quality. Few new drugs typically cannot be effectually delivered by conventional dosage form. Hence, benefits from targeted, localized delivery of therapeutic agents are other driving forces for the current scenario. Nanosponge technology has been introduced to assist the release of drug in a controlled manner over time to reduce systemic toxicity and severe reactions. Nanosponges are tiny sponges with a size of about a virus (250 nm^{-1} μm), which consist of cavities that can be filled with a wide variety of hydrophilic as well as hydrophobic drugs, which can be further incorporated into a pharmaceutical dosage form such as oral, parenteral, topical or inhalation. The sighting of nanosponge has become a noteworthy step in overcoming certain problems such as drug toxicity, poor bioavailability, physiochemical in-stability, and patient non-acceptability.

INTRODUCTION: Authentic targeted drug delivery systems have been a fantasy for always in the past and today as well. But it has been mainly unsatisfied by the difficult chemistry that is involved in the new development systems. Targeting drug delivery has long been problematic for medical investigators, *i.e.*, how to get them to the right place in the body and how to control the release of the drug to prevent overdoses.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(7).3087-00

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(7).3087-00

The recent development of a novel molecule called nanosponges has the probable capability to solve this problem. An advance version of nano-particulate systems is entitled to nanosponges. These are designed with a hyper cross-linked polymer-based colloidal structure. Nanosponges are spongy polymeric delivery systems that are minor sphere-shaped particles with great porous external.

These do not really sponge-like structured shape, more like a network of molecules in three-dimensional structures. Nanosponges are very small, with a size of about a virus having a diameter below 1 μ. These are fused in solution along with tiny molecules coined as cross-linkers that helps to break different parts of the polymer

together. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. It is also possible to control the size of nanosponge particles. By varying the proportion of cross-linker to polymer, the nanosponge particles can be made larger or smaller [1, 2, 3].

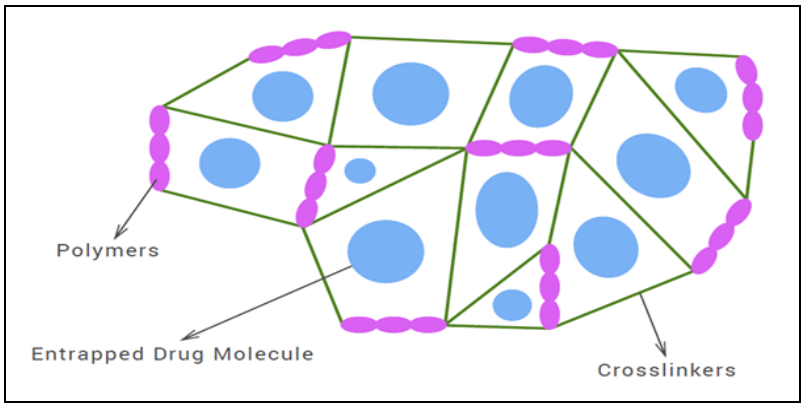

FIG. 1: THEORETICAL IMAGE OF NANOSPONGE

TABLE 1: ADVANTAGES AND DISADVANTAGES OF NANOSPONGES [4, 5, 6]

Advantages	Disadvantages
Improved bioavailability - targeted site delivery	Loading capacity of drug molecule required
Accommodate both lipophilic and hydrophilic drug	Very large molecules can't be accommodated
Improve aqueous solubility of poorly soluble molecules	
Improve patient compliance - prolonging dosing intervals	
Non-irritating, non-mutagenic, non-allergic and non-toxic	
Improve stability – protect from external factors	
Stable over a wide range of pH (1-11) and temperature	
Free-flowing & compatible with other ingredients.	

Characteristics of Drugs Suitable For Nanosponges: [7, 8, 9, 10]

- Dug candidates should have a molecular weight in between 100 to 400 Daltons.
- Drug molecule having a maximum five condensed rings is more preferred.
- Solubility in water should be less than 10 mg/ml, BCS class II drugs most commonly used.
- Melting point of the substance should be below 250 °C.

TABLE 2: CONSTITUENTS OF NANOSPONGES [11]

Polymers	Copolymers	Crosslinkers	A polar solvents
▪ Hyper cross-linked Polystyrenes Cyclodextrins and its derivatives like Alkyloxycarbonyl Cyclodextrins,	▪ Poly (valerolactoneally lvalerolactone)	▪ Carbonyl di imidazoles Carboxylic acid dianhydrides	▪ Ethanol
▪ Methyl β-Cyclodextrin Hydroxy Propyl β-Cyclodextrins	▪ Poly (valerolactone-allylvalerolactone oxepanedione)	▪ Di arylcarbonates,	▪ Dimethylacetamide
▪ Poly valerolactone	▪ Ethyl Cellulose	▪ Di chloromethane	▪ Dimethylformamide
▪ Eudrgit RS 100	▪ Polyvinyl alcohol	▪ Diisocyanates	
▪ Acrylic polymers		▪ Diphenyl Carbonate	
		▪ Epichloridine	
		▪ Gluteraldehyde	
		▪ Pyromellitic anhydride	
		▪ 2, 2-bis (acrylamido) Acetic acid	

Method of Preparation: [12, 13, 14, 15]

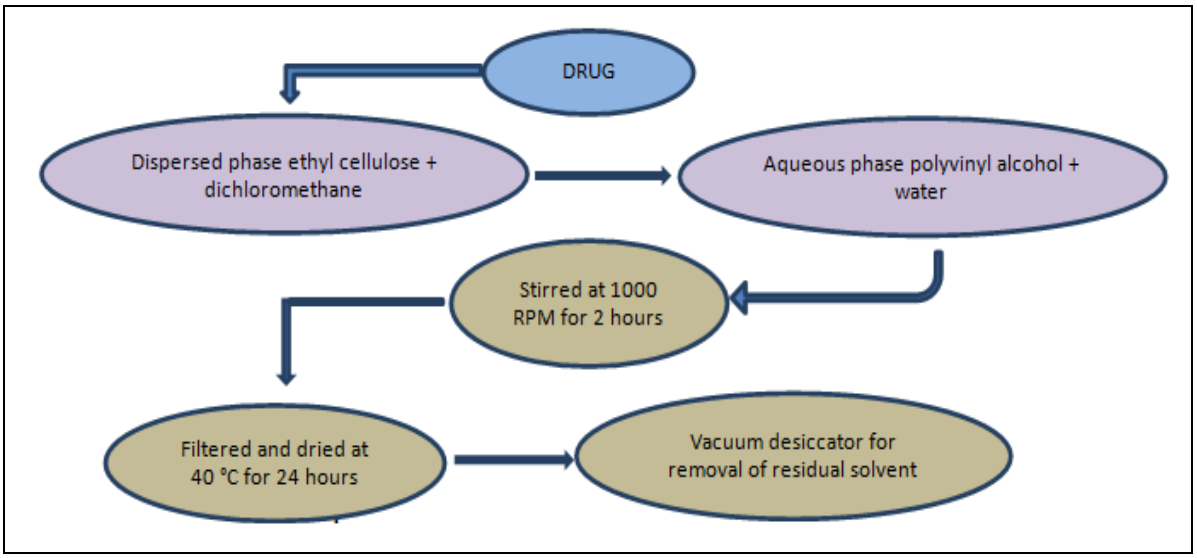

FIG. 2: EMULSION SOLVENT DIFFUSION METHOD

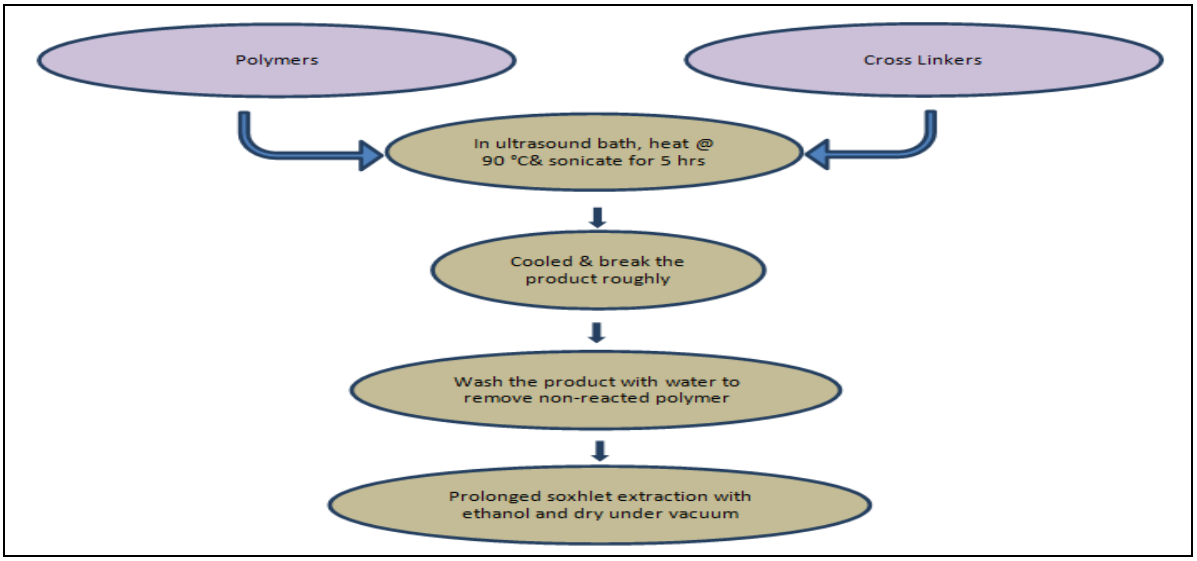

FIG. 3: ULTRASOUND ASSISTED SYNTHESIS

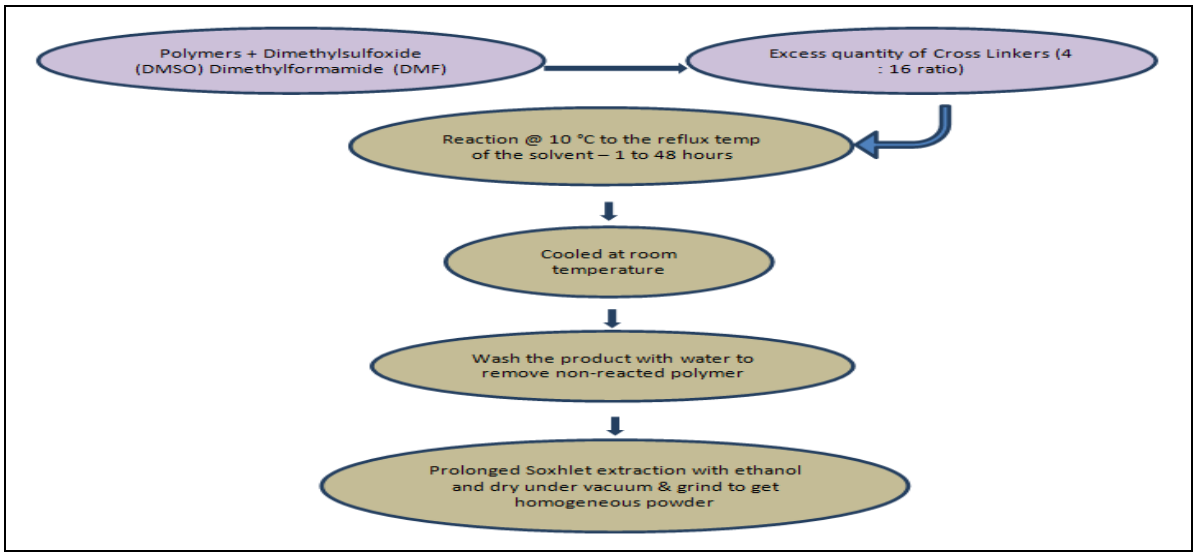

FIG. 4: SOLVENT METHOD

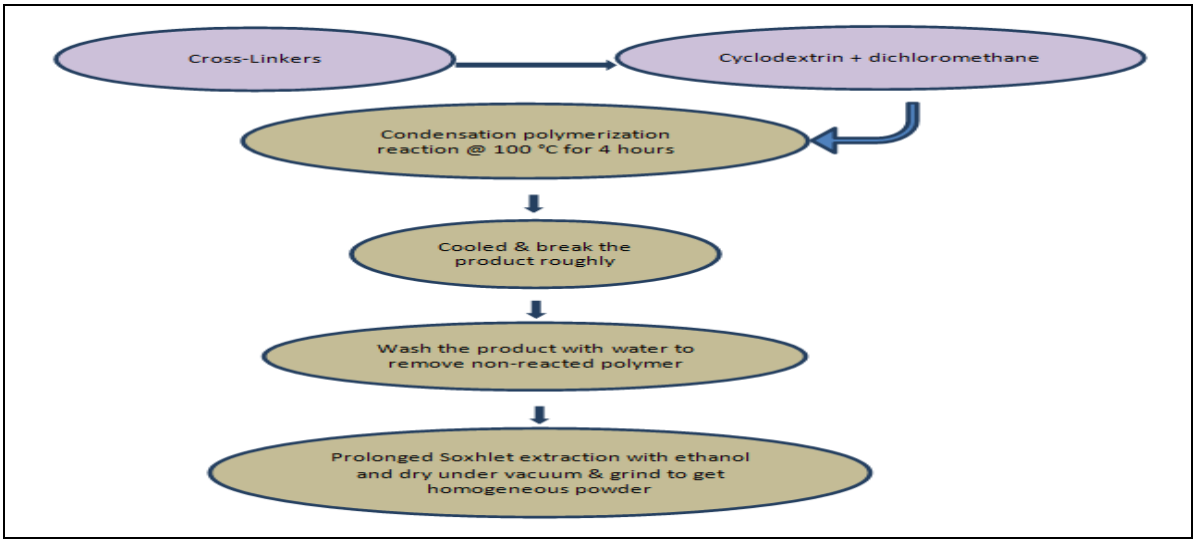

FIG. 5: FROM HYPERCROSS-LINKED B-CYCLODEXTRINS

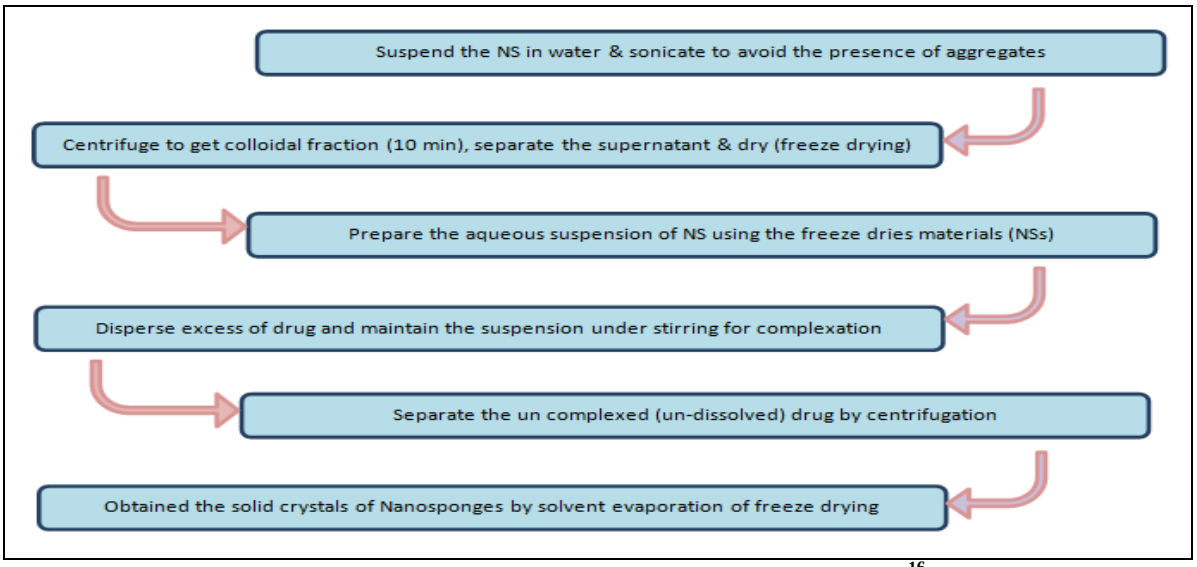

FIG. 6: LOADING OF DRUG INTO NANOSPONGES [16]

Effort Engaged for Nanosponges Ground Work by Various Arenas: E. G. Chadwick *et al.*, the discovery paves the way for a more economical production method for porous silicon. The related surface pore structure is examined in detail using scanning electron microscopy and transmission electron microscopy techniques while the internal pore structure is explored using focused ion beam milling and ultramicrotome cross-sections.

Analysis of the etched samples indicates a disordered pore structure with pore diameters ranging up to 15 nm on porous silicon particles ranging up to 5 µm in size. Crystallographic orientation did not appear to affect the surface pore opening diameter. Internal pore data indicated pore depths of up to 1 µm dependent on the particle size and etching conditions applied [17].

N. Eskandari Sabzi *et al.*, develop an application of β-cyclodextrin-based nanosponges with the tiny mesh-like structure as porous three-dimensional nanocatalyst in the one-pot three-component condensations of various aromatic aldehydes with activated methylene compounds such as dimedone, thiobarbituric acid, 4-hydroxycoumarin, 4-hydroxy -6-methyl-2-pyrone and nucleophiles including indole and amines. This nanosponge catalyst afforded the privileged N- containing organic scaffolds as key intermediates in pharmaceutical chemistry in very short reaction times [18].

Mina Jafari Nasab *et al.*, were prepared β-Cyclodextrin- epichlorohydrin nanosponge polymer, from the stepwise polymerization of β-cyclodextrin with epichlorohydrin under basic conditions and characterized by FT-IR

spectroscopy, thermogravimetric analysis, scanning electron microscopy and Brunauer–Emmett–Teller. An efficient synthesis of spiro [indoline-3, 4′-pyrano [2, 3-c] pyrazole] and pyranopyrazole derivatives is described using β-CD/EP as a stationary micro-vessel and basic heterogeneous catalyst *via* a four-component reaction under solvent-free conditions [19].

Barbara Mognetti *et al.,* were proposed the use of β-cyclodextrin based nanosponges to deliver paclitaxel as an alternative to classical formulation in Cremophor EL. Nanosponges dissolved and encapsulated paclitaxel up to 2 mg/ml. The paclitaxel-loaded nanosponges formed a water-stable colloidal system avoiding the re-crystallization of paclitaxel. The *in-vitro* release studies showed an almost complete release in 2 h without an initial burst effect. Delivery of paclitaxel *via* nanosponges increased the amount of paclitaxel entering cancer cells and lowers paclitaxel IC_{50}, therefore enhancing its pharmacological effect [20].

Anny Leudjo Taka *et al.,* were reported the synthesis and characterization of a novel bio nanosponge filter for applications in water treatment. Firstly the oxidized multi-walled carbon nanotubes (MWCNTs) were chlorinated using oxalyl chloride and then phosphorylated *via* an amidation reaction. The phosphorylated carbon nanotube (pMWCNT) obtained was polymerized with β-cyclodextrin (βCD) using hexamethylene-diisocyanate (HMDI) as a linker. The resulting polymer (pMWCNT-βCD) was decorated by a sol-gel method with TiO_2 and Ag nanoparticles to obtain a biopolymer nanocomposite, pMWCNT-βCD/TiO2-Ag. For a better evaluation of the target material, CD polymer and pMWCNT-CD polymer were also synthesized for comparison purposes [21].

Francesco Trotta *et al.,* were synthesized Cyclodextrin based carbonate nanosponges starting from native β-cylodextrin and active carbonyl compounds *i.e.* carbonildiimidazole. In this work they were used to form inclusion complexes with three different gases *i.e.* 1-methylcyclopropene, oxygen and carbon dioxide. The encapsulation of gases were proved by direct reaction to known adduct (1-methylcyclopropene), by gravimetric analysis (CO_2) and by oxymeter (Oxygen).

The complexetion of oxygen or carbon dioxide could be useful for many biomedical applications. In particular the oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases. 1-methylcyclopropene included in β-cyclodextrin nanosponges showed superior antiethylenic performances in long lasting cut flowers in comparison with marketed products [22].

Sharad S. Darandale *et al.,* were studying significance of lipid composition on free propofol concentration in aqueous phase and associated pain on injection. Three different nanoformulations, namely long-chain triglyceride (LCT)/medium-chain glyceride (MCG)-based nanoemulsion (ProNano), MCG-based self-nanoemulsifying formulation (PSNE), and lipid-free nano-formulation (PNS) were accessed for the same. *In-vitro* and *in-vivo* performances of developed formulations were compared with Diprivan®. ProNano showed minimum free propofol concentration (0.13%) and hence lower pain on injection (rat paw-lick test, 6 ± 2 s) compared to Diprivan®, PSNE, and PNS (0.21%, 0.23% and 0.51% free propofol, respectively, and rat paw-lick test; 12 ± 3, 14 ± 2, and 22 ± 3 s, respectively) [23].

S. Swaminathan *et al.,* were synthesized new swellable cyclodextrin-based poly (amidoamine) nanosponges, named PAA-NS10 and PAA-NS11, by cross-linking β-cyclodextrin with either 2, 2-bisacrylamidoacetic acid or with polyamidoamine segments deriving from 2, 2-bisacrylamidoacetic acid and 2-methylpiperazine, respectively. Water uptake studies showed a tremendous swelling capacity of both nanosponges, forming hydrogels. Time-dependent swelling experiments in various aqueous media showed that the nanosponge hydrogels were stable over a period of at least 72 h maintaining their integrity. Thermal analysis showed that the two nanosponges were stable up to 250 and 300 °C, respectively. Both PAA-NS10 and PAA-NS11 were converted to aqueous nano-suspensions using the high-pressure homo-genization technique. *In-vitro* BSA release studies were carried out showing a prolonged release of albumin from the two swollen BSA loaded β-CD PAA-NS over a period of 24 h [24].

Roberta Cavalli *et al.,* were prepared nanosponges from β-cyclodextrins as nanoporous materials for

possible use as carriers for drug delivery. The structure of β-cyclodextrin-based nanosponges was principally investigated by FT-IR, DSC and RX analyses. Sizes, morphology, and toxicity were also examined. The capacity of the nanosponges to incorporate molecules within their structure was evaluated using drugs with different structures and solubilities. The nanosponges were found capable of carrying both lipophilic and hydrophilic drugs and of improving the solubility of poorly water-soluble molecules [25].

V. Crupi *et al.,* were prepared cyclodextrin nanosponges (CDNS), which are a very promising class of cross-linked polymers, swollen in aqueous solution give rise to cyclodextrin-based hydrogel in different states-gel or liquid suspension-depending on the hydration level of the system. The spectral de-convolution analysis gives evidence of the existence of a characteristic cross-over hydration level associated with the rearrangement of water molecules in more cooperative, bulk-like networks as a consequence of saturation sites of water confinement of nanosponges. These interpretations are further confirmed by the inspection of the estimated collective intensities [26].

Usman Zubair *et al.,* synthesized microporous carbon spheres with pore size ranges from 5 to 11 Å from hyper-cross-linked polymer β-cyclodextrin. Sulphur is incorporated in the micropores by solution impregnation followed by melt infusion. The resultant carbon sulphur (C/S) composite is wrapped in reduced graphene oxide (rGO) to provide conductive pathways to access the sulphur in micropores and to protect the surface-adhered sulphur. The cathode material obtained from rGO wrapping delivers an initial discharge capacity of 1103 mA h g^{-1} at 0.1 ºC, maintaining a capacity of 626 mA h g^{-1} at 0.2 ºC with a capacity loss of 0.2% per cycle for more than 100 cycles [27].

Monica Vercelli *et al.* were evaluated the effects of innovative Si-applications on. Soilless-grown *Cucumis sativus* L. and *Cucurbita pepo* L. Crop growth, powdery mildew incidence, and abiotic stress resistance. Two experiments were carried out in a non-heated glasshouse on benches. Two new Si treatments (Si–Nano-sponge complex, and one experimental fertilizer) were compared with the traditional K_2SiO_3. Topas®EC 10 was used as a control fungicide treatment. Biometric parameters and incidence and severity of powdery mildew were measured. *Cucumis sativus* plants showed a severe powdery mildew infection, and no significant effect of the Si treatments was found. *Cucurbita pepo* plants were initially grown under lower disease pressure conditions, and the positive effect of Si treatments was found [28].

V. Jaishree *et al.* were synthesized nanosponges are some of the materials used for cancer detection. Using specific crosslinkers, such as specific antibodies against cancer cells individual cancer cells can be located. With the aid of a novel set of lipid-coated, targeted quantum dots a method for quantifying multiple specific biomarkers on the surfaces of individual cancer cells was also developed. This approach to quantitative biomarker detection stands to improve the histopathology methods used to diagnosis pancreatic and other cancers and enable the development of methods to spot cancer cells circulating in the bloodstream [29].

Weiwei Gao *et al.,* have formulated nanoparticles which offered a unique set of properties for drug delivery including high drug loading capacity, combinatorial delivery, controlled and sustained drug release, prolonged stability and lifetime, and targeted delivery. To further enhance the therapeutic index, especially for localized applications, nanoparticles have been increasingly combined with hydrogels to form a hybrid biomaterial system for controlled drug delivery. Integrating therapeutic nanoparticles with hydrogel technologies creates a unique and robust hybrid biomaterial system that enables effective localized drug delivery [30].

Ludovica Seglie *et al.,* were investigated the influence of different degrees of cross-linking of β-cyclodextrin-based nanosponges (β-CD-NSs) on the activity of the incorporated 1-methyl-cyclopropene (1-MCP) to extend the postharvest longevity of carnation cut flowers. The polymeric β-CD-NSs were synthesized from cyclodextrins at three varying reticulations, β-CD-NS 1:2, β-CD-NS 1:4, and β-CD-NS 1:8. In particular, the lowest suspended concentration (0.25 μL L−1) of the β-CD-NS 1:8 complex proved best for maintaining cut flower ornamental quality. The potential for the formulated 1-MCP-loaded β-CD-NS suspension to

induce prolonged vase life was demonstrated. Its use could yield benefits, such as a reduction in total dose and frequency of administration [31].

F. Castiglione *et al.,* were studied the effect of the macrocycle size on the gel-to-sol evolution of cyclodextrin-based hydrogel is here investigated by using Fourier transform infrared absorption in attenuated total reflectance geometry (FTIR-ATR). Different types of nanosponges obtained by polymerization of α- and β-cyclodextrin (CDNS) with an activated derivative of ethylenediamine-tetraacetic acid have been progressively hydrated in order to follow the evolution of these systems from a gel state to a liquid suspension. The in a deep analysis of the high-frequency vibrational dynamics of the hydrogel during its gel-sol evolution revealed that the microscopic origin of this phenomenon is strictly connected to different hydrogen bond environments in which water molecules confined in the pores of nanosponges can arrange [32].

Mitra Naghdi *et al.,* were studied regarding the major challenge of contamination for human health and environment since their concentrations are increasing. Contaminants occur in air, soil and aquatic media, then finally end up in drinking water. Contaminants cause many health issues to living organisms, by disruption of endocrine systems and feminization of male fish, for instance. They discussed methods to remove contaminants using nanomaterials, such as nanoparticles, nanotubes, and nanostructured membranes. New processes based on nanostructured materials such as TiO_2 nano-wires or nanofiltration membranes can achieve up to 95 % removal of contaminants [33].

Vahini Raja *et al.,* were designed a novel Co_3O_4/NiO nanosponges for the photocatalytic degradation of organic contaminants were synthesized by a simple precipitation technique. The formation of sponge-like nanostructures was clearly evident through the TEM analysis. The photocatalytic efficiency was tested against rhodamine B (RhB) and congo red (CR) dye solutions. Co_3O_4/NiO nanosponges showed excellently and enhanced photocatalytic efficacy compared to those of Co_3O_4, NiO nanoparticles, and standards like TiO_2 and ZnO. The trapping experiment revealed that the reactive oxygen species (ROS) identified was $OH radical. These findings certainly open up a new way for synthesizing a morphology dependent photocatalyst [34].

F. Castiglione *et al.,* studied the crosslinking and inclusion/release properties of cyclodextrin nanosponges (CDNS). CDNS shows the swelling capability and a hydrophilicity/hydrophobicity balance that can be dramatically modified by the type and quantity of cross-linking agents. The vibrational properties of CDNS thus synthesized have been investigated by Fourier transform infrared spectroscopy in attenuated total reflectance geometry and Raman spectroscopy in the dry state at room temperature. The quantitative analysis of the O–H stretching region (3,000–3,800 cm^{-1}) allowed us to obtain structural information on the role played by primary and secondary OH groups in the hydrogen bond network of the polymer. Also, the contribution of interstitial and intra-cavity crystallization water molecules is reported. The observed relaxation parameters point out that the ester formation occurs mainly at the primary OH groups of CDs, also supporting the interpretation of vibrational spectra [35].

L. A. Pavlova *et al.,* were synthesized hydrophilic ionic nanosponges with quaternary pyridinium groups on the basis of 4-vinylpyridine and its polymer. Their synthesis relies on the use of bior poly-functional agents alkylating pyridine in dilute solutions in a thermodynamically good solvent. Individual intra-molecularly cross-linked soluble macromolecules with molecular masses from 6000 to 400000 are prepared at various degrees of dilution. 1, 4-Bis (halomethyl) benzenes, p-vinylbenzyl chloride, and poly (vinylbenzyl chloride) are used as N-alkylating agents. The shapes and sizes of macromolecules are determined *via* the methods of diffusion, sedimentation, viscometry, dynamic light scattering, atomic force microscopy, and transmission electron microscopy [36].

Singireddy Anandam *et al.,* were prepared cyclodextrin nanosponges by doing polymerization of cyclodextrins with suitable polyfunctional agents, which leads to highly cross-linked porous structures, referred to as cyclodextrin nanosponges. The conventional heating approach for the synthesis of nanosponges can lead to nonuniform

reaction conditions caused by sharp thermal gradients in the bulk solution. A facile method for the synthesis of cyclodextrin nanosponges by microwave irradiation with a significant reduction in reaction time is used. Response surface methodology and Box–Behnken design were used for the optimization of the process parameters including microwave power level (A), reaction time (B), and stirring speed (C). Two dependent variables, practical yield, and particle size were measured as responses [37].

Fabrizio Caldera *et al.,* were prepared for the β-CD nanosponges using apple polyphenols. Rutin, phloridzin, and chlorogenic acid are some of the most important and characteristic polyphenols found in apples and their by-products (cider, apple juice, apple pomace, *etc.*). Despite their antioxidant power, their low stability under light or heating conditions restricts the use of this kind of molecules as nutraceuticals. To deal with this issue, encapsulation seems to be an alternative solution. Based on the obtained results, it can be concluded that β-cyclodextrin nanosponges (β-CD NS) are promising agents for the encapsulation of polyphenols. Using these encapsulating agents, other polyphenols from apple and its by-products could be encapsulated in order to enhance their bioavailability [38].

Pravin K. Shende *et al.,* were formulated β-cyclodextrin nanosponges with acetylsalicylic acid (ASA), a non-steroidal anti-inflammatory drug. The selected drug was formulated into inclusion complexes by grinding and precipitation with β-cyclodextrin and freeze-drying with pyromellitic dianhydride (PMDA) cross-linked β-cyclodextrin nanosponges. The *in-vitro* and *in-vivo* studies indicated a slow and prolonged ASA release from PMDA cross-linked β-cyclodextrin nanosponges over a long period [39].

D. Li *et al.,* were synthesized a new class of organic nanoporous polymers using cyclodextrins as basic building blocks. These processable nanoporous polymers were named 'nanosponges' because they have nanometer-size pores (distribution 0.7-1.2 nm) and exhibit superior ability to absorb organic molecules in water. The significant potential of the study is that hazardous organic contaminants may be reduced to parts-per-trillion levels in water by these polymers, as measured by ion-trap mass spectroscopy and UV-visible spectroscopy [40].

S. Sapino *et al.,* were prepared and characterized a nanosponges based stable formulation, which increases the stability and effectiveness of antioxidants is based on the inclusion in supra-molecular structures (nanoparticles, cyclodextrins, liposomes, *etc.*). In this work, they have studied the inclusion of gamma-oryzanol (GO) in β-cyclodextrin-based nanosponges, which in the last few years have been chosen for their ability to encapsulate a great variety of substances to decrease their side-effects and to protect them from degradation. The inclusion complex was prepared in 1:1 w/w ratio and characterized by DSC, XRPD and membrane diffusion runs. The photo-degradation of GO upon either UVA or UVB irradiation was found to be slowed down by inclusion in nanosponges [41].

Shankar Swaminathan *et al.,* were developed nanosponges (NS) with a class of hyper-branched polymers, nano-structured to form three dimensional meshwork; obtained by reacting cyclodextrins with a crosslinker like diphenyl carbonate. Two distinct forms *viz.* crystalline and para-crystalline of NS were identified and extensively characterized by the use of high-resolution transmission electron microscopy (HR-TEM), X-ray powder diffraction (XRPD), scanning electron microscope, atomic force microscope, optical microscope, and Fourier transform infrared attenuated total reflectance spectroscopy (FTIR-ATR). The crystallinity of NS was found to be an important factor in solubilization, *in-vitro* kinetics, and encapsulation behavior and can be tuned to give a tailored drug release profile or formulation characteristics [42].

Monica R. P. Rao *et al.,* were synthesized a Cyclodextrin based Gabapentin nanosponges and the nanosponge–drug complexes were characterized by FTIR, DSC and PXRD as well as evaluated for taste and saturation solubility. The complexes were coated on espheres by a suspension layering technique followed by coating with ethyl cellulose and eudragit RS-100. The complexes showed partial entrapment of drug nanocavities. A significant decrease in solubility

(25%) was observed in the complexes than the pure drug in different media. The microspheres of nanosponge complexes showed the desired controlled release profile for 12 h. Nanosponges effectively masked the taste of Gabapentin and the coating polymers provided controlled release of the drug and enhanced taste-masking [43].

Nirosha Manyam *et al.,* were studied to enhance Trimethoprim solubility by preparing Trimethoprim nanosponges loaded extended-release tablets to delay the drug release at the urinary tract. From the evaluation, it was concluded that nanosponge loaded extended-release tablets of trimethoprim showed delayed drug release up to 10 h with enhanced solubility and dissolution.

Hence, the nanosponge technique will be a challenging approach for enhancing the solubility of poorly soluble drugs [44]. Subhash Chandra Bose *et al.,* were prepared Lansoprazole loaded nanosponges by Emulsion solvent diffusion method using ethylcellulose, PVA and pluronic F-68 and dichloromethane as a solvent. The drug release from nanosponges was found to extend up to 12 h. The optimized nanosponges were formulated into the enteric-coated tablet and evaluated for weight variation, hardness, friability and dissolution studies.

In-vitro release of drug from enteric-coated tablet follows zero-order and showed controlled release behavior for a period of 24 h. The data obtained in this study suggest that nanosponges of lansoprazole are promising for controlled drug delivery, which can reduce dosing frequency [45].

Dr. Prathima Srinivas *et al.,* were formulated the controlled release Voriconazole Nanosponges for topical and oral delivery. Nanosponges using three different polymers ethylcellulose, Poly (methyl methacrylate), and pluronic F-68 (poloxamer 188) were prepared successfully using PVA as surfactant by emulsion solvent evaporation method.

The polymers studied were found to be the efficient carriers for voriconazole nanosponges showing diffusion-controlled release. The nanosponge systems have been found to have good potential for prolonged drug release [46]. Patil Bhagyashree Subhash *et al.,* produced controlled release Artesunate Nanosponges for topical and oral delivery. Nanosponges using three different polymers ethylcellulose, Poly (methyl methacrylate) and Pluronic F-68 (poloxamer 188) were prepared successfully using PVA as surfactant by emulsion solvent evaporation method. These small sponges can circulate around the body until they encounter the target site and stick on the surface and began to release the drug in a controlled and predictable manner, which is more effective for a particular given dosage [47].

Monica R. P. Rao *et al.,* were evaluated nanosponges loaded with efavirenz by a solvent evaporation method, and the nanosponge with higher drug loading capacity was selected for further studies. Binary and ternary complexes with EFA, NS, and PVP K30 were prepared. The saturation solubility was found to be 17-fold higher with ternary complex in distilled water and about 4-fold in simulated gastric fluid. *In-vitro* dissolution was improved 3 folds with a ternary complex. Ternary nanosponge complexes were found to have a 2-fold increase in the oral bioavailability of efavirenz as compared to plain drug [48].

Barbara Mognetti *et al.,* were developed paclitaxel-loaded nanosponges, a water-stable colloidal system avoiding the recrystallization of paclitaxel. The *in-vitro* release studies showed an almost complete release in 2 h without an initial burst effect. The study demonstrates that the delivery of paclitaxel *via* nanosponges increased the amount of paclitaxel entering cancer cells and lowers paclitaxel IC_{50}, therefore enhancing its pharma-cological effect. β-cyclodextrin based nanosponges can, therefore, be considered an alternative system to solubilize and deliver the paclitaxel [49].

Shankar Swaminathan *et al.,* were worked to enhance the solubility of Itraconazole so that the bioavailability problems are solved. A solid dispersion technique has been used for drug incorporation. The effect of a ternary component copolyvidonum on the solubility of itraconazole has been studied. Phase solubility studies have been carried out with a rationale of comparing the solubilization efficiency of nanosponges, copoly-vidonum and combination. It was found that the solubility of itraconazole was enhanced by more than 50-folds with a ternary solid dispersion system. Using copolyvidonum in conjunction with

nanosponges helps to increase the solubilization efficiency of nanosponges as evident from the phase solubility studies [50].

Singireddy Anandam *et al.,* were studied to enhance the dissolution rate and stability of poorly water-soluble drug quercetin by complexation with cyclodextrin-based nano-sponges. The particle sizes of plain and quercetin-loaded nanosponges are between 40 and 100 nm with low polydispersity indices. Zeta potential is sufficiently high to obtain a stable colloidal nanosuspension.

The dissolution of the quercetin nanosponges was significantly higher compared with the pure drug. The stability of encapsulated quercetin nanosponge was tracked in a simulated intestinal fluid. A marked improvement in the photostability was also observed [51].

Andreea Alexandra Olteanu *et al.,* formulated nano-sponge complexes and hecomplexing properties of the polymers were investigated against repaglinide (a hypoglycemic agent, practically insoluble in water). Solubility studies were performed according to the method reported by Higuchi and Connors, and the phase solubility diagrams were plotted. The repaglinide-nano-sponges complexes were prepared, lyophilized and the resulted inclusion complexes were characterized by FT-IR and NMR. The solubility profile and the loading capacity of the cyclodextrin based polymers were also determined [52].

S. Swaminathan *et al.,* were synthesized new swellable cyclodextrin-based poly (amidoamine) nanosponges, named PAA-NS10 and PAA-NS11, by crosslinking β-cyclodextrin with either 2, 2-bisacrylamidoacetic acid or with polyamidoamine segments deriving from 2, 2-bisacrylamidoacetic acid and 2-methylpiperazine, respectively.

Both PAA-NS10 and PAA-NS11 were converted to aqueous nano-suspensions using the High-Pressure Homogenization technique. *In-vitro* BSA release studies were carried out showing a prolonged release of albumin from the two swollen BSA loaded β-CD PAA-NS over a period of 24 h [53]. Roberta Cavalli *et al.,* were prepared nanosponges from β-cyclodextrins as nanoporous materials for possible use as carriers for drug delivery. The structure of β-cyclodextrin-based nanosponges was principally investigated by FT-IR, DSC and RX analyses. Sizes, morphology, and toxicity were also examined. The capacity of the nanosponges to incorporate molecules within their structure was evaluated using drugs with different structures and solubilities. The nanosponges were found capable of carrying both lipophilic and hydrophilic drugs and of improving the solubility of poorly water-soluble molecules [54].

S. S. Darandale *et al.,* were formulated the complex of curcumin with β-cyclodextrin nanosponge obtained with dimethyl carbonate as a crosslinker. The particle size of loaded nanosponge was found to be 487.3 nm with a minimum polydispersibility index (0.476). The loaded NS have shown more solubilization efficiency (20.89 μg/ml) in comparison with plain curcumin (0.4 μg/ml) and β-CD complex (5.88 μg/ml). The zeta potential was sufficiently high (−27 mV) which indicates the formation of a stable colloidal nanosuspension. The *in-vitro* drug release of curcumin was controlled over a prolonged period of time [55].

Monica Rao *et al.,* were prepared β-Cyclodextrin (β-CD) based nanosponges (NSs) cross-linking β-CD with carbonate bonds, which were porous as well as nanosized. Telmisartan was incorporated by the solvent evaporation method. Saturation solubility and *in-vitro* dissolution study of the β-CD complex of TEL was compared with plain TEL and NS complexes of TEL. It was found that solubility of TEL was increased by 8.53-fold in distilled water; 3.35-fold in 0.1 N HCl and 4.66-fold in phosphate buffer pH 6.8 by incorporating $NaHCO_3$ in drug–NS complex than TEL. It was found that the $NaHCO_3$ in NS based complex synergistically enhanced the dissolution of TEL by modulating microenvironmental pH and by changing the amorphization of the drug. The highest solubility and *in-vitro* drug release were observed in the inclusion complex prepared from NS and $NaHCO_3$. An increase of 54.4% in AUC was seen in the case of the ternary NS complex whereas the β-CD ternary complex exhibited an increase of 79.65 % [56].

Khalid A. Ansari *et al.,* were worked to increase the solubility, stability, and permeation of resveratrol by complexation with cyclodextrin-based nanosponges (NS). Nanosponges are

developed using hyper-cross-linked cyclodextrin polymers nanostructured to form three-dimensional networks; they are obtained by reacting cyclodextrin with a cross-linker such as carbonyl-diimidazole.

The *in-vitro* release and stability of resveratrol complex were increased compared with the plain drug. Cytotoxic studies on HCPC-I cell showed that resveratrol formulations were more cytotoxic than plain resveratrol. The permeation study indicates that the resveratrol NS formulation showed good permeation in pigskin. The accumulation study in rabbit mucosa showed better accumulation of resveratrol NS formulation than plain drug [57].

Monica R. P. Rao *et al.,* were studied to enhance solubility and dissolution of rilpivirine using beta-cyclodextrin-based nanosponges. These nano-sponges are biocompatible nanoporous particles having high loading capacity to form supra-molecular inclusion and non-inclusion complexes with hydrophilic and lipophilic drugs for solubility enhancement. Beta-cyclodextrin was crosslinked with carbonyl diimidazole and pyromellitic-dianhydride to prepare nanosponges. The nano-sponges were loaded with rilpivirine by a solvent evaporation method. Solubility enhancement was evident in bio-relevant media.

A 3-fold increase in dissolution with ternary complexes was observed. Animal studies revealed a nearly 2-fold increase in oral bioavailability of rilpivirine. It was inferred that electronic interactions, hydrogen bonding, and van der Waals forces are involved in the supra-molecular interactions [58].

Upendra Nagaich *et al.,* were formulated the nanosponges of peppermint oil, and herbal approach to reduce the side effects of chemicals as sun protecting factors. Nanosponges were evaluated for particle size, surface morphology, and *in-vitro* sun protection efficiency. 2^3 factorial designs were used to optimize the formulation for peppermint oil loaded nanosponges. Sun protection factor was calculated and it was found to be 5.28713 ± 0.722, concluded that nanosponges formulated can be efficiently used as a sun-protecting agent with no or fewer side effects [59].

TABLE 3: DIFFERENT PHARMACEUTICAL DOSAGE FORMULATION [4, 6, 16, 60, 61, 62]

Drug	Route of administration	Indication
Nateglinide	Oral	Anti-diabetic
Trimethoprim	Oral	Antibacterial
Miconazole nitrate	Topical	Antifungal
Lemmongrass	Topical	Antipyretic
Glipizide	Oral	Anti-diabetic
Flurbiprofen	Oral	Anti-inflammatory
Voriconazole	Oral & Topical	Antifungal
Omeprazole	Oral	Anti-ulcerative
Econazole nitrate	Topical	Broad-spectrum anti-mycotic agent
Telmisartan	Oral	Anti-hypertensive
Lamotrigine	Oral	Antiepileptic
Nystanin	Topical	Antifungal
Gammma-oryizanol	Topical	Antihypertensive
Ketoconazole	Topical	Antifungal
Lansoprazole	Oral	Proton pump inhibitor
Camptothecin	Parenteral	Anti-cancer
Clotrimazole	Topical	Antifungal
Dexamethasone	Oral & Parenteral	Brain tumors
Isoniazid	Topical	Anti-tuberculosis
Reservatrol	Oral & Topical	Antioxidant
Acetylsalicylic acid	Oral	Analgesic
Celecoxib	Topical	Nonsteroidal anti-inflammatory drug
Itraconazole	Oral & Topical	Antifungal
Cephalexin	Topical	Antibiotics
Acyclovir	Oral & Topical & Parenteral	Antiviral
Piroxicam	Oral	Nonsteroidal anti-inflammatory drug
Paclitaxel	Parenteral	Anti-cancer
Ibuprofen	Topical	Nonsteroidal anti-inflammatory drug

Doxorubicin	Parenteral	Antineoplastic
5-fluorouracile	Parenteral & Topical	Antineoplastic
Tamoxifen	Oral	Breast cancer
Progesterone	Oral	Hormone
Ciprofloxacin	Oral	Antibiotics
Nelfinavirmesylate	Oral	Antiviral
Cilostazole	Oral	Antiplatelet agent
Cymbopogoncitratus	Oral	Antipyretic

Factors Influences Nanosponges Formulation: [8, 13, 63, 64]

- Type of polymer.
- Type of drugs.
- Temperature
- Method of preparation.
- Degree of substitution.

Evaluation of Nanosponges: [2, 7, 9, 61]

- Particle size determination.
- Determination of loading efficiency.
- Porosity.
- Swelling and water uptake.
- Resiliency (Viscoelastic properties).
- Compatibility Studies.
- Zeta potential.
- Thermo-analytical methods.
- Solubility studies.
- Drug release kinetics.
- Thin-layer chromatography.
- Infra-red spectroscopy.
- *In-vitro* release studies.
- Permeation studies.
- Microscopy studies.
- Photodegradation study.
- X-ray diffraction study.

CONCLUSION: Nanosponges have the capability to include both lipophilic and hydrophilic drugs. Nanosponges can release them in a precise and expectable manner at the target site. By controlling the ratio of polymer to cross-linker the particle size and release rate of nanosponge formulation can be modulated. Nanosponges facilitate the uses of insoluble molecules and can protect the active moieties from external physiochemical degradation. Because of their small size and spherical shape nanosponges can be developed in various dosage forms like parenteral, topical, aerosol, tablets and capsules.

ACKNOWLEDGEMENT: The author would like to acknowledge the support from his family and colleagues from INTAS Pharmaceuticals, Ahmedabad.

CONFLICTS OF INTEREST: There are no conflicts of interest.

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How to cite this article:
Satpathy TK, Chaubey N, Usha SB and VR Naidu: Nanosponges – novel emerging drug delivery system. Int J Pharm Sci & Res 2020; 11(7): 3087-00. doi: 10.13040/IJPSR.0975-8232.11(7).3087-00.