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NANOSPONGE: A NOVEL APPROACH IN DRUG DELIVERY SYSTEM

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ABSTRACT

Effective targeted drug delivery systems have been a dream for long time. Site specific or targeted drug delivery is used to treat many diseases like cardiovascular disease, Osteo-diseases, hormonal deficiency diseases like Parkinson's disease, auto-immune diseases like arthritis, diabetes. The invention of nanosponges has become a significant step towards overcoming these problems. The sponge acts as a three-dimensional network. 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. Owing to their small size and porous nature they can bind poorly-soluble drugs within their matrix and improve their bioavailability. They can be crafted for targeting drugs to specific site, prevent drug and protein degradation and prolong the drug release in a controlled manner. This review attempts to elaborate the features of nanosponges, preparation, Characterization and applications.

INTRODUCTION

The area of drug delivery technology is evolving rapidly and becoming highly competitive day by day. The developments in the delivery systems are being utilized to optimize the efficacy and the cost effectiveness of the therapy. The challenges faced by drug development industry are:

• Sustained release technology for reducing irritation of a wide range of APIs thereby increasing patient/client compliance and results.

• Enhanced formulation stability ensuring long term product efficacy and extended shelf life.

The nanosponge delivery system fulfills these requirements.[1]

Targeting the drug delivery has long been a problem for medical researchers how to get them to the right place in the body and how to control the release of the drug to prevent overdose[2]. The development of new and complex molecules called Nanosponges has the potential to solve these problems.

Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities in which a large variety of substances can be encapsulated[2]. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecule[2]. Nanosponges are tiny mesh like structures. The nanosponge is about the size of a virus with a backbone of naturally degradable polyester. The long strength polyester strands are mixed in solution with small molecules called cross linkers that have an affinity for certain portions of the polyesters. They cross link segments of the polyester to form a spherical shape that has many pockets / cavities where drug can be stored. The nanoscale materials are small enough to be effective in attaching to or passing through cell membranes. The nanosponge can be engineered to be of specific size and to release drugs over time- not just in the "burst" mode common with other delivery methods[3].

The engineering capacity of nanosponge is due to the relatively simple chemistry of its polyesters and linking material (peptides). Compared to many other nanoscale drug delivery systems, nanosponge should be able to scale (e.g. ramp up to commercial production levels) without requiring unusual equipment or procedures. The polyster is predictably biodegradable, which means that when it breaks up in the body, the drug can be released on a known schedule[7]

Nanosponge were originally developed for topical delivery of drugs. Nanosponges are tiny sponges with a size of about a virus with an average diameter below 1μm [4]. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more

effective for a particular given dosage [5]. Nanosponges are capable of providing solutions for several formulation related problems. Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability. They can be crafted for targeting drugs to specific sites, prevent drug and protein degradation and prolong drug release in a controlled manner [6].

Nanosponges are obtained by suitable cross linking process and also by different organic and inorganic materials. Nano sponges can encapsulate various types of molecules by forming inclusion and non inclusion complexes.

Cross linking process: Highly cross linked cyclodextrins and highly cross linked polystyrene (natural derivative of starch)are used for the fabrication of nanosponges insoluble in water and commonest organic solvents,nontoxic,porous,stable above 300°c which may be used to encapsulate, carry and /or selectively release a great variety of substances

Organic and inorganic materials Some examples of Nanosponges formed by usingOrganic and inorganic materials are Titanium or othermetal oxide based nanosponges, silicon nanospongeparticles. Carbon coated metallic Nanosponges [5].

INTERESTING FETURES OF NANOSPONGES

An important character of these sponges is their aqueous solubility; this allows The use of these systems effectively for drugs with poor solubility[5]. The Nanosponges are capable of carrying both lipophilic and hydrophilic drugs. . Nanosponges could be used to increase aqueous solubility of poorly watersoluble drugs, to remove pollutants from contaminated water, or as nano carriers for biomedical applications. Nanosponges have been used for removal of organic impurities in water [8,9]. This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. Nanosponge and Nanosponge systems are non irritating and non-mutagenic, non-allergic and nontoxic. Extended release-continuous release up to 12h allows incorporation of immiscible liquid improves material processing-liquid can be converted to powders. They can be formed in a sub microns spherical particle. They can be obtained in a wide range of dimensions, from 1micron to 10 microns. The cavities of the framework have a tunable polarity. Different functional groups can be linked to the structure due to sub micron dimensions of the particle. Nanosponge can disperse at molecular level, highly insoluble principles, stabilizing and protecting their structures, from chemicals, light, oxygen, etc. efficacy and shelf life of drugs can be prolonged if compared to the non-complexed form. By using Nanosponge as drug delivery system, higher therapeutic activities are observed being the concentration of the active molecule the same [10,20].

ADAVANTAGES

1. Targeted site specific drug delivery.
2. Can be used to mask unpleasant flavours and to convert liquid substances to solids.
3. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
4. Nanosponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the nanosponge, after mixing with a chemical called an adjuvant reagent.
5. Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
6. Production through fairly simple chemistry called "click chemistry" (methods for making the nanosponge particles and for attaching the linkers).
7. Easy scale-up for commercial production.
8. The drug profiles can be tailored from fast, medium to slow release, preventing over- or under-dosing of the therapy
9. Predictable release.
10. Biodegradable.[11]

CLASSIFICATION OF NANOSPONGE

Nanosponges are encapsulating type of nanoparticles which encapsules the drug molecules within its core. By method of associating with drugs, the nanoparticles can be classified into the following:-

1. Encapsulating nanoparticles

This type is represented by nanosponges and nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles containing many holes that carry the drug molecules in their aqueous core.

E.g. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles containing many holes that carry the drug molecules.Nanocapsules such as poly (iso-butyl-cyanoacrylate) (IBCA) are also encapsulating nanoparticles.

2. Complexing nanoparticles

This type of nanoparticles attracts the molecules by electrostatic charges.

3. Conjugating nanoparticles

This type of nanoparticles links to drugs through covalent bonds. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non-toxic and stable at high temperature up to 300oC. They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities of Nanomeric size and tunable polarity.[12,21].

PREPARATION OF NANOSPONGES

Nanosponges are prepared by using hyper cross-linked-cyclodextrins and Emulsion Solvent Diffusion method.

a) Hyper Cross Linked _- Cyclodextrins.

Nanosponge has been recently developed hyper cross linked cyclodextrin polymers nano structured to form 3-dimensional networks; a roughly spherical structure, about the size of a protein, with channels and pores inside. They are obtained by reacting cyclodextrin with a cross-linker such as di isocianates, diaryl carbonates, dimethly carbonate, diphenyl carbonate, and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2- bis(acrylamido)acetic acid. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. Nanosponge with low cross linking gives a fast drug release.

b) Emulsion Solvent Diffusion Method

This method uses different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000rpm for 2 hrs. Then Nanosponge formed were collected by filtration and dried in the oven at 400 c for 24 hrs. The dried Nanosponge was stored in vacuum desiccators to ensure the removal of residual solvent.[8,9,13,14].

FACTORS INFLUENCE NANOSPONGE FORMATION

Type of polymer

Type of polymer used can influence the formationas well as the performance of Nanosponges. For complexation, the cavity size of nanosponge should be suitable to accommodate a drug molecule of particular size.

Type of drugs

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below [25].

- Molecular weight between 100 and 400
- Drug molecule consists of less than five condensed rings
- Solubility in water is less than 10mg/mL
- Melting point of the substance is below 250°C

Temperature

Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge

complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature.

Method of preparation

The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases freeze drying was found to be most effective for drug complexation.

Degree of substitution

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule [26].

MECANISUM OF DRUG RELEASE FROM NANOSPONGE

The active ingredient is added to vehicles in the entrapped from since the nanospong particles have an open structure (they do not have continues membrane surrounding them) the active substance is free to move in or out from the particles into the vehicle until the equilibrium is reached when the vehicle become saturated. Once product is applied to skin, the active substance that already in vehicle will become unsaturated, therefore distributing the equilibrium. This will start flow of active from nanosponges particles into vehicle from it, to skin until vehicle is either dried or absorbed. Even after that nanospones particles retained on the surface of the stratum corneum will continue to gradually release active to skin providing prolong release over time[22].

FACTOR AFFECTING DRUG RELEASE FROM NANOSPONGE

- Physical and chemical properties of entrapped actives.
- Physical properties of Microsponge system like pore diameter, pore volume, resiliency etc. Properties of vehicle in which the microsponges are finally dispersed.
- Particle size, pore characteristics, compositions can be considered as programmable parameters and microsponges can be designed to release given amount of actives in response to one or more external triggers like; pressure, temperature and solubility of actives.
- Pressure Rubbing/ pressure can release active ingredient from microsponges onto skin.
- Temperature change some entrapped actives can be too viscous at room temperature to flow spontaneously from microsponges onto the skin. Increased in skin temperature can result in an increased flow rate and hence release.
- Solubility Microsponges loaded with water-soluble ingredients like antiperspirants and antiseptics will release the ingredient in the presence of water. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system [24].

EVALUATION

Nanosponge were evaluated by particle size determination, morphology and surface topography, loading efficiency and production yield, true density, polymer or monomer composition, resiliency, compatibility studies, dissolution tests.

Particle Size Determination

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded nano and can be performed by laser light diffractometryor Malvern zeta seizer. Cumulative percentage drug release from nano sponges of different particle size will be plotted against time to study the effect of particle size on drug release. Particles larger than 30 microns can impart gritty feeling and hence particles of sizes between 10 and 25 microns are preferred to use in final topical formulation [13,14].

Morphology and Surface Topography of Nanosponges

For morphology and surface topography, the prepared Nanosponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the nano and Nanosponge can be studied by scanning electron microscopy [15].

Determination of Loading Efficiency and Production yield

The loading efficiency (%) of the Nanosponges can be calculated according to the following equation.

Loading Efficiency=Actual Drug Content in Nanosponge/ Theoretical Drug Content ×100

The production yield of the Nanosponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the Nanosponge are obtained [16].

Determination of True Density

True density of nano particles can be determined using an ultra-pycnometer under helium gas [17].

Polymer/ monomer composition

Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile. Selection of monomer is dictated both by ultimately to be entrapped and by the vehicle into which it will be dispersed.

Resiliency (Viscoelastic properties)

Resiliency of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release.

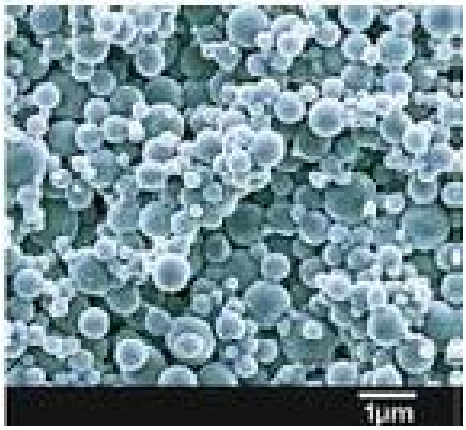
Hence resiliency of sponges will be studied and optimized as per the requirement by considering the release as a function of cross-linking with time [18].

Compatibility studies

Thin layer chromatography (TLC) and Fourier transform infra-red spectroscopy (FT-IR) are used to study the Compatibility of drug with reaction adjuncts .Effect of polymerization on crystalinity of the drug can be studied by powder x-ray diffraction (XRD) and Differential Scanning Colorimeter (DSC). For DSC, approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 c/min over a temperature range 25–430 c in atmosphere of nitrogen [19].

Dissolution profile

Dissolution profile of Nanosponge can be studied by use of the dissolution apparatus usp xxiii with a modified basket consisted of 5m stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by a suitable analytical method studied by use of the dissolution apparatus usp xxiii with a modified basket consisted of 5m stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by a suitable analytical method [19].



Porous nanospong[23]

APPLICATIONS

As a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies

Many industrial processes involving chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields, and the frequent need to operate at high

temperatures and pressures requires consumption of large amounts of energy, and very large amounts of cooling water in the down-stream process. All these drawbacks can be eliminated or significantly reduced by using enzymes as biocatalysts. These enzymes operate under mild reaction conditions, have high reaction speed, and are highly specific. The administration of these molecules presents various problems.

A number of systems for carrying enzymes and proteins have been developed, such as nano and microparticles, liposomes and hydrogels. Carriage in a particular system can protect proteins from breakdown, modify their pharmacokinetics and improve their stability in-vivo. Now, it has been found that Cyclodextrin based nanosponges are particularly suitable as carrier to adsorb proteins, enzymes, antibodies and macromolecules. In particular when enzymes are used, it is possible to maintain their activity, efficiency, prolong their operation and extends the pH and temperature range of activity and allows the conduct of continuous flow processes. Moreover, proteins and other macromolecules can be carried by adsorbing or encapsulating them in cyclodextrin nanosponges[27]

Harvesting of rare Cancer Marker from Blood:

It has been seen that a new type of nanoparticle, whose interiors is decorated with different types of _bait' molecules, is used to selectively trap specific families of proteins from blood and protect them from degradation by enzymes in blood [28].

Topical agents

Nanosponge delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on skin. Conventional dermatological and personal-care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short term over medication followed by long term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficiency. a wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder [29]. Econazole nitrate, an antifungal used topically to relive the symptoms of superficial candidasis, dermatophytosis, versicolor and skin infections available in cream, ointment, lotion and solution. Adsorption is not significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrates Nanosponge were fabricated by emulsion solvent diffusion method, and these Nanosponges were loaded in hydrogel as a local depot for sustained drug release[13].

Encapsulation of gases

Cyclodextrin based carbonate Nanosponge was used to form inclusion complexes with three different gases, i.e. 1-methylcyclopropene, oxygen and carbondioxide. The complexetion of oxygen or carbondioxide could be useful for many biomedical applications. In particular, the oxygen-filled Nanosponge could supply oxygen to the hypoxic tissues which are present in various diseases [30]. Because of its super porous nature, the Nanosponge also has been explored as an effective gas carrier. Nanosponge formulation shows the ability to store and release oxygen in a controlled manner. In future, they could be one useful tool for the delivery of some vital gases [31].

Antiviral application:

Nanosponges can be useful in the ocular, nasal, pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to the nasal epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as respiratory sinctial virus, influenza virus & rhinovirus. They can also be used for HIV, HBV, and HSV. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α, acyclovir (Eudragit based) [32].

Solubility enhancement:

Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs as well as providing controlled release profile. However the molecular dimensions and conformation are critical parameters influencing inclusion complexation within nanosponges and thus may not be universally applicable to all molecules. Nanosponges of Cefpodoxime proxetil (CP) have been prepared to improve dissolution rate of CP [33].

More effectiveness than direct injection:

Recent research suggests that nanosponge could be up to five times more effective at reducing tumor growth than direct injection. The drug delivery system is likened to be filling virus-sized sponges with an anti-cancer drug, attaching chemical linkers that bond to a receptor on thesurface of tumor cells, then injecting the sponges into the body. When the sponges come into contact with a tumor cell, they either attach to the surface or are sucked into the cell, where they off-load their deadly contents in a predictable and controlled manner [34]

Floriculture:

Nanosponges have been recently developed and proposed for delivering preservative and anti - ethylene compounds in order to improve cut flower vase life [35].

FUTURE PROSPECTS

Nanosponge are become a promising carriers for specific delivery of drug to lung,liver and spleen.nanoporous titanium oxides have extremely wide applications ranging from chemical sensing to solar energy. A new and simple approach for preparing Pd/Ag and Pd/Ag/Au nanosponges, which comprise network nanowires has been reported in study. This in situ strategy demonstrate for the first time how to prepare alloy nanosponge with network nanowires via self regulated reduction sodium dodecyl sulphate(SDS) and adding the second and third metal salt in the synthesis period, without additional reduction agent[36]. Sponge like alginate nanoparticles as a new potential system for the delivery of antiscence oligoneucleotides and study of their ability to protect ON from degradation in the presence of serum is also a focus area of research. Increasingly used in topical drug delivery system leading to the release of active substance on the epidermis, coupled to their maintenance at the site of action and improved delivery system maximising the time permanence of active compounds on the skin. Nanosponge delivery system are used to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter(OTC) and personal care products[37].

CONCLUSION

Nanosponge offers entrapment of ingredients, and thus reduced side effects improved stability, increases elegance and enhanced formulation flexibility. Nanosponge can be effectively incorporated into a topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled-release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals. The next tests will be a series of injections against whole tumors. In parallel to these tests, the approach must also be evaluated for toxicity. Like all nonmedical materials, Nanosponge will need lengthy phased trials, which means thatcommercial availability is still years away [5].

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