Nanosponges: a potential nanocarrier for novel drug delivery—a review

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ABSTRACT

The ideal delivery system will solubilize the drug, lead the therapy to the target site, and release the therapy to fulfill the individual need of the patient and disease stage. Nanosponges are one of such effective drug carriers which conquer the problems of drug toxicity and poor bioavailability as they can load both hydrophilic and hydrophobic drugs. Nanosponges are tiny in size with a 3-dimensional network and a nanometric cavity size. Nanosponges are highly porous having unique ability to entrap active moieties and offer a unique advantage of programmable release. They are biologically safe and simple to produce. Nanosponges can be prepared by cross linking different types of cyclodextrins with a carbonyl or a dicarboxylate compound as a cross linker. Nanosponge technology has been explored for various applications like enhancing the bioavailability of drug molecules and delivery of drugs into the oral, topical as well as parenteral routes. Nanosponges can also be used as a carrier for biocatalysts in the delivery and release of enzymes, proteins, vaccines and antibodies.

1. Introduction

Nanosponges are tiny mesh–like structures (Figure 1) in which a large variety of substances can be encapsulated[1,2]. They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs by their inclusion and non–inclusion behavior[3]. Nanosponges have recently been developed and proposed for drug delivery. Nanosponges can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability[4]. Nanosponges are able to load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility[5]. Nanosponges are more like a three-dimensional network or scaffold. The backbone is a long length of polyester which is mixed in solution with small molecules called crosslinkers that act like tiny grappling hooks to fasten different parts of the polymer together[6].

Figure 1. Molecular structure of cyclodextrin carbonates nanosponges.
can be stored[11].

The cross-linking-to-cyclodextrin ratio can be varied during preparation to improve the drug loading and to obtain a tailored release profile[12-14]. Their highly porous nanomeric nature enables drug molecules to orient themselves in nanosponge’s inclusion as well as interact in a non-inclusion fashion, which offers higher drug loading compared with the parent cyclodextrin molecules[12].

Nanosponges show a remarkable 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 sectors[15,16].

The engineering capacity of nanosponges is due to the relatively simple chemistry of its polyesters and cross-linking peptides, compared to many other nanoscale drug delivery systems[17]. Nanosponges are water soluble but does not breakup chemically in water. They mix with water and use it as a transport fluid. They can be used to mask unpleasant flavors, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site[17].

The nanosponges are solid in nature[18]. 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]. The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges[19]. For oral administration, the complexes may be dispersed in a matrix of 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 the complex may be simply carried in sterile water, saline or other aqueous solutions. For parenteral administration they can be effectively incorporated into topical hydrogel[20,21]. Nanosponges are encapsulating type of nanoparticles which encapsulate the drug molecules within its core[22].

2. Chemicals used for the synthesis of nanosponges

2.1. Polymers

Polymers used for the synthesis of nanosponges are including: hypercross linked polystyrenes, cyclodextrins and its derivatives like Methyl β-cyclodextrin (β-CD), alkoxy carbonyl cyclodextrins, 2-hydroxy propyl β-CDs and copolymers like poly (Valero lactone–allylvalero lactone) and poly (Valero lactone–allyl Valero lactone oxepanedione) and ethyl cellulose and PVA.

2.2. Crosslinkers

Crosslinkers used for the synthesis of nanosponges contain diphenyl carbonate, diarylcarbonates, diisocyanates, pyromellitic anhydride, carbonyldiimidazoles, epichloridrine, glutaraldehyde, carboxylic acid dihydrides, 2,2- bis(acrylamido) acetic acid and dichloromethane[3].

3. Methods of preparation of nanosponges

3.1. Solvent method

In this method the polymer was mixed with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethylsulfoxide. This mixture was added to excess quantity of the crosslinker, preferably in crosslinker/polymer 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. Preferred cross linkers are carbonyl compounds (dimethyl carbonate and carbonyl diimidazole)[19].

After completion of the reaction, the solution was allowed to cool at room temperature, then the product was added to large excess of bidistilled water and recovered the product by filtration under vacuum and subsequently purified by prolonged Soxhlet extraction with ethanol. The product was dried under vacuum and grinded in a mechanical mill to obtain homogeneous powder[23].

3.2. Ultrasound-assisted synthesis

In this method nanosponges were obtained by reacting polymers with crosslinkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size[18]. The polymer was mixed and the crosslinker in a particular molar ratio in a flask. The flask was placed in an ultrasound bath filled with water and heated it to 90 °C. The mixture was sonicated for 5 h. Then the mixture was allowed to cool and the product 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[18,23].

3.3. Loading of drug into nanosponges

Nanosponges for drug delivery should be pretreated to
obtain a mean particle size below 500 nm. The nanosponges were suspended in water and sonicated to avoid the presence of aggregates and then centrifuged the suspension to obtain the colloidal fraction. The supernatant was separated and dried the sample by freeze drying. The aqueous suspension of nanosponges was prepared and dispersed the excess amount of the drug and maintained the suspension under constant stirring for specific time required for complexation. 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. Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex.

4. Characterization of nanosponges

4.1. Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of nanosponges on the solubility of drug. Phase solubility diagrams indicate the degree of complexation. In this method the drug was added to an Erlenmeyer flask containing an aqueous solution of various percentages of nanosponges. The Erlenmeyer flask was stirred on a mechanical shaker at room temperature. When a steady state was reached, the suspension was filtered by centrifugation using a 3000 Dalton molecular filter. The solution obtained was analyzed to determine the drug concentration by high performance liquid chromatography.

4.2. Microscopy studies

Scanning electron microscopy and transmission electron microscopy can be used to study the morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product observed under electron microscope indicates the formation of the inclusion complexes.

4.3. Thermoanalytical methods

Thermoanalytical 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.

4.4. X-ray diffraction and single crystal X-ray structure analysis

Powder X-ray diffraction can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the drug and polymer molecules. A diffraction pattern of a physical mixture is often the sum of those of each component, while the diffraction pattern of complexes is apparently different from each constituent and leads to a “new” solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation.

The complex formation of drug with nanosponges alters the diffraction patterns and also changes the crystalline 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.

4.5. Single crystal X-ray structure analysis

It is used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established.

4.6. Infra-red spectroscopy

Infra-red spectroscopy is used to estimate the interaction
between nanosponges and the drug molecules in the solid state. Nanosponges bands often change only slightly upon complex formation. 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. The technique is not generally suitable to detect the inclusion complexes and is less clarifying than other methods[25].

The application of infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infrared spectral studies give 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[25].

4.7. Thin layer chromatography

In thin layer chromatography, the $R_f$ values of a drug molecule diminish to considerable extent and this helps in identifying the complex formation between the drug and nanosponge[25].

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].

\[
\text{Loading efficiency} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} \times 100
\]

4.9. Particle size and polydispersity

The particle size can be determined by dynamic light scattering using 90Plus particle size reequipped with MAS OPTION particle sizing software. From this the 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 a measure of surface charge. It can be measured by using additional electrode in the particle size equipment[24]. For zeta potential determination, samples of the nanosponges were diluted with 0.1 mol/L KCl and placed in the electrophoretic cell, where an electric field of about 15 V/cm was applied. The mean hydrodynamic diameter and polydispersity index of the particles were calculated using the cumulated analysis after averaging of the total measurements[3].

5. Application of nanosponges

Due to their biocompatibility and versatility, nanosponges have many applications in the pharmaceutical field. They can be used as excipients in preparing tablets, capsules, pellets, granules, suspensions, solid dispersions or topical dosage forms[27]. They can encapsulate variety of drugs as shown in Table 1. Nanosponges can act as multifunctional carriers for enhanced product performance and elegance, extended release, reduced irritation, improved thermal, physical and chemical stability of product. Following are the application of nanosponges which shows versatility of nanosponges.

### Table 1

| Drug                  | Therapeutic activity | Nanosponges vehicle | Attributes                              | Administration route | References |
|-----------------------|----------------------|---------------------|----------------------------------------|----------------------|------------|
| Itraconazole          | Antifungal           | β-CD, copolyvidonum | Enhanced drug solubility               | Oral, topical        | [12]       |
| Dexamethasone         | Anti-inflammatory    | β-CD, diphenylcarbonate | Enhanced drug solubility               | Oral, parenteral     | [13]       |
| Flurbiprofen          | Anti-inflammatory    | β-CD, diphenylcarbonate | Sustained drug release                 | Oral                 | [13]       |
| Doxorubicin           | Antineoplastic       | β-CD, diphenylcarbonate | Sustained drug release                 | Parenteral           | [13]       |
| Nelfinavir mesylate   | Antiviral            | β-CD, dimethylcarbonate | Enhanced drug solubilization         | Oral                 | [14]       |
| Gamma-oryzanol        | Antioxidant          | β-CD, diphenylcarbonate | Enhanced stability, solubility, permeation | Topical             | [39]       |
| 5-Fluorouracil        | Antineoplastic       | β-CD                | Enhanced drug stability               | Parenteral, topical  | [49]       |
| Tamoxifen             | Antiestrogen         | β-CD, carbonyldimidazole | Enhanced bioavailability, solubility | Oral                 | [50]       |
| Resveratrol           | Antioxidant          | β-CD, carbonyldimidazole | Enhanced stability, permeation, cytotoxicity, controlled drug release | Oral, topical       | [51]       |
| Acetylsalicylic acid  | Anti-inflammatory    | β-CD, pyromellitic dianhydride | Prolonged drug release               | Oral                 | [52]       |
| Curcumin              | Antineoplastic       | β-CD, dimethylcarbonate | Enhanced activity, solubilization     | Parenteral           | [53]       |
5.1. Nanospheres as a sustained delivery system

Acyclovir is a widely used antiviral agent due to its efficacy in the treatment of herpes simplex virus infections[28]. 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 nanospheres showed a sustained release of the drug from the two types of nanospheres indicating the encapsulation of acyclovir within the nanostructures. The percentages of acyclovir released from Carb–nanospheres and nanospheres after 3 h 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 nanosphere surfaces[29].

5.2. Nanospheres in solubility enhancement

Swaminathan et al. studied a formulation of itraconazole in Nanospheres[12]. Itraconazole is a BCS Class II drug that has a dissolution rate limited poor bioavailability. Nanospheres improved the solubility of the drug more than 27-fold. When copolyvidonum was added as a supporting component of the nanosphere formulation, this exceeded to 55-fold. Nanospheres 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[12].

5.3. Nanospheres in drug delivery

Nanospheres are nanomeric in size and have spherical shape, therefore, nanospheres 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 poor bioavailability. β–CD based nanospheres were formed by cross–linking β–CD with carbonate bonds. TEL was incorporated into the nanospheres. Saturation solubility and in vitro dissolution study of β–CD complex of TEL was compared with plain TEL and nanosphere 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–nanospheres complex than TEL. The highest solubility and in vitro drug release was observed in inclusion complex prepared from nanospheres and NaHCO₃[30].

Paclitaxel is used for cancer chemotherapy having poor water solubility. β–CD based nanospheres 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 nanospheres: not only its cytotoxicity is greatly increased after 72 h incubation, but even intracellular paclitaxel concentration is significantly enhanced when compared to plain paclitaxel[31].

Econazole nitrate, an antifungal agent used topically to relieve 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 nanospheres were fabricated by emulsion solvent diffusion method and these nanospheres were loaded in hydrogel as a local depot for sustained drug release[32].

5.4. Nanospheres for protein delivery

Long term stability is a critical point in the successful development of pharmaceuticals, including macromolecular ones like proteins[33]. However, proteins can reversibly (or sometimes, even irreversibly) denature upon lyophilization 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) nanospheres named nanospheres 10 and nanospheres 11, were synthesised by cross–linking β–CDs with either 2,2–bis–acylamidoacetic acid or a short polyamido–amine chain deriving from 2,2–bis–acylamidoacetic acid and 2–methyl piperazine respectively. The formulated β–CD based poly (amidoamine)–nanospheres were found to be stable at 300 °C and high protein complexation capacity was observed[35].

5.5. Nanospheres 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[36]. 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[37].

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 nanosponges formulations as oxygen delivery systems for topical application which have the ability to store and to release oxygen slowly over time[38].

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[39].

5.8. Earlier work done on nanosponges

Wong et al. reported that three dimensional nanosponges plays an important role in the fractionalization of peptides for proteomic applications[40].

Moura and Lago studied catalytic growth of carbon nanotubes and nanofibers on vermiculite to produce flotable hydrophobic “nanosponges” for oil spill remediation[41].

Arkas et al. reported that nanosponges have the property of encapsulating organic pollutants from water. Ceramic porous filters can be impregnated with these nanosponges resulting in 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 established that polycyclic aromatic hydrocarbons can be removed very efficiently (more than 95%). Representatives of the pollutant group of trihalogen methanes, mono aromatic hydro carbons, and pesticides (simazine) can also be removed (>80%)[42].

Alongi et al. reported novel flame retardants containing cyclodextrin nanosponges and phosphorous compounds to enhance ethyl vinyl acetate copolymer combustion properties[43].

Alongi et al. studied 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. A significant decrease of the oxidation induction time has been observed in presence of β–CD nanosponges[44].

Lee et al. synthesized graphite–naofiber–supported porous Pt–Ag nanosponges and mesoporous platinum nanosponges as electrocatalysts for the oxygen reduction reaction[45,46].

The precise control of chiral photoreactions or photochirogenesis is one of the most challenging topics in current photochemistry. A supramolecular approach to photochirogenesis provides a convenient and also promising tool to facilitate excited-state chirality transfer from chiral host topochiral substrate.

Liang et al. developed 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[47].

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[48].

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 statement

We declare that we have no conflict of interest.

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References

[1] Trotta F, Zanetti M, Cavalli R. Cyclodextrin–based nanosponges as drug carriers. Beilstein J Org Chem 2012; 8: 2091–2099.
[2] Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: a novel class of drug delivery system–review. J Pharm Pharm Sci 2012; 15(1): 103–111.
[3] Swaminathan S, Vavia PR, Trotta F, Cavalli R, Tumbiolo S, Bertinetti L, et al. Structural evidence of differential forms of nanosponges of beta–cyclodextrin and its effect on solubilization of a model drug. J Incl Phenom Macrocycl Chem 2012; 76: 201–211.
[4] Patel EK, Oswal RJ. Nanosponge and microsponges: a novel drug delivery system. Int J Res Pharm Chem 2012; 2(2): 237–244.
[5] Swaminathan S, Darandale S, Vavia PR. Nanosponge–aided drug delivery: a closer look. Pharm Formal Qual 2012; 12:15.
[6] Shinde G, Rajesh KS, Bhatt D, Bangale G, Umalkar D, Virag G. Current status of colloidal system (nano range). Int J Drug Formal Res 2011; 26: 39–54.
[7] Szejli J. Cyclodextrin technology. Berlin: Springer Science & Business Media; 1988, p. 450.
[8] Trotta F, Tumiatti W, inventors; Sea Marconi Technologies Sas, assignee. Cross-linked polymers based on cyclodextrins for removing polluting agents. WO/2003/085002. 2003 October 16.
[9] Trotta F, Cavalli R. Characterization and application of new hyper cross–linked cyclodextrins. Compos Interfaces 2009; 16: 39–48.
[10] Lembo D, Cavalli R. Nanoparticulate delivery systems for antiviral drugs. Antivir Chem Chemother 2010; 21: 53–70.
[11] Kumar MH. Nanosponge: an innovative drug carrier system—a review. Pharm Regul Aff 2012; 1: 203.
[12] Swaminathan S, Vavia PR, Trotta F, Torne S. Formulation of betacyclodextrin based nanosponges of itraconazole. J Incl Phenom Macrocycl Chem 2007; 57(1–4): 89–94.
[13] Cavalli R, Trotta F, Tumiatti V. Cyclodextrin–based nanosponges for drug delivery. J Incl Phenom Macrocycl Chem 2006; 56: 209–213.
[14] Vavia PR, Swaminathan S, Trotta F, Cavalla R. Application of nanosponges in drug delivery. In: Proceedings XIII International Cyclodextrin Symposium; 2006 May 14–17; Turin, Italy. Berlin: Springer; 2006. p. 207.
[15] Swaminathan S. Studies on novel dosage forms[dissertation]. Mumbai: Mumbai University; 2006.
[16] Liang L, Liu DP, Liang CC. Optimizing the delivery systems of chimeric RNA, DNA oligonucleotides beyond general oligonucleotide transfer. Eur J Biochem 2002; 269: 5753–5758.
[17] Salisbury D. Nanosponge drug delivery system more effective than direct injection. Nashville: Vanderbilt University; 2010. [Online] Available from: http://news.vanderbilt.edu/2010/06/nanosponge–drug–delivery–system–more–effective–than–direct–injection–116830/ [Accessed on 20th December, 2012]
[18] Alongi J, Poskovic M, Frache A, Trotta F. Role of β–cyclodextrin nanosponges in polypropylene photooxidation. Carbohydr Polym 2011; 86: 127–135.
[19] Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, Vallerio R, inventors; Sea Marconi Technologies Sas, assignee. Ultrasound–assisted synthesis of cyclodextrin–based nanosponges. EP 1786841 B1. 2007 June 16.
[20] Sharma R, Walker RB, Pathak K. Evaluation of the kinetics and mechanism of drug release from econazole nitrate nanosponges loaded carbapol hydrogel. Indian J Pharm Edu Res 2011; 45(1): 25–31.
[21] Sharma R, Pathak K. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation. Pharmac Dev Technol 2011; 16(4): 367–376.
[22] Cavalli R, Rogero CM, Mognetti B, Berta GN, Tumiatti V, Trotta F, inventors; Sea Marconi Technologies Sas, assignee. Cyclodextrin–based nanosponges as a vehicle for antitumoral drugs. WO 2009/003656 A1. 2009 January 8.
[23] Lala R, Thorat A, Gargote C. Current trends in β-cyclodextrin based drug delivery systems. Int J Res Ayurveda Pharm 2011; 2(5): 1520–1526.
[24] Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D, et al. Cyclodextrin–based nanosponges encapsulating camptothecin: physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm 2010; 74: 193–201.
[25] Singh R, Bharti N, Madan J, Hiremath SN. Characterization of cyclodextrin inclusion complexes—a review. J Pharm Sci Technol 2010; 23(3): 171–183.
[26] Challia R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an update review. AAPS PharmSciTech 2005; 6(2): E329–E357.
[27] Moya–Ortega MD, Alvarez–Lorenzo C, Concheiro A, Loftsson
T. Cyclodextrin–based nanogels for pharmaceutical and biomedical applications. Int J Pharm 2012; 428: 152–163.
[28] O’Brien JJ, Campoli–Richards DM. Acyclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1989; 37: 233–309.
[29] Lembo D, Swaminathan S, Donalisoa M, Civra A, Pasterod L, Aquilanod D, et al. Encapsulation of acyclovir in new carboxylated cyclodextrin–based nanospheres improves the agent’s antiviral efficacy. Int J Pharm 2013; 443: 262–272.
[30] Rao M, Bajaj A, Khole I, Munjapara G, Trotta F. In vitro and in vivo evaluation of β–cyclodextrin–based nanospheres of telmisartan. J Incl Phenom Macrocycl Chem 2013; 77: 135–145.
[31] 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 nanosphere formulation. J Incl Phenom Macrocycl Chem 2012; 74: 201–210.
[32] Sharma R, Walker RB, Pathak K. Evaluation of kinetics and mechanism of drug release from econazole nitrate nanospheres loaded carbopol hydrogel. Indian J Pharm Edu Res 2011; 45(1): 25–31.
[33] Klibanov AM, Scheffiliti JA. On the relationship between conformation and stability in solid pharmaceutical protein formulations. Biotechnol Lett 2004; 26: 1103–1106.
[34] Shewarts D, Sofia S, Friess W. Integrity and stability studies of precipitated rhBMP–2 microparticles with a focus on ATR–FTIR measurements. Eur J Pharm Biopharm 2006; 63: 241–248.
[35] Swaminathan S, Cavalli R, Trotta F, Ferruti P, Ranucci E, Gerges I, et al. In vitro release modulation and conformational stabilization of a model protein using swellable polyamidoamine nanospheres of β–cyclodextrin. J Incl Phenom Macrocycl Chem 2010; 68: 183–191.
[36] Mateo G, Palomo JM, Fernandez–Lorente G, Guisan JM, Fernandez–Lorente R. Improvement of enzyme activity, stability and selectivity via immobilization techniques. Enzyme Microb Technol 2007; 40: 1451–1463.
[37] Boscolo B, Trotta F, Ghilaudi E. High catalytic performances of Pseudomonas fluorescens lipase adsorbed on a new type of cyclodextrin–based nanospheres. J Mol Catal B Enzym 2010; 62: 155–161.
[38] Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosphere formulations as oxygen delivery systems. Int J Pharm 2010; 402: 254–257.
[39] Sapino S, Carlotti ME, Cavalli R, Ugazio E, Berlier G, Gastaldi L, et al. Photocatalytic and antioxidant properties of gamma–oryzanol in beta–cyclodextrin–based nanospheres. J Incl Phenom Macrocycl Chem 2013; 75: 69–76.
[40] Wong VN, Fernando G, Wagner AR, Zhang J, Kinsel GB, Zauscher S, et al. Separation of peptides with polyionic nanospheres for MALDI–MS analysis. Langmuir 2009; 25(3): 1459–1465.
[41] Moura FCC, Lago RM. Catalytic growth of carbon nanotubes and nanofibers on vermiculite to produce floatable hydrophobic “nanospheres” for oil spill remediation. Appl Catal B Environ 2009; 90: 436–440.
[42] Arkas M, Allabashi R, Tsiourvas D, Mattausch EM, Perfile R. Organic/inorganic hybrid filters based on dendritic and cyclodextrin “nanosphones” for the removal of organic pollutants from water. Environ Sci Technol 2006; 40(8): 2771–2777.
[43] Alongi J, Poskovic M, Frache A, Trotta F. Novel flame retardants containing cyclodextrin nanosphones and phosphorous compounds to enhance EVA combustion properties. Polym Degrad Stabil 2010; 95: 2093–2100.
[44] Alongi J, Poskovic M, Frache A, Trotta F. Role of β–cyclodextrin nanosphones in polypropylene photooxidation. Carbohydr Polym 2011; 86: 127–135.
[45] Lee CL, Wu CC, Chiou HP, Syu CM, Huang CH, Yang CC. Mesoporous platinum nanosphones as electrocatalysts for the oxygen reduction reaction in an acidic electrolyte. Int J Hydro Energy 2011; 36: 15045–15051.
[46] Liang W, Yang C, Nishijima M, Fukushima G, Mori T, Mele A, et al. Cyclodextrin nanosphere–sensitized enantio differentiating photoisomerization of cyclooctene and 1,3-cyclooctadiene. Beilstein J Org Chem 2012; 8: 1305–1311.
[47] Yang CY, Liao TG, Shuai HH, Shen TL, Yeh JA, Cheng CM. Micropatterning of mammalian cells on inorganic–based nanosphones. Biomaterials 2012; 33: 4988–4997.
[48] Cavalli R, Trotta F, Tumiatti W, Serpe L, Zara GP. 5–Fluorouracile loaded β–cyclodextrin nanosphones: in vitro characterization and cytotoxicity. In: Proceedings XIII International Cyclodextrin Symposium; 2006 May 14–17; Turin, Italy. Berlin: Springer; 2006.
[49] Torne S, Darandale S, Vavia P, Trotta F, Cavalli R. Cyclodextrin–based nanosphones: effective nanocarrier for tamoxifen delivery. Pharm Des Technol 2013; 18(3): 619–625.
[50] Ansari KA, Vavia PR, Trotta F, Cavalli R. Cyclodextrin–based nanosphones for delivery of resveratrol: in vitro characterisation, stability, cytotoxicity and permeation study. AAPS PharmSciTech 2011; 12(1): 279–286.
[51] Shende PK, Trotta F, Gaud RS, Deshmukh K, Cavalli R, Biasizzo M. Influence of different techniques on formulation and comparative characterization of inclusion complexes of ASA with β–cyclodextrin and inclusion complexes of ASA with PMDA cross–linked β–cyclodextrin nanosphones. J Incl Phenom Macrocycl Chem 2012; 74: 447–454.
[52] Darandale SS, Vavia PR. Cyclodextrin–based nanosphones of curcumin: formulation and physicochemical characterization. J Incl Phenom Macrocycl Chem 2013; 75: 315–322.