NANOSPONGE AS A NEW NANOENGINEERING HORIZON FOR DRUG DELIVERY: A REVIEW

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Abstract

Nanosponges are exceptionally permeable, 3D organized, minor size, nanometric cavity size nanocarrier having remarkable capacity to entangle dynamic drug moieties. Nanosponge giving novel drug delivery just as upgrading solubility and bioavailability. The fundamental spotlight is given on cyclodextrin polymer nanostructured inside a 3D network. Indeed, even the cyclodextrin structure edifices with different sort of lipophobic/hydrophobic drug molecules. The incorporated molecules release be fluctuated by modifying structure to acquire quickly and drag out dru molecule release just as at explicit target site. Cyclodextrin nanosponge pull in extraordinary consideration for fathoming issue of bioavailability, deficient solubility, poor disintegration rate, pharmacokinetic issue of different medicaments and expanding drugs productiveness and decreasing superfluous antagonistic impact. It prompts a novel drug delivery framework**.**

Keywords : Cyclodextrins, Nanosponges, Cross linking agent, Biocompatible**.**

INTRODUCTION

Nanosponges are tiny mesh-like structures in which different substance can be encapsulated[1-2]. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water suitable molecules[2-3]. The nanosponge is about the size of a viruswith a 'backbone' (a scaffold structure) ofnaturally degradable polyester also a 3D structure[12]. The long lengthpolyester strands are mixed in the solution with smallmolecules called as cross-linkers that have anaffinity for certain portions of the polyester. They'cross link' segments of the polyester to form aspherical shape that has many pockets (orcavities) where drugs can be stored[3]. These chemical cross linkers enablesnanosponge to get bind at preferentially to the target site[3-4].Predictable release is one of major advantage of this system compared to other nanoparticle

delivery system[5].These nanosponges represent a novel class ofnanoparticles usually obtained by the naturalderivatives. As compared to the othernanoparticles, they are insoluble in both water andorganic solvents, porous, non toxic and stable athigh temperatures up to 300°C.It has been reported that, by reacting cyclodextrins(cyclic oligosaccharides) with suitable cross-linkingreagents, a novel nanostructured material consisting ofhyper-cross-linked cyclodextrins can be obtained, knownasnanosponges[1].Cyclodextrins are cyclic oligomers of D-glucopyranose units linked by (alpha-1, 4) linkages. A cyclodextrin has a characteristic structure with primary hydroxyl groups extending from the narrow edge and secondary hydroxyl groups extending from the wider edge which impart to cyclodextrins their peculiar hydrophilic outersurface and a lipophilic cavity[5].

This review include an emerging approach to prepare multifunctional cyclodextrin derivatives by bringingabout crosslinking of cyclodextrin polymers. Cyclodextrin-based nanosponges are a promising and aninnovative form of a drug delivery system whichcomprises a nanostructured three-dimensional networkof crosslinked cyclodextrin molecules with a porousstructure capable of encapsulating hydrophilic as well ashydrophobic drug molecules[5-6].Themaincommon cyclodextrins in these delivery systems are α, β and γ, with 6, 7 and 8glucopyranose unit. Among these, β-CD is mainly selected in the nanosponge preparation, because itis the cheapest and most useful one, with its higher dimension of inner cavity[6]. Cyclodextrin based NanospongeCDNSs are known to be non-allergic and biodegradable[6]. Most of the CDNS formulations have high zeta potential value (more than -20 mV) which makes stable nanosuspension in water with little tendency to aggregate longer time. This characteristic of CDNSs can improve the aqueous solubility of poorly water-solublemolecules and overcome major barrier inthe delivery of lipophilic drugs in physiological media[6].

Boons of the Nanosponge

- It is Targeted site specific drug delivery.
- May be used to mask unpleasant flavours and to convert liquid substances to solids [10].
- Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
- Nanosponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the nanosponge,
- Particles can be made smaller or larger by varying the proportion of cross-linker to the polymer.
- The drug profiles can be varied from fast, medium to slow release, preventing over or under-dosing of the therapy .
- Improved stability, increased elegance and enhanced formulation flexibility.
- Nanosponges systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.
- These are the self sterilizing as their average pore size is 0.25µm, where bacteria will not be able to penetrate .
- Extended release - continuous action up to 12 h.

- It is Biodegradable and Biocompatible[58].

CDNSs are biocompatible, nontoxic and safe for use. The drug release from these nanosponges can be customized by tuning the type and degree of crosslinking. It possess numerous advantages ranging from improved solubility, stability, permeation, bioavailability, modulation of drug release to efficient drug targeting in case of anticancer therapeutics. In addition, delivery of proteins, enzymes and gases is possible. This syatem offer many advantages and various applications. The natural CDs with their characteristics are mention in Table 1.

Table 1 - Types of natural CDs and their characteristics[56,57,41]

Properties	Alpha-CDs	Beta-CDs	Gamma-CDs
The no. of units of glucose	6	7	8
Dimensions (nm)			
Height	0.78	0.78	0.78
Outer diameter	1.37	1.53	1.69
Inner diameter	0.57	0.78	0.95
The Molecular weight	972	1135	1297
The size of cavity	174	262	472
The solubility of water	14.5	1.85	23.2
Applications	Oral, Parental, Topical	Oral, topical	Oral, Parental, Topical

Drug release Mechanism from the Nanosponges

Naosponge has open structure which provides free movement of drug substance entrapped in vehicle in the outward and inward direction from the nanosponge till the equilibrium reached.Whereas in case of gels or cream, the equilibrium will get disturb because drug itself is in vehicle and tend to become unsaturated. The drug will flow from the nanosponge to the vehicle and further into the skin until and unless the vehicle is absorb or dried. The nanosponge retained onsurface layer of skin that is stratum corneum will further release the drug to the skin leading to the prolong release of drug over the certain time[58] as shown in fig. 5.

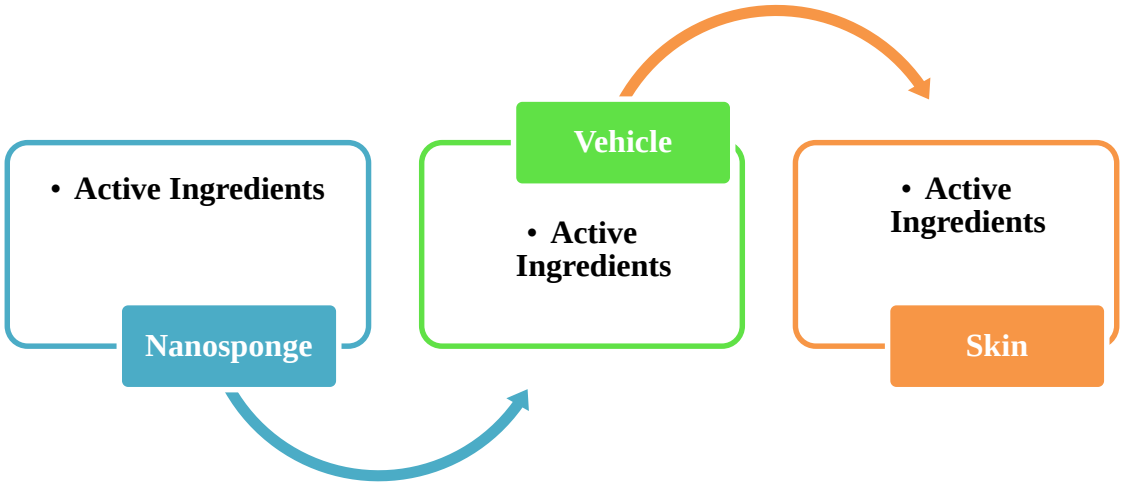

Fig. 5- Mechanism of drug release

APPLICATION OF NANOSPONGES

In Anticancer therapy

Paclitaxel is the drugs used for treating cancer related to lungs and ovary. Amphiphils was develop as carrier system in the form of the nanoparticle which will encapsulate paclitaxel .Due to this encpaulation the resultant effect is increase in solubility and loading capacity further forming inclusion complex. The extended release were found to be 24 hr for the nancapsule and 12 hr for the nanosponge [8].

Paclitaxel is has poor dissolution and water solubility.Hence , to overcome this theβ-CD based nanosponges is formulated of the paclitaxel. The effect od drug is enhanced by formulating it in the form of the nanospongedrugd intracellular conc os increase as compare to plain drug[15].

In Gene therapy

Gene therapy has enormous promise for the treatment of an extensive variety of clinical situations. Cyclodextrins has great affinity toward nucleic acids and ability to attenuate the other gene carries for attenuation[10-11]. The main reasons for incorporating CDs is to minimize the cyctotoxicity by offering a cellular uptake of the nanosponge loadedwith the drug[8].Further this will offer the good delivery of the nucleic acids , DNA and greater amount of proteins expression in mucosa of respiratory system[13].

In drug delivery

Nanosponges are nanomeric in size and have spherical shape, therefore, nanosponges can be prepared in different dosage form like topical, parenteral, aerosol, tablets and Capsules[1]. Telmisartan (TEL) is a BCS Class II drug having the dissolution rate limited bioavailability. β-CD based nanosponges were formed by the cross-linking β-CD with carbonate bonds. TEL was formulated into the nanosponges. Saturation solubility and in vitro dissolution study of β-CD complex of TEL was compared with the plain drug TEL and nanosponge

complexes of TEL. It was found that solubility of TEL was increased by 8.53 fold in distilled water, 3.35-fold in 1 mol HCl and 4.66 fold in phosphate buffer pH 6.8 by incorporating $NaHCO_3$ in drug-nanosponges complex than TEL. The highest solubility and in vitro drug release was observed in inclusion complex prepared from nanosponges and $NaHCO_3$[1,13,14].

In Sustained delivery system

Acyclovir is majorily used as a antiviral agent in the treatment of the herpes simplex virusinfections[16]. Acyclovir has low absorption through the gastrointestinal tract and its incomplete with varaing its pharmacokinetic properties when taken orally. The nanosponge formulation of acyclovir has shown the sustained release of the drug. Hence, nanosponge formulation has of acyclovir has overcome the pharmacokinetic issue of the drug. Therelease of acyclovir from Carb-nanospongeswas 70%, respectively[17].

Nanosponge for protein delivery

Proteins are with one of the ajor issue is the long term stability issue[1,18].Proteins get reversibly denature upon lyophilization. Thus, a major problem in proteinformulation process is the maintaining the structure of protein during the formulation process as well as for the long term stability[19].

The new swellable cyclodextrinbasedpoly (amidoamine) nanosponges named nanosponges

10 and nanosponges 11, were synthesised by the crosslinkingβ-CDs with either 2,2-bis-acrylamidoaceticacid or polyamido-amine chain derivingfrom 2,2-bis-acrylamidoacetic acid and 2-methylpiperazine respectively. The formulated β-CD based poly(amidoamine)-nanosponges were found to be stable at 300 °C and high protein complexation capacity was observed and overcome stability issue of protein[20].

Nanospongeinthe enzyme immobilization

The problem of the enzyme immobilization is particularlyrelevant for the lipases, as it modulates properties likeenantio selectivity andreactionrates[21].

The synthesis of Platinum- Silver graphite-naofiber-supported porous nanosponges and mesoporous platinumnanosponges as electrocatalysts for the purpose of oxygenreductionreaction[22,23].

Nanosponges as protective agent from light or degradation

Gamma-oryzanol is the ferulic acid ester mixture, majorly used asa antioxidant of natural sourceandwidelyuse for stabilizingpharmaceuticalraw materials, food, even used as a sunscreen in thecosmetics industry, it is with huge applicability. Photodegradation and instability are its major limitations. Gamma-oryzanol has been protected from photodegradation by encapsulating in nanosponges. Even this nanosponge were also formulated as emulsions and gel[25].

Nanosponges in solubility enhancement

The formulation of itraconazoleinNanosponges was done[27]. Itraconazole drug having poor solubility, dissolution and biavaliabilty, which is BCS class II drug hence nanosponge approach was choosen.Nanosponges has successfully improved solubility of the itraconazole by grater than 27 folds. Further when the supporting component was added in the above formulation the solubility increase by grater then 55 folds. Mechanism involve in enhancing solubility of drug by nanosponge is by increasing wetthing ability of drug and masking the various lipophilic groups in itraconazole as well as by decreasing crystallinityofthedrug[27]. Hence, enhancing solubility poorwater soluble drugs.

For Oral delivery systems

For solid drug the major limiting factor is its dissolution , as per oralbioavailability is concern. The dissolution processacts as the rate-controlling step for the hydrophobic drugs and, hence degree of absorption can be determine. Manyhydrophobic drugs have incomplete absorption fromthe gastrointestinal tract.Acetylsalicylic acid (ASA), one of the BCS Class III drug having NSAIDs(nonsteroidal anti inflammatory) activity was formulated for its prolong release with into pyromellitic dianhydride and then cross-linked with β-cyclodextrin nanosponges. The release data of in nanosponge was obtained by *in vivo* and*in vitro* studies. Shown the delay release of drug over a prolong period of the 24 hr. These obtained results indicate that the many drugs with poor water solubility can be used for oral delivery for formulating the particular dug in nanosponge formulation[28].

Topical delivery systems

For topical application the nanosponge can be used in form of crems, gels etc. Resveratrol, a herbal molecule which is important to treat various human diseases and due to its antioxidant properties but has poor slobility and stability, hence its was formulated in nanosponge which has enhance its solubility and stability.Resveratrol-loaded nanosponges has not only increase solubility but also its permeation in *in vitro* studies using the porcine skin[7].

Patent in field of cyclodextrin based nanosponge are given in Table 2.

Table 2: Patents of cyclodextrin based nanosponge

Title	Publication Number	Publication Date
Preparation of crosslinked cyclodextrin resins with enhanced porosity	US4958015 A [50]	1990
Cyclodextrin polymer and cyclodextrin film	EP0502194 A1 [51]	1992

formed therefrom		
Cross-linked polymers based on cyclodextrins for removing polluting agents	US20050154198A1 [52]	2003
Ultrasound-assisted synthesis of cyclodextrinbased nanosponges	US20080213384A1 [55]	2006
Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies	EP2294190A1 [54]	2010
Cyclodextrin-based nanosponges as a vehicle for antitumoral drugs	EP2175847A1 [53]	2011

Method of synthesis of Nanosponges

Emulsion solvent diffusion method

The nanosponges were prepared with Ethyl cellulose and Polyvinyl alcohol in variable ratios. This method having two phases that are continuous phase and dispersed phase. The dispersed phase having ethyl cellulose and drug were added in dichloromethane (20 ml) and gently mixed in a continuous phase which containing exact quantity of PVA in water (150 ml). The solution was stirred continuously for 2hrs. at 1000 rpm. After stirring is over, by using vacuum filtration formed nanosponges were collected. After filtration the nanosponges were dried for 24 hrs at 40°C in an oven and for the withdraw of residual solvent it was stored in a vacuum desiccator[4] as shown in fig. 2.

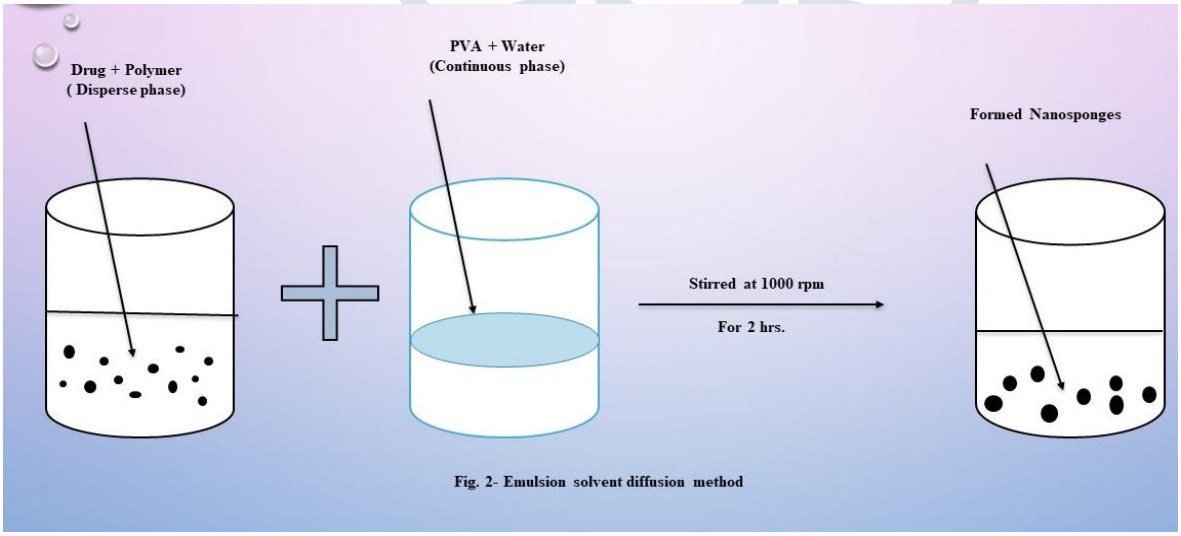

Fig.2. Emulsion solvent diffusion method

Formulation of nanospongesby Hyper-croslinked ß-CDs

The various types of CDs with carbonate compounds as a crosslinking agent can be used to prepare nanosponges. In round bottomed flask added 100 ml of dimethylformamide and 17.42 g of anhydrous ß-CD for complete dissolution. Then carbonyl diimidazole (9.96 g) was added and the solution was reacted at 100°C for 4 hrs. After completion of condensation polymerization, the hyper-crosslinked CDs were broken roughly and to withdraw dimethylformamide excess amount of deionized water was mixed. At last Soxhlet extraction was used with ethanol to withdraw the unwanted reagents. The achieved ß-CDs nanosponges were dried in oven at 60°c for overnight and later broken into mortar. In water the obtained nanosponges were added. The retained colloidal part in water was collected and lyophilized. Hyper-crosslinked ß-CDs nanosponges were obtained with spherical shape and submicron in dimension[4] as shown in fig. 1.

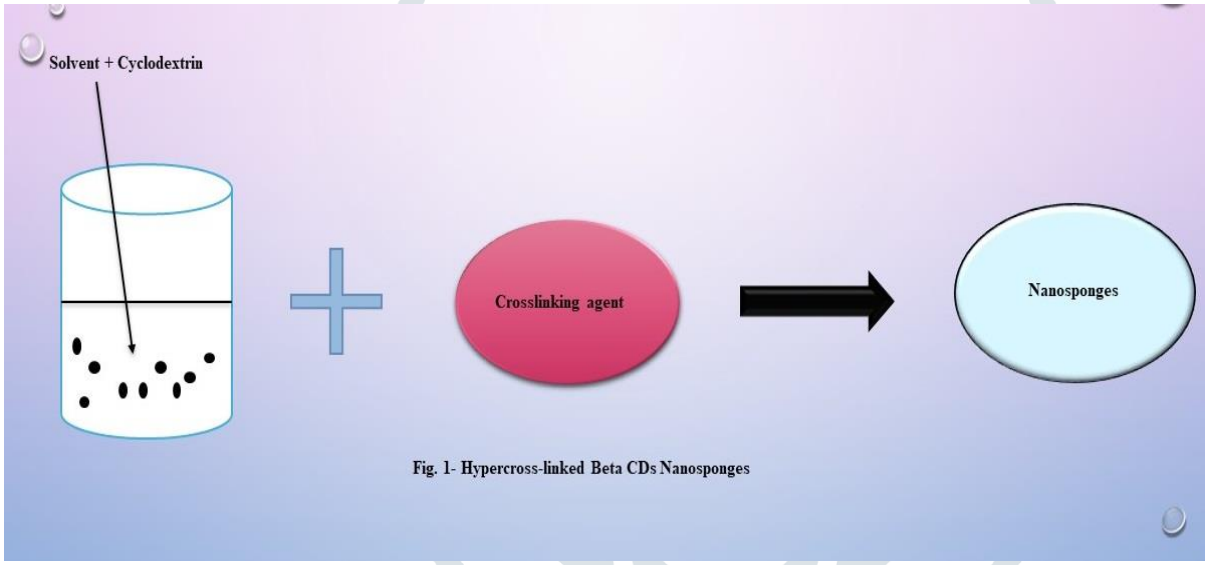

Fig.1- Hypercross-linked Beta CDs Nanosponges

Solvent Method

solvent method, a polymer was added in a suitable solvent like Dimethylformamide and Dimethylsulfoxide as shown in fig. 3. Then excess amount of crosslinker was added in that mixture. Molar ratio of crosslinker/polymer preferably in 4:16. Temperature of reaction mixture was increasing at 10°C to solvent reflux temperature for 1-48 hrs. After reaction completed, at room temperature the mixture was cooled. In excess bidistilled water the formed nanosponges were mixed. Then recovered the formed nanosponges with filtration. At last the Soxhlet extraction was used with ethanol to withdraw unreacted reagents. Preferred crosslinkers are Dimethyl carbonate and carbonyl diimidazole[1] as shown in fig 3.

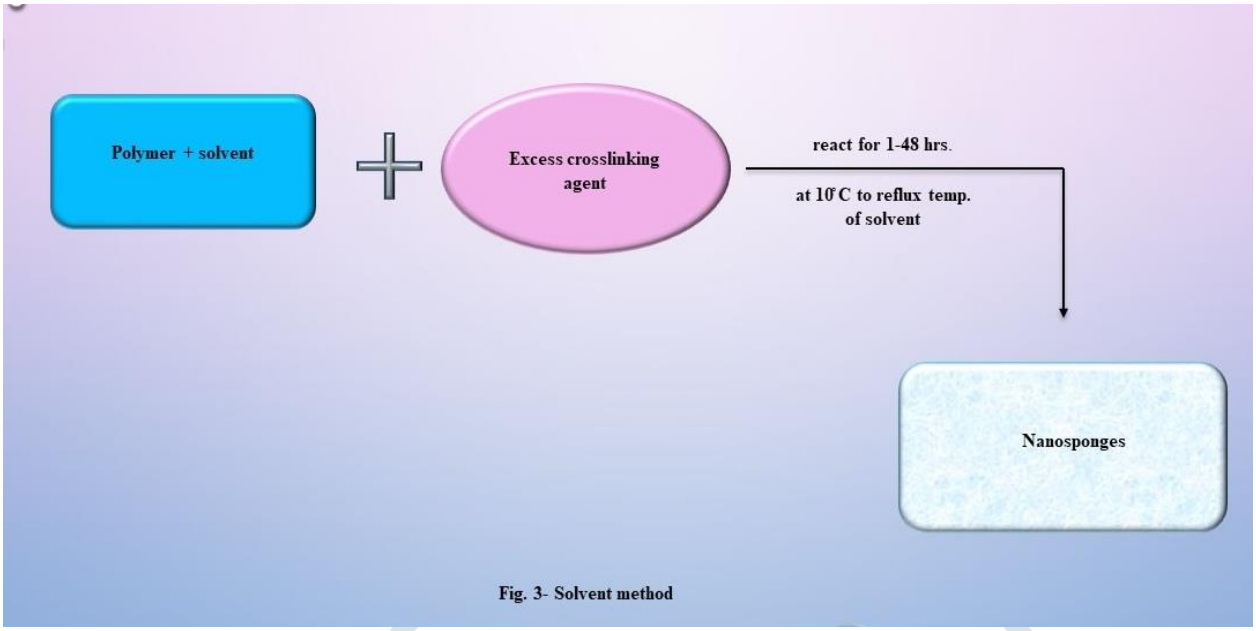

Fig.3. Solvent Method

Ultrasound-assisted synthesis

The nanosponges were achieved by reaction of crosslinking agent and polymers. In this method solvents are not used. In a suitable ratio the polymer and crosslinking agent were mixed into flask. On a ultrasound bath the flask was kept and sonicate the mixture for 5hrs. at a 90°C temperature. Then at a room temperature the solution was cooled and roughly broken the obtained nanosponges. To withdraw the unreacted reagents the obtained nanosponges were washed with distilled water. At last the Soxhlet extraction was used with ethanol for purification of nanosponges. The obtained nanosponges were were dried and for further purpose it was stored at 25°C. The obtained nanosponges were uniform and spherical in shape[3] as shown in fig 4.

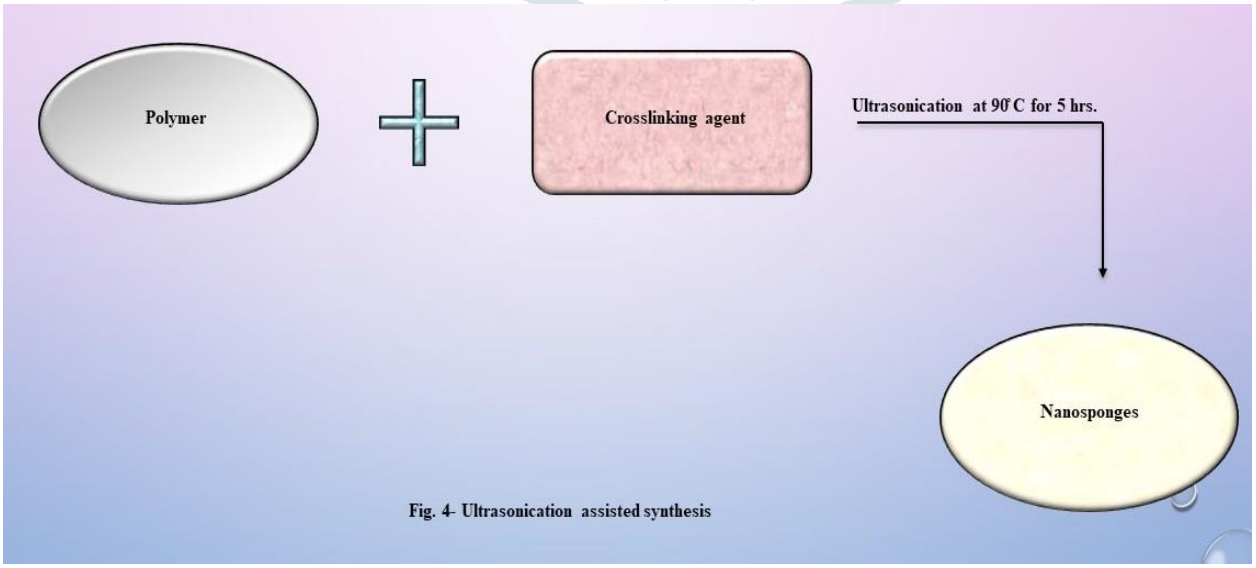

Fig.4- Ultrasound assisted synthesis

Loading of drug into nanosponges

To achieve the average particle size below 500nm the nanosponges for delivery of drug should be pretreated. In water the obtained nanosponges were suspended and to remove the aggregation of particles the solution was sonicated and to achieve the colloidal fraction the solution was centrifuged. After centrifugation of suspension separate the supernatant and by using lyophilization/freeze drying sample was dried. Nanosponge suspension was formulated and mixed excess quantity of drug into suspension. After addition of drug, it kept for continuous stirring for a particular time. After completion of stirring, by centrifugation the unreacted drug was removed. The nanosponges can be achieved by lyophilization/freeze drying. The structure of nanosponges are very important. The loading of drug into nanosponges are better in crystalline nanosponges compared to paracrystalinenanosponges[1].

Factors affecting nanosponges formulation

Type of polymers

The polymers which are using in the preparation of the nanosponges may be affect the performance and formation of the nanosponges.The cavity of nanosponges should have appropriate size where drug can fit easily[3].

Few examples polymers, cross-linkers and solvent are shown in Table 3.

Table 3- Examples of polymer, solvent and cross- linkers

Polymers	EthylCellulose and PVA, Eudragit RS 100, Copolymers like Poly (valerolactone -allylvalerolactone), Hyper crosslinked Polystyrenes, Cyclodextrins and its derivatives like Methyl β- Cyclodextrin, 2-Hydroxy Propyl β-Cyclodextrins.
Cross-linkers	Dichloromethane, Carbonyl Diimidazole, Diphenyl Carbonate,Di-Isocyanates, Pyromellitic anhydrid,Diarylcarbonates, Glutarldehyde, Carboxylic acid dianhydrides.
Solvents	Dimethylacetamide, Dimethyl Sulfoxide, Ethanol, Dimethylformamide.

Type of Drugs

The drug molecule compounded with nanosponges should have following ideal properties:

1. The molar mass of drug substance should be between 100-400 Dalton.

2. The drug substance should not have more than five condensed rings.
3. The solubility of drug substance should not be more than 10 mg/ml.
4. The melting point should not be above 250°C[4].

Examples of drug used for cyclodextrin based nanosponge are given in Table 4.

Table 4- Drugs used for cyclodextrin based nanosponge

Drug	Nanosponge vehicle	Indication	Reference
Paclitaxel	ß-Cyclodextrin	Cancer	44,45
Camptothecin	ß-Cyclodextrin	Cancer	35,46
Tamoxifen	ß-Cyclodextrin	Breast cancer	43
Resveratrol	ß-Cyclodextrins	Cardiovascular disease, Inflammation	47
Itraconazole	ß-Cyclodextrin&Copolyvidonum	Antifungal	48
Dexamethasone	ß-Cyclodextrin	Brain tumors	49

Temperature

The changes in temp can affect the Drug/Nanosponges complexation. The increase in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge complex may be due to the result of possible reduction of the drug/nanosponge interaction forces, such as Hydrophobic forces and Van-Der Waals forces with increase in the temperature

Method of preparation

The method for the loading of the drug into nanosponge can affect the Drug/Nanosponge complexation. The effectiveness of the method depends on the nature of the drug and polymer. In most of the cases Freeze drying was found to be most effective for drug complexation.

Degree of substitution

The type, number, and position of substituent of the parent molecule can be highly influence the compounding capacity of nanosponges[3].

CHARACTERIZATION OF NANOSPONGE

Particle size and polydispersity Index

Particle Size AnalyserNanoplus a particle sizing software is majorily used for determining the particle size by using dynamic light scattering. This will provide data of the mean diameter through which the polydispersity index would be able to identify of the nanosponge[31,32,2]. PDI is an index ofthe width or variation within the particle size distribution of the given sample. Generally higher the value of PDI wider the particle size distribution and monodisperse sample generally possed lower PDI value. . PDI could be calculated by the following equation:

PDI = Δd/davg

Where,

Δd is the width of distribution denoted as SD and davg is the average particle size denoted as MV (nm) in particle size data sheet[33]. Refrence value are given in Table 5

Table 5- PDI

Type of dispersion	PDI
Monodisperse standard	0-0.05
Nearly monodisperse	0.05-0.08
Midrange polydispersity	0.08-0.7
Very polydisperse	0.7

Zeta potential

Zeta potential is the measure of surface charge. It can be measured by using additional electrode in the particle size equipment[33].

Infra red spectroscopy

Infra-red spectroscopy is used to estimate the interactionbetweendrugs molecule in solid state and nanosponges.Nanosponges bands often change only slightly uponcomplex formation. If the fraction of the guest moleculesencapsulated in the complex is less than 25%, The technique is not generally suitable todetect the inclusion complexes and is less clarifying thanothermethods[25].

Powdered X ray diffractometry

Powder x-beam diffractometry is used to recognize consideration complex in strong stateas well as crystallinity. If fluid is considered, at that point it has no diffraction example of their own and absolutely varies from incomplexednanosponge. On the off chance that tranquilize is a strong substance examination ought to be made between diffractogram of accepted mind boggling and mechanical blend of dry and it adjusts diffraction

patterns.A diffraction example of a physical blend results from mix of two parts. Be that as it may, edifices having diffraction design for the most part contrasts from the constituent they contain and offer ascent to " new" strong stage having diverse diffractograms. They offer ascent to various crests for a blend and valuable in deciding concoction decay and complex development[29].

Entrapment Efficiency

Nanosponge entrapment efficiency can be determined by quantitative estimation of the drug loaded into nanosponges by the UV spectrophotometer and high performance liquid chromotography methods. The entrapment efficiency (%) of nanosponges can be calculated according to the following equation[4].

$$\text{Entrapment Efficiency} = \frac{\text{calculated drug content in nanosponge}}{\text{Theoratical drug content}} \times 100$$

Microscopy studies

Scanning Electron Microscopy (SEM) andTransmission Electron Microscopy (TEM) are used to study the microscopic aspects regarding size of drugs nanosponges as wll as cavities present and drug loaded into cavities (drug/nanospongecomplex)[34,35].

Thermo-analytical methods

Thermo-analytical methods is for determining whether drug is compatible with the other ingredients used or drug substance undergoes few change regarding endo and exothermic peak before the thermal degradation of nanosponge.Melting, decomposition, oxidation or polymorphic transition which gives idea about change in the drug substance. Obtained thermogram by DSC and DTAwere observed for the shifting, broadening and appearance of new peaks or disappearance of particular peaks. Mostly changes in weight loss also provide indication for the formation of inclusion complexes [38].

Phase Solubility study

Phase solubility method is one of the majorily used method for studying inclusion complexation describedby Higuchi and Connors, providing the effect of formulated nanosponge on the solubility of drug[39,40,41]. In this method the drug in nanosponge form was added to anShakingflaskincubatorcontaining an aqueous solution of various percentagesofnanosponges. The Shaking flask incubator's temperature and required rpm speed was maintained.after completion of given time the suspension was taken out and centrifugation was done using a molecular filter of 3 000 Dalton. The supernatant solution obtained wasfurther analyzed to determinethe drug concentration by UV visible spectroscopy method.

In-vitro study of drug release

Franz Diffusion cell is commonly used by using dialysis membrane for studying drug release of formulated nanospongewith diffusional area of 2.26 cm^2 and 11 ml of receptor volume. The dialysis membraneto be used must be soaked for 8 hr in the medium to be used and this membrane will act as barrier between receptor and donor compartment. Then the nanosponge of 1 g was placed on donor chamber which was further seal by aluminum foil from the atmosphere.Compartment receptor was further filled with the6.8 pH phosphate buffer of by the volume of 11 ml.During the experiment, the temperature and speed was maintained that is the 37±0.5ºC and at 100 rpm of stirring, solution of receptor side compartment was further kept at Teflon-coated magnetic stirring bars. As per the reported time intervals the aliquot was collected from the receptor chamber and replaced by same volume of the media for maintain sink condition. Further sample was analyzed for drug release using UV visible spectrophotometer[42].

CONCLUSION

The nanosponges are novel class of drug delivery system and it consist of three-dimensional network. The nanosponge structure consist of cavities on their surface where drug molecule can be incorporated. The nanosponges are biocompatible with various types of drug molecule and due to which they are non-toxic, non-irritant and non-allergenic. The nanosponges have good ability to incorporate lipophilic/hydrophilic drug molecules. The nanosponges can be prepared into the different dosage forms such as parenteral, topical, capsules, aerosols and tablets. The nanosponges not only having the ability to solve the solubility problem of drug but also enhance the permeation, prolonging release of drug substance, stability and bioavailability. The cyclodextrin based nanosponges are also used for the delivery of important pharmaceutical gases and proteins. The nanosponges contains wide range of applications in pharmaceutical and medicines as well as in various field like environment, cosmetics and the agriculture. From above study we can conclude that nanosponges have multipurpose use, therefore this system is appropriate for delivery of active ingredient in nanomedicine.

REFERENCES

1. Panda S, Vijayalakshmi S, Pattnaik S, Swain RP. Nanosponges: A novel carrier for targeted drug delivery. **Int J PharmTech Res.** 2015,8(7),213–24.

2. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, Verma A. Nanosponges: A potential nanocarrier for novel drug delivery-a review, **Asian Pacific J Trop Dis.** 2014,4(S2),S519–26.

3. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system - Review, **J Pharm Pharm Sci**. 2012,15(1),103–11.

4. Bolmal UB, Manvi F V, Rajkumar K, Sowjanya Palla S, Paladugu A, Reddy KR.: Recent Advances in Nanosponges as Drug Delivery System, **Int J Pharm Sci Nanotechnol .** 2013,6(1),34–44.

5. Chilajwar S V., Pednekar PP, Jadhav KR, Gupta GJC, Kadam VJ.: Cyclodextrin-based nanosponges: A propitious platform for enhancing drug delivery, **Expert Opin Drug Deliv**. 2014,11(1),11–20.

6. Allahyari S, Trotta F, Valizadeh H, Jelvehgari M, Zakeri-Milani P.: Cyclodextrin-based nanosponges as promising carriers for active agents,**Expert Opin Drug Deliv .** 2019,16(5),467–79.

7. Trotta F, Zanetti M, Cavalli R.: Cyclodextrin-based nanosponges as drug carriers,. **Beilstein J Org Chem.** 2012,8,2091–9.

8. Lakkakula JR, Maçedo Krause RW.: A vision for cyclodextrin nanoparticles in drug delivery systems and pharmaceutical applications, **Nanomedicine**. 2014,9(6),877–94.

9. Adeoye O, Cabral-Marques H.: Cyclodextrin nanosystems in oral drug delivery: A mini review. **Int J Pharm** . 2017,531(2),521–31.

10. Conceicao J, Adeoye O, Cabral-Marques HM, Lobo JMS. :Cyclodextrins as Drug Carriers in Pharmaceutical Technology: The State of the Art, **Curr Pharm Des.** 2017,24(13),1405–33.

11. Lai WF. Cyclodextrins in non-viral gene delivery, **Biomaterials .**2014, 35(1), 401-11.

12. Vishwakarma A, Nikam P, Mogal R, Talele S: Review on nanosponges: A benefication for noveldrug delivery,**Int J Pharm Tech Res**. 2014,6(1),11-20.

13. Teijeiro-Osorio D, Remuñán-López C, Alonso MJ. :Chitosan/cyclodextrin nanoparticles can efficiently transfect the airway epithelium *in vitro***, Eur. J. Pharm. Biopharm**.2009, 71(2), 257–263 .

14. Rao M, Bajaj A, Khole I, Munjapara G, Trotta F.: In vitro andin vivo evaluation of β- cyclodextrin-based nanospongesoftelmisartan, **J Incl Phenom Macrocycl Chem**.2013, 77,135-145.

15. Mognetti B, Barberis A, Marino S, Berta G, Francia SD, Trotta F, et al. In vitro enhancement of anticancer activity of paclitaxel by a cremophor free cyclodextrin-based nanosponge formulation. **J Incl Phenom Macrocycl Chem** 2012; 74: 201-210.

16. O'Brien JJ, Campoli-Richards DM. Acyclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1989; 37: 233-309.

17. Lemboa D, Swaminathan S, Donalisioa M, Civraa A, Pasterod L, Aquilanod D, et al. Encapsulation of acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. **Int J Pharm**.2013, 443, 262-272.

18. Klibanov AM, Schefiliti JA. :On the relationship between conformation and stability in solid pharmaceutical protein formutations, **Biotechnol Lett.** 2004, 26,1103-1106.

19. Shewarts D, Sofia S, Friess W.: Integrity and stability studies ofprecipitated rhBMP-2 microparticles with a focus on ATR-FTIRmeasurements, **Eur J Pharm Biopharm.**2006,63, 241-248.

20. Swaminathan S, Cavalli R, Trotta F, Ferruti P, RanucciE,Gerges I, et al.: In vitro release modulation and conformationalstabilization of a model protein using swellable polyamidoaminenanosponges of β-cyclodextrin, **J Incl Phenom Macrocycl Chem.** 2010, 68, 183-191.

21. Mateo C, Palomo JM, Fernandez-Lorente G, GuisanJM,Fernandez-Lorente R.: Improvement of enzyme activity, stabilityand selectivity via immobilization techniques.,**Enzyme MicrobTechnol.**2007, 40, 1451-1463.

22. Lee CL, Chao YJ, Chen CH, Chiou HP, Syu CC.: Graphitenanofiber-supported porous Pt-Ag nanosponges: synthesis andoxygen reduction electrocatalysis, **Int J Hydro Energy** 2011, 36,15045-15051.

23. Lee CL, Wu CC, Chiou HP, Syu CM, Huang CH, Yang CC.:Mesoporous platinum nanosponges as electrocatalysts for theoxygen reduction reaction in an acidic electrolyte, **Int J HydroEnergy.**2011, 36, 6433-6440.

24. Mamba BB, Krause RW, Malefetse TJ, Gericke G, Sithole SP.: Water Institute of Southern Africa (WISA) Biennial Conference 2008, Sun City, South Africa, **Special Edition**, 2009, 35(2), 56.

25. Sapino S, Carlotti ME, Cavalli R, Ugazio E, Berlier G, GastaldiL, et al. Photochemical and antioxidant properties of gammaoryzanolin beta-cyclodextrin-based nanosponges, **J InclPhenomMacrocycl Chem.** 2013, 75,69-76.

26. Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, VaviaP.:Nanospongeormulations as oxygen delivery systems, **Int JPharm.**2010,402, 254-257.

27. Swaminathan S, Vavia PR, Trotta F, Torne S.: Formulation ofbetacyclodextrin based nanosponges of itraconazole**, J InclPhenomMacrcycl Chem.** 2007,57(1-4), 89-94.

28. Mognetti, B.Barberis, A.Marino, S.,Berta, G., De Francia, S.,Trotta,Cavalli, R. *J.:* **Inclusion Phenom. Macrocyclic Chem**. **2012,***74*, 201–210.

29. Lee CL,Chiou HP, Syu CC.:Graphitenanofiber-supported porous Pt-Ag nanosponges: synthesis andoxygen reduction electrocatalysis. **Int J Hydro Energy** 2011, 36,15045-15051.

30. Alongi, J., Poskovic, M., Frache, A. and Trotta, F., 2011.: Role of β-cyclodextrinnanospongesin polypropylene photooxidation,**Carbohydrate Polymers**. *86*(1), 127-135.

31. Renuka S, Kamla P.: Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation, **Pharm Dev Technol**. 2011,16(4),367-376.

32 . Shankar S, Linda P, Loredana S, Francesco T, Pradeep V, Dino A, Michele T, Gianpaolo Z, Roberta C.: Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity, **Eur J Pharm Biopharm**. 2010, 74,193-201.

33. Wolfgang S .: Sample preparation in Light Scattering from Polymer Solutions and Nanoparticle Dispersions, **Springer Berlin Heidelberg GmbH & Co**.2007, 43-44

34. Singh R, Bharti N, Madan J, Hiremath SN.: Characterization of cyclodextrin inclusion complexes-a review**, J Pharm Sci Technol.** 2010,2(3),171-183.

35. Shankar S, Linda P, Loredana S, Francesco T,Pradeep V, Dino A, Michele T, GianpaoloZ,Roberta C.: Cyclodextrin-based nanospongesencapsulatingcamptothecin: Physicochemicalcharacterization, stability and cytotoxicity**, Eur JPharmBiopharm**.2010, 74, 193-201.

36. Roger AR, valentine JS. Pharmaceuticalapplications of Cyclodextrins. 2.: In Vivo Drug Delivery**, J.Pharm.Sci**. 1996, 85(11),1142-1169.

37. Patel EK, Oswal RJ.: Nanosponge and microsponges: a novel drug delivery system, **Int J Res Pharm Chem.** 2012, 2(2),237-244.

38. Ramnik S, Nitin B, Jyotsana M, Horemat SN.:Characterization of Cyclodextrin Inclusion complexes –A Review, **J Pharm Sci Tech**.2010,2(3),171-183.

39. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, ValleroR,inventors. Sea Marconi Technologies Sas, assignee.: Ultrasoundassistedsynthesis of cyclodextrin-based nanosponges, EP 1786841 B1. 2007 June 22.

40. Singh R, Bharti N, Madan J, Hiremath SN.: Characterizationof cyclodextrin inclusion complexes-a review**, J Pharm SciTechnol.**2010, 2(3), 171-183.

41. Challa R, Ahuja A, Ali J, Khar RK.: Cyclodextrins in drugdelivery: an update review,**AAPS PharmSciTech.**2005, 6(2),E329-E357

42. Renuka S and Kamla P .: Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topicalhydrogelformulation**,PharmDevTechnol**.2011,367-376.

43. Jenny A, Merima P, Alberto F, Francesco T.:Role ofβ- cyclodextrin nanosponges in polypropylene photooxidation, **Carbohydrate Polymers**. 2011,86,127– 135.

44. Torne SJ, Ansari KA, Vavia PR, Trotta F, Cavalli R.: Enhanced oral Paclitaxel bioavailability after administration of Paclitaxel loaded nanosponge,**Drug Delivery**. 2010,17(6),419–425.

45. Ansari KA, Torne SJ, Vavia PR, Trotta F, Cavalli R.:Paclitaxel loaded nanosponges: in-vitrocharacterization and cytotoxicity study on MCF-7 cell line culture, **Curr Drug Deliv**.2011,8(2),194- 202.

46. Rosalba M, Roberta C, Roberto F, Chiara D,Piergiorgio P, Leigh E, Li S, Roberto P. : Antitumoractivity of nanosponge-encapsulatedCamptotechin in human prostate tumors.
CancerRes,2011; 71:4431

47. Khalid AA, Pradeep RV, Francesco T, Roberta C.: Cyclodextrin-based nanosponges for delivery ofResveratrol: In Vitro characterisation, stability,cytotoxicity and permeation Study, **AAPSPharmSciTech**. 2011, 12(1), 279-286.

48. Shankar S, Vavia PR, Francesco T, SatyenT.:Formulation of Betacyclodextrin based nanosponges of Itraconazole,**J Incl PhenomMacrocycl Chem**. 2007,57, 89–94.

49. Lala R, Thorat A, Gargote C.: Current trends in β-cyclodextrin based drug delivery systems, **Int JResAyur Pharm**. 2011, 2(5), 1520-1526.

50. Vitaglione P, Sforza S, Galaverna G, Ghidini C, Caporaso N, Vescovi PP, et al.: Bioavailability oftrans-resveratrol from red wine in humans,**Mol Nutr Food Res**. 2005,49(5),495-504.

51. Madaan K, Lather V, Pandita D.: Evaluation of polyamidoamine dendrimers as potential carriersfor quercetin, a versatile flavonoid, **Drug Del**. 2016,23(1),254-62.

52. Madhavi BB, Kusum B, Chatanya CK, Madhu MN, Harsha VS, Banji D.: Dissolution enhancementof efavirenz by solid dispersion and PEGylation techniques, **Int J Pharm Invest.** 2011,1(1),29.

53. Purvis T, Mattucci ME, Crisp MT, Johnston KP, Williams RO.: Rapidly dissolving repaglinidepowders produced by the ultra-rapid freezing process, **AAPS Pharm Sci Tech**. 2007,8(3),E52-E60

54. Gilardi G, Trotta F, Cavalli R, Ferruti P, Ranucci E, Di NG, et al., inventors; Sea Marconi Technologies Sas Di Vander Tumiatti, assignee. Cyclodextrin nanosponges as a carrier for biocatalysts,and in the delivery and release of enzymes, proteins, vaccines and antibodies. European patentEP2294190A1. 2011 Mar 16.

55. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Roggero C, Vallero R, inventors; Sea MarconiTechnologies Di W TumiattiSas, assignee.: Ultrasound-assisted synthesis of cyclodextrin-basednanosponges. United States patent US20080213384A1. 2006 Sep 04.

56. Vyas A, Saraf S, Saraf S.: Cyclodextrin based novel drug delivery systems,**J Incl Phenom Macro**.2008,62(1-2),23-42

57. Tejashri G, Amrita B, Darshana J.:Cyclodextrin based nanosponges for pharmaceutical use: Areview, **Acta Pharmaceut**. 2013,63(3),335-58.

58. Osmani Riyaz Ali M.Thirumaleshwar Shailesh, Bhosale Rohit R, Kulkarni Parthasarathi K. Nanosponges: The spanking accession in drug delivery-An updated comprehensive review, **Der Pharm Sin**. 2014,5(6),7–21.

59. Cavalli, R., Rogero, C.M., Mognetti, B., Berta, G.N., Tumiatti, V. and Trotta, F.:Inventors;Sea Marconi Technologies Sas, assignee, Cyclodextrin-based nanosponges as a vehicle for antitumoraldrugs**. WO**.2009, 3656, 1.

60. Jilsha, G. and Viswanad, V.:Nanosponges: A novel approach of drug delivery system. **Int J Pharm Sci Rev Res**. 2013,*19*(2),119-123.