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Review On
Nanosponges: A Benefication For Novel Drug Delivery

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Abstract: Effective drug delivery at a targeted site had given the possibility to perform the precise function to control the release rates and have a better compliance on the health care system but the chemistry possessing complex form had made conditions complicated. But the invention of nanosponges has given a significant approach toward solving this problem. Nanosponges are tiny sponges having size of about a virus and can be filled with variety of drugs. This sponges can circulate around the body until interact with specific target site and stick on surface and start releasing drug in a controlled manner. Some cyclodextrins based nanosponges proposed nanodelivery system and form porous insoluble nanoparticle having crystalline and amorphous nature. Important characteristic of these sponges is their solubility in aqueous form and give a effect to the drugs with poor solubility. This review is focusing on the preparation methods, applications of nanosponges in the field of drug delivery.
Key Words: Nanosponges, Controlled release, Quasi-emulsion solvent diffusion, Resiliency, Breast cancer.

Introduction :

The system, known as "nanosponge," uses a nanoparticle-sized system to deliver the drug payload. “Nanosponges” perceived important invention in the field representing versatile activities of β-cyclodextrin, anodic Tio_2 forming their layers which will provide a base to deliver both hydrophilic and hydrophobic compounds, Nanosponges had offered an excellency in forming the content having reduced side effects provided with adequacy in improving stability, formulation flexibility[1,2]. Nanosponges provide excellent topical delivery of drugs[2]. Nanosponges embraces nanotechnology which is applied to pharmacy as nanomaterials, diagnosing and focusing right place in the body and controlling release of the drug[3]. Nanosponges is about the size of virus which has been backed by naturally degradable polyster[4,5]. The polyster streams mixed with the solution having molecules called cross-linkers and provide extent of bond in nanometric form improves drugs bonding, providing different spherical shapes having pockets to store the drug[4,5]. Nanosponges giving a sustained growth in energy costs and power consumption to give an alternative source of energy though wind or solar and their storage to improve the safety of electrolytes and focused on creating solid- state batteries using polymer or ceramic[6]. The dimensions of nanosponges in nanometric form improves drugs bioavailability and modifies pharmacokinetic parameters. Average diameter of nanosponges is below 1µm[1]. Nanosponges obtained from natural derivatives such as alginate provide a 3D structure and because of

its selective nature expertise its regenerated properties by following washing with eco-compatible solvents, stripping with inert hot gases, changing ph and ionic strength[7,10]. Due to their soluble nature they mix with water and utilize transport fluid without breaking up convert liquid substances to solids. Nanosponges in the presence of compounds possessing magnetic properties can be magneties[8]. Their crystalline property maintains the loading capacity and it may be either paracrystalline or in crystalline form[8]. In treatment of human prostate cancer cells by nanosponges took the encapsulation of campothecin exerting anti-tumour activity, glucose units cross linked with different agents and obtained as drug carriers using active carbonyl compound and resulting in increased therapeutic index[11]. They form great geometry, polarity, stabilize a compatible environment with cavity[12]. Cyclodextrin nanosponges developed from different organic or inorganic materials for example- Titanium or other metal oxide, Silicon nanosponge paricles, carbon-coated metallic nanosponges. Nanosponges in treatment of water had influenced a great deal of success for aromatic chlorohydro carbons, provided with great mechanical strength which kept removal of dust formation during application[13,14]. This whole system of treatment of have been mediated by controlled release of β-cyclodextrin polymer or nanosponges which had limited the toxicity and emerged as promising tool in drug delivery . Cyclodextrins nanosponges from complex with hydrophilic and lipophillic molecules and consist of six to eight units[14,15] . Nanosponges had widen its popularity and utilization in setting an aim to provide good conditions for the drugs to act on specific site and diagnose the proper activity of the body organs.

Advantages[16,17,18,19] :

1) This technology provide entrapment of active contents and side effects are less.
2) It provides improved stability, elegance and formulation flexibility.
3) It is non-mutagenic.
4) Non-irritating, non-toxic.
5) It provide extended release condition which is continuous action up to 12hr.
6) Drug is protected from degradation.
7) Therapeutic provide onset of action.Formulations are cost effective.
8) It can be used to mask unpleasant flavours and to convert liquid substances to solids2. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
9) Nanosponge particles are soluble in water, so encapsulation can be done within the nanosponge, by the addition of chemical called an adjuvant reagent.
10) Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
11) Easy scale-up for commercial production.
12) The drug profiles can be vary from fast, medium to slow release in case of dosing therapy.
13) Predictable release.
14) Biodegradable.

Disadvantages:

1) Nanosponges include only small molecules.
2) Depend only upon loading capacities

Chemical used for the synthesis of nanosponges[20]:

1) Polymers

-Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β- Cyclodextrin.
-Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β- Cyclodextrins and copolymers like Poly (valerolactone-allylvalerolactone and Ethyl cellulose & PVA.

2) Crosslinkers

-Diphenyl Carbonate, Diarylcarbonates, Carbonyldiimidazole,Epichloridine Glutarldehyde, Carboxylic acid dianhydride, Acetic acid and Dichloromethane.

Synthesis of nanosponges :

It is one of the important criteria for the formation of product obtained activity in β-cyclodextrin, titanium oxide.

1) Solvent method:

The solvent required will be mix with the polymer mainly in a polar aprotic solvent for example-dimethylforamide, dimethylsulfoxide then add this mixture to cross linker in a exceed quantity, the ratio for cross linker/ molar ratio is preferred as 4 to 16. The reaction is proceed with a solvent reflux temperature and time ranging from 1 to 48 hr[21]. The cross linkers which may preffered are dimethyl carbonate and carbonyl di-imidazole. The reaction is completed and solution is allow to cool at room temperature then product is added to excess of bi-distilled water and product is recovered by filtration under vaccum and simultaneously purify by prolonged soxhlet extraction with ethanol. Finally product is dried under vaccum and grinded in a mechanical mill to obtain homogeneous powder[20].

2) Ultrasound assisted synthesis:

Nanosponges are obtained by reacting polymer with cross linkers without adding or without using solvent and sonification is maintained. The size obtained by this technique wil be spherical and uniform. The polymer is mix with a cross linkers in a balanced ratio in a flask. The flask is placed in a molar ratio in an ultrasound bath field with water and temperature maintained at 90ºc. the mixture is sonicated for 5hr. Then the mixture is kept to cool and product is break roughly then the product is washed with water to remove non-reacted polymer and subsequently purified by soxhlet extraction with ethanol. The product is dried under vaccum at 25ºc until its further use is utilized[1,2,21].

3) Loading of drug into nanosponges[1,2,22]:

Nanosponges obtained should be pretreated to maintain mean particle size blow 500nm. Nanosponges are suspended in water and were sonicated to avoid presence of aggregates and particles and got centrifuged to obtain colloidal fraction, then supernatant is separated and dried sample by freezing by drying.

Further proceeding start with preparing aqueous suspension of nanosponges and excess amount of drug is dispensed for maintaining suspension under constant stirring for specific time period for complexation is over the undissolved drug (uncomplexed condition) is separated from complexed drug with the process of centrifugation. This process helps in evolving solid crystals of nanosponges by solvent evaporation or freeze drying. Nanosponges crystal play important part in complexation with drug. Para-crystalline nanosponges revealed different loading capacities when compared to crystalline nanosponges poorly crystalline nanosponges had act drug loading as a mechanical mixture rather then inclusion complex.

Preparation of nanosponges:

Nanosponges prepared prepared mainly on the criteria of delivery system, polymer and nature of drug and solvents.

1) Nanosponges prepared from hyper-cross linked β-cyclodextrins[23,24]:

Prepared from β-cyclodextrins act as nanosporous materials performed their work as carriers for drug delivery. Due to this 3-d networks are formed which may be a roughly spherical structure about the size of a protein having channels and pores in the internal part. Reacting cyclodextrin with a cross linker such as di-isocianates, diaryl carbonates, carbonyl di-imidazoles etc. Sponges size is controlled according to porosity,surface charge density for the attachment to different molecules. Nanosponges are synthesized in neutral or acidic form depend

on cross linker used. They consist of solid particales and converted in crystalline form. Capacity of nanosponges to encapsulate drug having different structures and solubility. They are used to increased aqueous solubility of poorly-water soluble drugs.

2) Emulsion solvent diffusion method[25]:

In this metod 2 phases are used in different proportion of organic and aqueous(ethyl cellulose and polyvinyl alcohol). The dispersed phase having ethyl cellulose and drug get dissolved in dichloromethane(20 ml) and a definite amount of polyvinyl alcohol added to 150 ml of aqueous continuous phase. Then, the mixture is stirred properly at 1000 rpm for 2hr. The required gnanosponges were collected by the process of filtration and kept for drying in oven at 40ºc for 24hr. Nanosponges which are dried were strored in dessicators and ensurity of removal of residual solvents is done.

3) Quasi-emulsion solvent diffusion[26,27]:

The nanosponges prepared using the polymer in different amounts. The inner phase is prepared using eudragit rs 100 and added to a suitable solvent. Drug used provided with a solution and dissolved under ultrasonication at 35ºc . This inner phase added into external phase containing pva act as emulsifying agent. The mixture is stirred at 1000-2000 rpm for 3hr at room temperature and dried in an air-heated oven at 40ºc for 12hr.

Evaluation of nanosponges:

1) Particle size determination[25,28]:

The size of particles are maintained during polymerization for the formation of free-following powders having fine aesthetic attributes. Particle size analysis of loaded and unloaded nanosponges performed by laser light diffractometry or malvern zeta sizer. Cumulative graph is maintained or ploted as particle size against time to study effect of particle size on drug release. Particles size greater then 30m impart gritty feeling and particles of sizes between 10 and 25 m preferred and used in final opical formulation.

2) Morphology and surface topography[29]:

For preparation of nanosponges in terms of morphology they are coated with gold-palladium under an atmosphere of orgon at room temperature and surface structure studied by scanning electron microscopy.

3) Determination of loading efficiency and production yield[30]:

The loading efficiency (%) of nanosponges calculated according to the equation.

$$\text{LOADING EFFICIENCY} = \frac{\text{ACTUAL DRUG CONTENT IN NANOSPONGES}}{\text{THEORITICA DRUG CONTENT}} \times 100$$

The yield of nanospartices can be determined by calculating initial weight of nanosponges as,

$$\textit{PRODUCTION YIELD} = \frac{\textit{PRACTICAL MASS OF NANOSPONGES}}{\textit{THEORITICAL MASS}} \times 100$$

4) Determination of true Density[31]:

The repeated mean determination can be use to calculate true density of nanoparticles & benzoyl peroxide using ultra-pycnometer under helium gas.

5) Resiliency[32]:

Viscoelastic properties of sponges is modified to produce beadlets which are softer and firmer when needed for final formulation. When cross linking got increased and tends to slow down rate of release . Resiliency are studied according to requirement by releasing function of cross-linking with time.

6) Dissolution tests[32]:

Dissolution profile of nanosponges are studied using dissolution apparatus usp having amodified basket consist of 5ml stainless steel mesh with a speed of rotation around 150 rpm. Proper dissolution medium is selected and solubility of active contents are considered to ensure sink conditions. Proper analytical method are used for the sample form dissolution medium.

Factor influence nanaosponges[33,34]:

1) Type of polymer:

Type of polymer is used which can influence formation as well as performance of nanosponges. For complexation, cavity size of nanaosponges should be suitable.

2) Temperature:

Temperature changes can affect drug/ nanasponges complexation . Increase in temperature decreases the magnitude of apparent stability constant of drug due to result of possible reduction of drug interaction forces.

3) Method of preparation:

The method of loading drug into nanasponges can affect drug complexation. Effectiveness of method depends on nature of drug and polymer.

4) Degree of substitution:

Nanosponges are greatly affected by type, number, position of substituent on parent molecule & due to this affects it's complexation.

Table 1. Example of Nanosponges

Drug	Nanosponges vehicle	Indication	Study	Reference
Camptothecin	β – Cyclodextrin	Cancer	Haemolytic activity, Cytotoxicity	22,47
Itraconazole	β – Cyclodextrin & Co-polyvidonum	Antifungal	Saturation solubility study	51
Econazole nitrate	β – Cyclodextrin , polyvinyl alcohol	Antifungal	Irritation study	48,49
Tamoxifen	β – Cyclodextrin	Breast cancer	Cytotoxicity	9
Paclitaxel	β – Cyclodextrin	Cancer	Bio- availability, Cytotoxicity	45
Resveratrol	β – Cyclodextrin	Breast tumors, Inflammation,	Cytotoxicity, Cytotoxicity	50
Dexamethasone	Ethyl cellulose	Antifungal	Drug release experiment	20
Temozolamide	Poly(Valerolactone-allylvalerolactone) & Poly(Valerolactolactone-Oxepanedione)	Brain tumors	Drug release study	52

Characterization of nanosponges:

1) Thermoanalytical methods[35]:

It show the changes occur in drug substance before undergoing thermal degradation of nanosponges. The change of drug may be melting, evaporation, oxidation, decomposition or polymeric transition. Changes in drug substance indicates formation of complex. DTA and DSC observed for broadening, shifting and appearance of new peaks. If changes in weight loss occurs can provide evidence for formation of inclusion complexes.

2) Microscopy studies[35,36]:

Scanning electron microscopy and Transmission electron microscopy used to study microscopic aspects of drug nanosponges and product. Difference in crystallization state of raw materials and product seen under electron microscope.(article-10-ref-10)

3) Solubility studies[35,36]:

It is the most widely used approach to study inclusion complex and mainly described by Higuchi and Connor's equation for phase solubility and helps in examine the effect on solubility of drug by nanosponge.

4) IR spectroscopy[35,36]:

It is used to estimate interaction between nanosponges and drug molecule in solid state.It often changes upon complex formation and if small fraction of molecule is encapsulated in complex less then 25 percent band and assigned to include part of other molecule which are marked by bands of spectrum of nanosponges. Regarding application of IR it is limited to some drugs containing properties/ bands such as carbonyl or sulfonyl groups.IR studies involve information of hydrogen in various functional groups. This results in shifting of absorbance bands to lower frequency and increase the intensity and bands got widen due to stretching vibration of the group involved in hydrogen bond formation. (article-10. Ref-24)

5) X-ray diffractometry[35,36]:

Powder x-ray diffractometry used to detect inclusion complex in solid state. If we consider liquid then it has no diffraction pattern of their own and totally differs from incomplexed nanosponge. If drug is a solid substance comparison should be made between diffractogram of assumed complex and mechanical mixture of dry and it alters diffraction patterns.A diffraction pattern of a physical mixture results from combination of two components. But complexes having diffraction pattern mainly differs from the constituent they contain and give rise to " new" solid phase having different diffractograms. They give rise to different peaks for a mixture and useful in determining chemical decomposition and complex formation.

-Single crystal X-ray structure analysis:

It may also be used to determine the inclusion structure and way it interact. Interaction between host and external molecules can be determined and a precise relationship can be established.

6) Loading efficiency[35,36,37]:

It describes the efficiency or determined by quantitative estimation of drug loaded into nanosponges by UV spectrophotometer & HPLC methods.

7) Zeta potential[37]:

It measure surface charge and by adding a electrode it can be measured in particle size equipment.

Drug used in Nanosponges drug delivery:

1) Econazole nitrate[25]:

It is an antifungal drug which is used to solve the symptoms of candidasis, dermatophysis and skin infections

which are available in cream, ointment, lotion. If adsorption is consider econazole nitrate is not applied to skin and require high concentration of active agents. They are fabricated by emulsion solvent diffusion method.

2) Bovine serum albumin[38]:

They come under the section of protein which are unstable in solution. Proteins can undergo denaturation upon action of lyophilization. Proteins formulation and development cause a drawback in maintaining a native structure during its proceess form and storage. They are encapsulated in swellable cyclodextrin based poly amido-amine.

3) Camptothecin[39]:

It is a plant alkaloid and also act as a antitumour agent due to its poor aqueous solubility, its therapeutic value get decreased and also due to lactone ring instability. They come under cyclodextrin based nanosponges to increase the solubility of poorly soluble forms and control the release.

4) "Cyclodextrin nanosponges" for removal of organic pollutant from water[40]:

β-cyclodextrin nanosponges are insoluble in water and they have got the property of encapsulating organic pollutant from water. Hybrid organic filter modules can be prepare by impregnating the porous filters with nanosponges. These filters are tested for effective purification of water and many water pollutants can be used. Using ths method polycylic aromatic hydrocarbon can be removed efficiently (> 95 percent). Pollutant group of tri halogen methanes and pesticides can also be removed (>80 percent).

Applications of Nanosponges:

1) Nanosponges as chemical sensors[41]:

Nanosponges which are the type of " metal oxides" act as a chemical sensors which is used in highly sensitive detection of hydrogen using nanosponge titania. Nanosponge structure intially have no point of contact so there is less hinderance to electron transport and it results in higher 3D interconnect nanosponges titania which is sensitive to H2 gas.

2) Nanpsponge for oral delivery[42]:

In oral application it forms the nanosponge system consist of pores which increase the rate of solubilization of poorly water soluble drugs which get entrapped the drug in pores. The surface area is increased due to nanosize form and increase rate of solubilization.

3) Solubility enhancement[42]:

β-cyclodextrin based nanosponges of itraconazole have enhance solubility of poorly soluble drug. The solubility increased by 50 folds compared to ternary dispersion system. Eg- copolyvidonum.

4) Nanosponges as a carrier for biocatalysts and release of enzymes, proteins, vaccines and antibodies[43,44]:

It includes the process applied in industry which correlate with operational condition. Reactions which are not specific give rise to low yields and require high temperatures and pressures which consume large amount of energy and cooling water in down-stream process. This are the drawbacks can be removed by using enzymes as biocatalysts as this operate under high reaction speed, mild condition.

5) Antiviral application[45,46]:)

Nanosponges used in nasal, pulmonary route of administration. It provide specificity to deliver antiviral drug on RNA to lungs or nasal route through nanocarriers for targeting virus which may cause infection to RTI such as influenza virus, rhinovirus. Drugs used as nanocarrriers are- Zidovudine, Saquinavir.

6) Cancer[45,46,47]:

Targeting drug to specific site avoiding the obstacle created by immune system. Different cancer cells had been treated by nanosponges like breast cancer or fast acting glioma type with help of single dose of injections.

Oxygen Delivery System [48,49,50] :

Characterized by using α, β and ϒ cyclodextrins and this are suspended in water and get saturated with water. A silicone form of membrane can also be used for oxygen permeation with the help of nanosponge/ hydrogel system. They can also applied it to hypoxic tissues caused in various type of diseases.

Conclusion :

From the above study it is concluded that nanosponges include lipophillic or hydrophilic drugs and release drug at target site in controlled manner.Polymer and cross-linker ratio can be balanced and release rate can be modified. Nanosponges permit the insoluble drugs and prevent the physiochemical degradation of active contents and controlled release. Their small size and spherical shaped had provided nanosponges to develop as different dosage forms like parenteral, aerosol, topical, tablets and capsules.

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