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An Interesting Nanosponges as a Nanocarrier for Novel drug delivery: A Review

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Abstract: ***Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. Targeting drug delivery has long been a problem for medical researchers 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. The development of new and complex molecule called 'nanosponges' has the potential to solve this problem Nanosponges have emerged as the most challenging drug delivery system. Nanosponges play a vital role in targeting drug delivery in a controlled released rate. A nanosponge is a novel and emerging technology which offers targeted and controlled drug delivery for topical as well as oral use. A large variety of substances or drugs can be encapsulated in to the wide cavities of nanosponges. Another important feature of these nanosponges is their water soluble. The nanosponges carry both lipophilic and hydrophilic substances and mostly improve the solubility of poorly water soluble drugs. Nanosponges play a vital role in targeting drug delivery in a controlled manner. A wide variety of drugs can be loaded into nanosponge for targeting drug delivery. Both lipophilic as well as hydrophilic drugs can be loaded into nanosponges. Nanosponge drug delivery system has emerged as one of the most promising fields in life science. In this review advantages and disadvantages, applications, preparative methods, loading of drug into the nanosponges, evaluation techniques, different formulations of drugs and recent studies on nanosponges have been discussed.***

Keywords: Nanosponges, Targeted Drug Delivery, Solubility Enhancement, Cyclodextrins, Cross-linkers

1. Introduction

Nanosponges are tiny mesh-like structures encapsulated with a large variety of substances [1,2]. They are spherical colloids nature with high solubilisation capacity for poorly soluble drugs by their inclusion and non- inclusion behaviour [3]. Schematic diagram of nanosponges with encapsulated drug within its core is shown in Figure 1. Nanosponges can solubilise lipophilic drugs and provide prolonged release and improve bioavailability of drugs [4]. Nanasponges have the ability to load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility [5]. Nanosponges resemble a three-dimensional network or scaffold. The backbone is a long length of polyester which is mixed with cross linkers that act like tiny grappling hooks to fasten different parts of the polymer together [6]. It has been reported that, by the reaction of cyclodextrins (cyclic oligosaccharides) with suitable cross-linking reagents, a novel nano structured material with hyper-cross-linked cyclodextrins can be obtained, known as nanosponges [7-9].Nanosponges can be synthesized as neutral or acid which have the swelling property according to the agent used as crosslinker [10]. The net effect is the formation of spherically shaped particles filled with cavities where drug molecules are stored [11]. The cross-linking-to-cyclodextrin ratio can be varied during preparation to improve the drug loading for obtaining a tailored release profile [12-14]. Their highly porous nanomeric nature enables drug molecules to orient themselves in nanosponges inclusion and to interact in a non- inclusion fashion, which offers higher drug loading capacity compared to the parent cyclodextrin molecules [12].

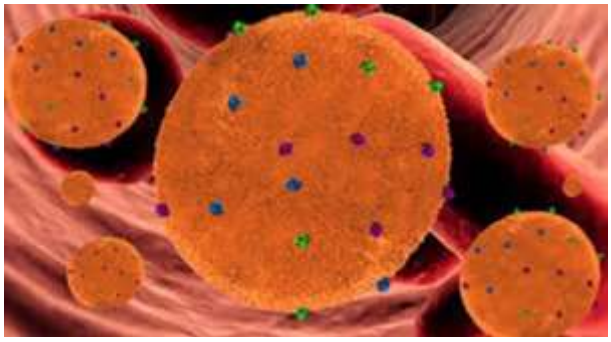

Figure 1: Schematic diagram of nanosponges with encapsulated drug within its core

Nanosponges have an advantage in comparison with the common nanoparticles. Indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sciences [15,16]. The nanosponges can be engineered due to the relatively simple chemistry of its polyesters and crosslinking peptides, compared to many other nanoscale drug delivery systems [17,20]. Nanosponges are water soluble but does not breakup chemically rather they mix with water and use it as a transport fluid. They can be used as masking agents for unpleasant flavours and in conversion of liquid substances to solids. The chemical linkers enable the nanosponges for

preferential binding to the target site [18]. Being solid in nature they have been found to be safe for oral and invasive routes, and thus they could serve as a potential carrier for drug delivery [14,15,17]. The tiny shape of nanosponges enables the pulmonary and venous delivery of drugs [19]. For oral administration, the complexes are added to the dispersion system in matrix containg excipients, diluents, lubricants and anti-caking agents suitable for the preparation of capsules or tablets. For parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical administration they can be effectively incorporated into topical hydrogel [21,22]. Nanosponges are encapsulating type of nanoparticles which encapsulate the drug molecules within its core [23].

2. Chemicals used for the Synthesis of Nanosponges

2.1. Polymers used for the Synthesis of Nanosponges

Some of the polymers that are used for the synthesis of nanosponges are cyclodextrins (such as Methyl β-cyclodextrin (Mβ-CD), 2-hydroxy propyl β-CDs (2HPβ-CD), alkyloxy carbonyl cyclodextrins), copolymers (like poly valero lactone-allylvalero lactone and poly valero lactone-allyl valero lactone oxepanedione), hypercross linked polystyrenes, ethyl cellulose and poly vinyl alcohol.

2.2. Crosslinked Polymers used for the Synthesis of Nanosponges

The crossslinkers used for synthesis of nanosponges are diarylcarbonates, diphenyl carbonate, diisocyanates, pyromellitican hydride, carbonyldiimidazoles, epichloridrine, glutarldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamido) acetic acid and dichloromethane [3].

3. Methods for the Preparation of Nanosponges

3.1. Solvent method

In this method the polymer was mixed with a suitable polar aprotic solvent such as dimethyl formamide, dimethyl sulfoxide. This mixture was added to excess quantity of the crosslinker in the molar ratio of 4 to 16. The reaction was carried out at temperature ranging from 10° C to the reflux temperature of the solvent, for time ranging from 1 to 48 h. The most preferred cross linkers are carbonyl compounds (dimethyl carbonate and carbonyl diimidazole) [20]. After completion, the solution was allowed to cool at room temperature, then the product was added to large excess of bidistilled water and the product is recovered by filtration under vacuum and subsequently the purification is done by prolonged Soxhlet extraction using ethanol. The drying process is carried under vacuum and further grinded in a mechanical mill to obtain homogeneous powder [24].

3.2. Ultrasound-assisted synthesis

In this method nanosponges were obtained by reaction of polymers with crosslinkers in the absence of solvent under the process of sonication. The nanosponges obtained by this method are spherical and uniform in their size [19]. The polymer and the crosslinker are mixed in a particular molar ratio in a flask. The flask was placed in an ultrasound bath filled with water and heated up to 90 °C. The mixture was kept in sonicator for 5 h. Then it was allowed to cool and was broken roughly. The product was washed with water to remove the non reacted polymer and subsequently purified by prolonged Soxhlet extraction with ethanol. The obtained product was dried under vacuum and stored at 25° C until further use [19,24].

3.3. Emulsion solvent diffusion method

Nanosponges can be prepared by using ethyl cellulose which is dissolved in dichloromethane. This mixture is added to the aqueous solution of polyvinyl alcohol stirred at 1000rpm for 2hrs with a magnetic stirrer. Then the product is filtered and dried in an oven at 40oC for 24 hours [24].

3.4. From hyper cross- linked beta cyclodextrin

In this the beta cyclodextrin is used as a carrier and this carrier is reacted with the cross-linker in neutral or acid form for the synthesis of nanosponges..The average diameter of a Nanosponge is below 1 μm but fractions below 500 nm can be selected [23,24].

3.5. Loading of drug into nanosponges

Nanosponges for drug delivery the nanosponges are pre-treated to obtain a mean particle size below 500 nm. The nanosponges were suspended in aqueous phase and sonicated to avoid the aggregation of particles and the suspension is centrifuged to obtain the colloidal fraction. The supernatant was separated from the suspension and then dried by freeze dryer [23]. The nanosponges were prepared by dispersing into the aqueous suspension and the excess amount of drug was added and maintained the suspension under constant stirring for specific time till it forms complex. After complexation, the uncomplexed (undissolved) drug was separated from complexed drug by centrifugation. Then the solid crystals of nanosponges was obtained by solvent evaporation or by freeze drying [19, 23]. Crystal structure of nanosponge plays a very important role in complexation with drug. Some studies revealed that paracrystalline nanosponges have greater loading capacities than crystalline nanosponges. In crystalline forms the drug loading occurs as an inclusion complex while in case of poorly crystalline nanosponges the drug loading occurs as a mechanical mixture [23].

4. Characterization of nanosponges

4.1. Solubility studies

Higuchi and Connors have described an approach to study inclusion complexation as the phase solubility method which examines the solubility of drug in nanosponge. Phase solubility diagrams indicate the degree of complexation [19,25, 26]. In this method Erlenmeyer flask was used.The drug containing an aqueous solution of various percentages of nanosponges is added to the flask. The Erlenmeyer flask was stirred on a mechanical shaker at room temperaturetill it reaches a steady state, the suspension was filtered by centrifugation using a 3000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 U.S.A).The solution was analyzed and the drug concentration is determined by high performance liquid chromatography [22].

4.2. Microscopy studies

The morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex) can

be studied by Scanning electron microscopy and transmission electron microscopy. The difference in crystallization state of the raw materials and the product observed under electron microscope indicates the complex formation [24,26].

4.3. Thermo analytical methods

Thermo analytical methods determine whether the drug substance undergoes some changes before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by differential thermal analysis and differential scanning calorimetry can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes [25].

4.4. *X-ray diffractiometry and single crystal X-ray structure analysis*

Inclusion complexation in the solid state can be detected by X-ray diffractometry. The liquid drug molecules have no diffraction pattern of their own. The diffraction pattern of the uncomplexed nanosponge differs from the newly formed substance which indaicates complex formation .In case of solid drug substances the diffractogram of the assumed complex and the mechanical mixture of the drug and polymer is compared [26]. A diffraction pattern of a physical mixture is the sum of those of each component, while the diffraction pattern of complexes differs from its constituents and leads to a "new" solid phase with different diffractograms. The chemical decomposition and complex formation is determined from the diffraction peaks [25]. When the complex is formed between the drug and nanosponge there is a change in its diffraction patterns and crystalkline nature of the drug. The complex formation leads to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks [25].

4.5. Single crystal X-ray structure analysis

The detailed inclusion structure and mode of interaction can be determined from this analysis. The interaction between the host and guest molecules and the precise geometrical relationship can be studied [25].

4.6. Infra-red spectroscopy

The interaction between nanosponges and the drug molecules in the solid state can be detected by Infra-Red spectroscopy. Upon complex formation the nanosponges bands changes. If the fraction of the guest molecules encapsulated in the complex is less than 25% bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges [26]. Infra-red spectroscopy is applicable to the drugs having some characteristic bands such as carbonyl or sulfonyl groups. This spectral study reveals information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band [26].

4.7. Thin layer chromatography

In thin layer chromatography, the Rf values of a drug molecule is determined. By diminishing the Rf value to considerable extent helps in identifying the complex formation between the drug and nanosponge [26].

4.8. Loading efficiency

The loading efficiency of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer and high performance liquid chromatography methods [2]. The loading efficiency (%) of nanosponges can be calculated according to the following equation [4].

$$Loading\ Efficiency = \frac{\{Drug\ Added - Free\ Drug\}}{Drug\ Added} \times 100$$

4.9. Particle size and Polydispersity Index

With the help of dynamic light scattering using 90 plus particle size reequipped with MAS OPTION particle sizing software the particle size and mean diameter and polydispersity index can be determined [24]. The measurements were made at a fixed angle of 90° for all samples. The samples were suitably diluted with Milli Q water for every measurement [3].

4.10. Zeta potential

Zeta potential is used for the measurement of surface charge by using additional electrode in particle size equipment. In this process nanosponges containing samples were taken and diluted with 0.1mol/l Kcl and placed in electrophoretic cell for an application of 15V/cm of electric field. From this the mean hydrodynamic diameter and poly dispersity index were determined after averaging of the total measurement [26-27].

5. Application of nanosponges

Nanosponges have many applications in the pharmaceutical field due to their biocompatibility and versatility. They can be used in preparation of tablets, capsules, pellets, granules, suspensions, solid dispersions or topical dosage forms [30]. Nanosponges can act as multifunctional carriers for enhanced product performance and elegancy, extended release, and have capacity to encapsulate variety of drugs. It can reduce irritation, improved thermal, physical and chemical stability of product. Following are the application of nanosponges which shows versatility of nanosponges. Names of few drugs with categories used for preparation of nanosponges are shown in table 1 below.

Table 1: Names of drugs with categories used for preparation of nanosponges

Drug	Therapeutic Indication
Palcitaxel	Anti-Cancer
Tamoxifen	Breast Cancer
Tamozolamide	Brain Tumor
Econazole	Anti-Fungal
Lansoprazole	Anti-Ulcer Drug
Bovine Serum Albumin	Protein Suppliment
Glibenclamide	Anti-Diabetic

5.1. Nanosponges as a sustained delivery system

Acyclovir is a widely used antiviral agent due to of its efficacy in the treatment of herpes simplex virus infections [31]. However, neither the parenteral nor the oral administration of the currently available formulations of acyclovir is able to result in suitable concentrations of the agent reaching at target sites. Acyclovir's absorption in the gastrointestinal tract is slow and incomplete; what's more, its pharmacokinetics following oral medication is highly variable. The in vitro release profiles of acyclovir from the two types of nanosponges showed a sustained release of the drug from the two types of nanosponges indicating the encapsulation of acyclovir within the nanostructures. The percentages of acyclovir released from Carb-nanosponges and nanosponges after 3h in vitro were approximately 22% and 70%, respectively. No initial burst effect was observed for either formulation, proved that the drug was not weakly adsorbed onto the nanosponge surfaces [31-32].

5.2. Nanosponges in solubility enhancement

Swaminathan et al. studied a formulation of itraconazole in Nanosponges [35]. Itraconazole is a BCS Class II drug that has a dissolution rate limited poor bioavailability. Nanosponges improved the solubility of the drug more than 27-fold. When copolyvidonum was added as a supporting component of the nanosponge formulation, this exceeded to 55-fold. Nanosponges solubilize drug by possibly masking the hydrophobic groups of itraconazole, by increasing the wetting of the drug, and/or by decreasing the crystallinity of the drug [34].

5.3. Nanosponges in drug delivery

Nanosponges are nanomeric in size and have spherical shape; therefore, nanosponges can be prepared in different dosage forms like topical, parenteral, aerosol, tablets and capsules [2]. Telmisartan (TEL) is a BCS Class II drug having dissolution rate limited bioavailability. β-CD based nanosponges were formed by cross-linking β-CD with carbonate bonds. TEL was incorporated into the nanosponges. Saturation solubility and in vitro dissolution study of β-CD complex of TEL was compared with plain 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 NaHCO3 in drug-nanosponges complex than TEL. The highest solubility and in vitro drug release was observed in inclusion complex prepared from nanosponges and $NaHCO_3$ [33]. Paclitaxel is used for cancer chemotherapy having poor water solubility. β-CD based nanosponges to deliver paclitaxel is an alternative to classical formulation in cremophor EL because cremophor reduces the paclitaxel tissue penetration. The biological effect of paclitaxel *in vitro* is highly enhanced by nanosponges not only its cytotoxicity is greatly increased after 72 h incubation, but even intracellular paclitaxel concentration is significantly enhanced when compared to plain paclitaxel [34]. Econazole nitrate, an antifungal agent used topically to relive the symptoms of superficial candidasis, dermatophytosis 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 nitrate nanosponges were fabricated by emulsion solvent diffusion method and these nanosponges were loaded in hydrogel as a local depot for sustained drug release [35].

5.4. Nanosponges for protein delivery

Long term stability is a critical point in the successful development of pharmaceuticals, including macromolecular ones like proteins [34]. However, proteins can reversibly (or sometimes, even irreversibly) denature upon lyophilisation and consequently adopt conformation markedly distinct from the native ones. Thus, a major obstacle in protein formulation development is the maintenance of the native protein structure both during the formulation process and upon the long term storage [34]. Swaminathan et al. reported new swellable cyclodextrin based poly (amidoamine) nanosponges named nanosponges 10 and nanosponges 11, were synthesised by crosslinking β-CDs with either 2,2-bis-acrylamidoacetic acid or a short polyamido-amine chain deriving from 2,2-bis-acrylamidoacetic acid and 2-methyl piperazine respectively. The formulated β-CD based poly (amidoamine)-nanosponges were found to be stable at 300° C and high protein complexation capacity was observed [38].

5.5. Nanosponges in enzyme immobilization

The issue of enzyme immobilization is particularly relevant for lipases, as it improves their stability and modulates properties such as enantio selectivity and reaction rates [39]. As a consequence, the demand for new solid supports, suitable for this family of enzymes is constantly growing. For this Boscolo et al., reported high catalytic performances of Pseudomonas fluorescens lipase adsorbed on a new type of cyclodextrin-based nanosponges [40].

5.6. Nanosponges as a carrier for delivery of gases

Gases play an important role in medicine, either for diagnostic or treatment purposes. The deficiency of adequate oxygen supply, named hypoxia, is related to various pathologies, from inflammation to cancer. It is sometime difficult to deliver oxygen in appropriate form and dosage in clinical practice. Cavalli et al. developed nanosponge's formulations as oxygen delivery systems for topical application which have the ability to store and to release oxygen slowly over time [41].

5.7. Nanosponges as protective agent from light or degradation

Gamma-oryzanol is a ferulic acid ester mixture, has recently attracted a great interest as natural antioxidant and usually employed to stabilize food and pharmaceutical raw materials, moreover as a sunscreen in the cosmetics industry. Its application is limited by its high instability and photodegradation. Gamma-oryzanol was encapsulated in nanosponges, showing a good protection from photodegradation. A gel and an O/W emulsion were formulated with the gamma-oryzanol-loaded nanosponges [42].

5.8. Nanosponges that soaks up toxin

The bloodstream [deviseda'nanosponge] based on polymeric nanopartIcles that can neutralize and remove a broad range of toxins from forming toxins (PFTs),which attack cells by boring holes in their membranes and altering their permeability, are one of the most common toxins produced by bacteria as well as venomous species of bees scorpions and snakes inhibiting pore-forming-toxins can reduce the severity of *Staphylococcus aureus* infections and has therapeutic potential for treating other common pathogen such as *Escherichia coli* (*E. coli*),

Listeria monocytogenes and *Streptococcus pneumoniae*. Transmission electron micrograph of a nanosponge showed approximately 85 nm in diameter. The nanosponge created by Liangfang Zhangand colleagues comprises an outer layer made of natural red blood cell (RBC) membranes, which attracts the toxins like a decoy,and an inner poly lactic coglycolic acid) (PLGA) nanoparticle core to absorb them. The biodegradable polymer core stabilizes the RBC membrane, enabling its survival in the blood stream during prolonged circulation, and locks away the captured PFTs. The RBC outer coating also helps the nanosponges evade the immune system and remain in circulation for upto 40 h. The 85nm diameter core shell nanosponges show activity against streptolysin PFT produced by *Streptococcus pyogenes* and melittin from bee venom.

5.9. More effectiveness than direct injection

Recent studies have concluded that the effect of nanosponge on tumors is 5 times more than the normal injection. The nanosponge drug delivery system is likely to be filled with virus-sized sponges and an anti-cancer drug which is then attached to chemical linkers that bond to a receptor on the surface of tumor cells, and then the sponges are injected into the body. When the sponges come into contact with a tumor cell, they are taken up by the cell or get attached to its surface and release its drug contents in a predictable and controlled manner [43,44].

5.10. Earlier work done on nanosponges

The three dimensional nanosponge's plays an important role in the fractionalization of peptides for proteomic applications was proposed by Wong et al. [45]. The catalytic growth of carbon nanotubes and nanofibers on vermiculite to produce flotable hydrophobic "nanosponges" for oil spill remediation was explained by Moura and Lago studied [46]. Arkas *et al*. reported that nanosponges have the property of encapsulating organic pollutants from water. These nanosponges were impregnated with ceramic porous filters resulting in formation of hybrid organic/inorganic filter modules. These hybrid filter modules were tested for the effective purification of water, employing a variety of water pollutants. It has been observed that polycyclic aromatic hydrocarbons can be removed very efficiently (more than 95%) the pollutant group including trihalogen methanes, mono aromatic hydro carbons, and pesticides (simazine) can also be removed (>80%) [47]. Alongi et al. reported novel flame retardants containing cyclodextrin nanosponges and phosphorous compounds to enhance ethyl vinyl acetate copolymer combustion properties [48]. The interaction between β-cyclodextrin nanosponges and two different ultraviolet stabilizers (namely, 2-hydroxy-4(octyloxy)-benzophenone and triphenyl phosphate) in the photooxidation of polypropylene exposed to UV light have been investigated by Alongi et.al. A remarkable reduction of the oxidation induction time has been observed in presence of β-CD nanosponges [49]. The synthesis of graphite-nanofiber-supported porous Pt-Ag nanosponges and mesoporous platinum nanosponges as electrocatalysts for the oxygen reduction reaction was studied by Lee *et al*. [50,51]. The study of chiral photoreactions or photochirogenesis and its precise control is one of the most challenging topics in current photochemistry. A supramolecular approach to photochirogenes provides a convenient and also promising tool to facilitate excited-state chirality transfer from chiral host toprochiral substrate. The pyromellitate-linked cyclodextrin nanosponges, employed for the first time as supramolecular reaction media for sensitizing the enantio differentiating photoisomerization of (Z)-cyclooctene and (Z,Z)-1,3-cyclooctadiene exhibited unique photochirogenesis behavior significantly different from the conventional sensitizer-modified cyclodextrins was proposed by Lee et.al [52]. Yang et al. developed non-cytotoxic scaffolds with a nanometer resolution through using silicon substrates as the backbone. This method was merged an optics based approach with chemical restructuring to modify the surface properties of an IC-compatible material, switching from hydrophilicity to hydrophobicity. Through this nanofabrication-based approach, they synthesized hydrophobic oxidized silicon nanosponges. This study had demonstrated the potential application of using these silicon-based nanopatterns such as influencing cellular behaviors at desired locations with a micro-/nanometer level [53].

6. Conclusion

Nanosponges are versatile drug carrier system as they carry both hydrophilic and hydrophobic drugs by forming inclusion and non inclusion complexes. They can deliver drugs by various routes like oral, topical and parenteral in a predictable manner to the target site. Besides their application in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, and catalysis, among others. Drugs delivered by nanosponges can be proved safe and effective and the pharmaceutical industries will benefit greatly if clinical studies can prove their potential for human use.

Conflict of Interest: There is no conflict of interest.

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