International Journal of Scientific Research in Science and Technology
Print ISSN: 2395-6011 | Online ISSN: 2395-602X (www.ijsrst.com)
doi : https://doi.org/10.32628/IJSRST229617

NANOSPONGES : A New Approach for Drug Delivery System

G. J. Dhumal*, A. S. Kulkarni, K. K. Bandal, R. H. Dambe, V. R. Thorat, T. T. Patil, K. K. Dhayagonde
Ashokrao Mane Institute of Pharmaceutical Sciences & Research Save, Tal- Shahuwadi, Dist- Kolhapur, Maharashtra, India

Article Info
Volume 9, Issue 6
Page Number : 170-178

Publication Issue
November-December-2022

Article History
Accepted : 05 Nov 2022
Published : 18 Nov 2022

ABSTRACT

An ideal drug delivery system will solubilize the drug and achieves proficient concentration of drug at the targeted site for a specific period of time in order to increase the bioavailability with minimal side effects. Topical drug delivery system challenged with many complications like poor permeability, skin irritation, allergic reactions etc. Nanosponges are one of the carriers which solve the difficulties of drug toxicity and poor bioavailability as they can entrap both lipophilic and hydrophilic drugs. Nanosponges are minute sized having diameter below 1µm with 3-dimensional network and they can easily penetrate through the skin. Nanosponges play vital role in targeting drug delivery in a controlled manner. They are highly porous in nature having ability to capsulate variety of drug moieties and offer controlled release at the targeted site. Nanosponges can be formulated as oral, parenteral, topical or inhalation dosage forms. Controlled release of the capsulated active agent at the targeted site and solubility improvement of poorly water-soluble drugs are key advantages of Nanosponges drug delivery systems. The present review discusses about Nanosponges, method of preparations, characterisation and applications particularly in the targeted drug delivery system.

Keywords : Nanosponges, Bioavailability, Controlled Release, Targeted Drug Release, Poorly Water-Soluble Drugs

I. INTRODUCTION

Delivery of the drug at the targeted site is the challenge faced while development of new drug delivery system. Also, some therapy requires controlled release of the drug at the targeted site with minimum side effects. Most of the drugs are water insoluble which affects the bioavailability. Now a days researches mainly focussing on the targeted drug delivery system with minimum side effects and controlled drug release in a predictable manner. An ideal drug delivery system will achieve the effective concentration of the drug at targeted site for a definite period of time in order to decrease the side effects. Effective targeted drug delivery system with controlled drug release have been a dream for longer period of time.[1, 2]

Newly developed Nanosponges are the porous polymeric colloidal system with a size of about a virus. Nanosponges are very tiny porous materials

having ability to entrap both hydrophilic and lipophilic drugs. They can solubilise the poorly water-soluble drugs and provide prolonged release with increased Bioavailability.[3] Nanosponges originally developed for topical drug delivery system. For example, cosmetic preparations, gels, Ointments, creams etc. In case of topical preparations, they release the active ingredients upon application to the skin and producing the highly concentrated layer at the absorbing site.[4] Nanosponges prevents the excessive accumulation of the drug in the Dermis and Epidermis and reduces the irritation of the active ingredients without reducing their efficacy. The delivery system containing polymeric bead having a very small pores which holds the active ingredients to provide controlled release. Now a days Nanosponges can be formulated as oral, parenteral and inhalational dosage form. In oral dosage form Nanosponges are dispersed in the matrix of excipients, diluents, lubricants and anticaking agent which is suitable for the preparation of tablets or capsules. In case of parenteral administration, they are mixed with sterile water, saline solution or any other aqueous medium.[5, 6]

Nanosponges are made up of microscopic particles having few nanometres wide cavities which capsulates the both hydrophilic and lipophilic substances. The nanosponges are encapsulating type of nanoparticles which encapsulates the both hydrophilic and lipophilic moieties within its core.[7] The nanoparticles are classified into three types namely Encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. Nanosponges and nano-capsules are the types of encapsulating nanoparticles. They can entrap the drug molecules in their aqueous core. Complexing nanoparticles are those that entrap the drug molecules by means of electrostatic charges. Conjugated nanoparticles are linked to drug molecules by covalent bonds. As compared to other nanoparticles nanosponges are soluble both in water and organic solvents, porous, non-toxic and stable at high temperature and having 3D structure containing nanomeric size cavities which allows the predictable release of drug.[8, 9]

Advantages[1, 2, 3]

- Nanosponges increases the solubility of the poorly water-soluble drugs which leads to increased bioavailability.
- Targeted site-specific drug delivery system
- It provides extended drug release at the targeted site
- Improved stability, Increased elegance and enhanced formulation flexibility
- Nanosponges offers entrapment of wide variety of substances with reduced side effects
- Nanosponges are stable over a wide range of pH (1-11) and temperature (up to 130^{o}C)
- Formulations are self-sterilizing as their pore size is about 0.25µm where bacteria cannot penetrate
- They have thermal, physical and chemical stability
- Less harmful side effects
- Nanosponges mask the unpleasant taste and flavour
- Reduces the dosing interval and increases the patient compliance
- Biodegradable

Disadvantages[2, 3]

- Drug delivery system have ability to incorporate only small particles
- Depend only upon loading capacity
- The loading capacity depends on the degree of crystallization

Composition of Nanosponges [1, 2, 3]

Nanosponges are complex structure normally made up from long linear molecules that are folded by

cross linking into spherical structure. Nanosponges are generally consist of three components namely

1. Polymers
2. Cross linking agents
3. Drug molecules

1. Polymers[10]

The type of polymer affects the formation as well as performance of the nanosponges. The cavity size of the nanosponges determines the drug loading capacity. The ability of the polymer to be cross-linked is depends on the functional and active groups to be substituted. The following are some suitable examples of polymers used in the formulation.

Ex. Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly (Valero lactone–allylvalerolactone) & Poly (valerolactone-oxepanedione) and Ethyl Cellulose & Poly vinyl acetate (PVA) etc.

The polymer selection is depending on the nature of the drug molecule and required release. The polymer should attach with the specific ligands to show targeted drug release.

2. Cross linkers[11]

The selection of crosslinking agents depends on the nature of the polymer as well as the drug molecule which is to be formulated. The list of crosslinking agents used for the manufacturing of nanosponges are listed below,

Carbonyl Di-imidazole, Diphenyl carbonate, Epichloridrine, Glutarldehyde, Carboxylic acid di anhydrides, Di-arylcarbonates, Di-Isocyanates, Pyromellitic anhydride, Carbonyl Di-imidazoles, Epichloridrine, Glutraldehyde, Carboxylic acid di-anhydrides, 2, 2- bisacrylamides.

3. Drug molecules[3, 13, 14]

Drug molecules used in the nanosponges should have the following characteristics

1. Molecular weight should be in the range of 100-400 Daltons.
2. It should consist less than five condensed rings
3. Melting point should below 250 ^{o}C
4. Solubility in water is less than 10/ml

Factors affecting nanosponge formulation[7, 14, 15, 16]

The formulation of nanosponges depends on the various factors which described as below,

Type of polymers and Crosslinking agents

The formulation and performance of the nanosponges depends on the type of polymers used. For better complexation of drug molecules in the formulation the cavity size provided by the polymeric material is very important. Hydroxy propyl β-Cyclodextrin possess good affinity to form complex with drug molecule as compared with α and γ Cyclodextrins. The crosslinking agents are responsible for the conversion of molecular Nano cavities into three dimensional nonporous structures. Depending on the nature of crosslinking agents' water soluble or insoluble nanosponges are formed. For example, epichlorohydrin is used as crosslinking agents for the development of hydrophilic nanosponges. Hydrophilic nanosponges modifies the rate of drug release and enhances the drug absorption across biological membrane. Diphenyl carbonate, Carbonyl di-imidazoles are used to formulate hydrophobic nanosponges as a carrier for the sustained drug release.

Nature and type of drug molecule

The type and nature of drug molecules determines the selection of polymers and copolymers in the formulation. The hydrophilic and lipophilic nature of the drug substance, dose of the active molecule are some important factors considered in the

formulation. Stable complex is not obtained with drugs having high melting point.

Temperature

Drug polymer complexation greatly affected by the temperature. Generally, the stability of drug polymer complex is decreased with increase in temperature which may be due to reduction in the drug-nanosponge interaction.

Method of preparation

Drug loading capacity is mainly depending on the method of preparation. Productivity of the method is generally influenced by the nature of drug molecule, polymers and temperature condition. Mostly freeze-drying method is used for effective drug complexation.

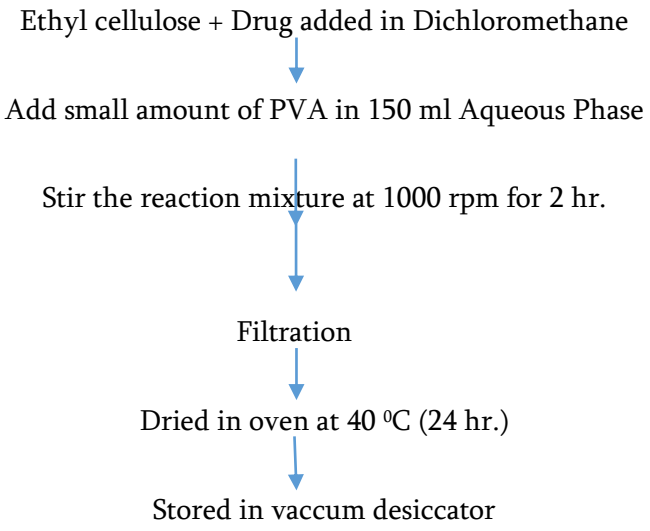
Degree of substitution

Position, type and number of the substituent on the parent polymeric molecule determine the nanosponge complex forming ability. The degree of cross linking is directly proportional to the number of substituents present. To obtain highly porous mesh type nanosponges, higher degree of cross linking is required.

Methods of preparation [3, 4, 15, 16, 17]

Emulsion Solvent Diffusion Method

In this method Ethyl Cellulose (EC) and Polyvinyl alcohol (PVA) are used in different proportions. The dispersed phase was prepared by dissolving ethyl cellulose and drug in 20 ml of Dichloromethane and slowly dissolves PVA in 150 ml of aqueous phase. The resulting reaction mixture was stirred at 1000 rpm for 2 hr. and nanosponges were collected by filtration. Filtered nanosponges were dried at 40 ^{0}C for 24 hr. Nanosponges were stored in the vacuum desiccator to remove the residual solvents. The flow chart of emulsion solvent diffusion method is given below-



Nanosponges prepared from hyper cross linked β-Cyclodextrins

Nanosponges were prepared by using different Cyclodextrin with carbonyl or di-carboxylate compound as cross-linking agents. The amount of Cyclodextrin used determines the drug loading capacity which will finally decides the drug release. In this method 100 ml of Dimethyl formamide and 17.42gm of anhydrous β-Cyclodextrin was taken in a round bottom flask and allow it to solubilize. To achieve the complete dissolution, add 9.96 g of carbonyl di-imidazole to the above mixture and allow to complete the reaction for 4 hr. at 100 ^{o}C. Excessive de-ionized water was added to remove Dimethyl formamide. The white powder thus obtained was dried in oven. The powder was then suspended in water and recovered. Different drug molecules can be encapsulated by controlling pore size, porosity and surface charge of sponges. Low cross linking nanosponges gives faster drug release.

Ultrasound assisted method

In this method nanosponges were synthesized by using polymers and cross-linking agents without solvent under sonication. Spherical and uniform sized nanosponges can be obtained by this method. Polymers and cross-linking agents are mixed in a flask with suitable proportion and place the flask in ultrasound water bath and heat to 90 ^{0}C. Sonicate

the mixture for 5-6 hr. and allow cooling. Wash the mixture with water to remove the unreacted polymer and again purify it with Soxhlet extraction using ethanol. The final product was dried under vaccum and stored at 25 ^{0}C. The process involving high energy input like probe sonication is alternative used for ultrasound method.

Loading of drug into Nanosponges

The mean particle size of nanosponges should be below 500nm which is obtained by pre-treatment. Nanosponges are suspended in water and sonicate the mixture to avoid agglomerations. The prepared nanosponges were suspended in the drug dispersion and freeze dried the mixture along with drug molecule. Allow the mixture for complexation under constant stirring for specific time interval. The uncomplexed drug was separated from above mixture by using centrifugation. Finally solid crystals of drug nanosponge complex were obtained by solvent evaporation or by freeze drying. Crystal structure of nanosponges affects the drug loading capacity; it is found that crystalline structure shows better complexation with drug molecule than Para crystalline form.

Characterization of Nanosponges

Porosity[18, 19]

The performance of the nanosponges is mainly depends on the Nanocavities and Nanochannels. The drug loading capacity of the nanosponge is affected by its porous structure. Hence to study the extent of nanocavities and nanochannels formed there is need to determine the porosity. Helium pycnometer is used to determine the porosity as helium is inert gas and has ability to penetrate inter and intra particular channels of material. By this method percent porosity is calculated by using following equation-

$$\% \text{ Porosity} = \frac{\text{Bulk volume} - \text{True volume}}{\text{Bulk volume}} \times 100$$

Zeta potential[20, 21]

The stability of the nanosponges can be estimated by means of zeta potential assessment. Zeta potential measures the surface charge of the system under characterization. The interaction with biological environment is affected by surface charge. Diffusion coefficient and electrophoretic mobility is calculated from either Smoluchowski equation or Stokes equation. While measuring the zeta potential two parameters need to be considered i.e., pH and electrolyte concentration. The nanosponge sample is first diluted with KCL solution and then place in electrophoretic cell having electric field of about 15V/cm.

Microscopy study[22]

To study the morphology of the Nanosponges i.e., particle size and shape scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are used. The formation of inclusion complex can be seen by this method. The difference in the crystallanity of raw material and final product was examined with the help of electron microscope. To study the moist sample ESEM can be used.

Particle size and polydispersity[23, 24]

Particle size analyzer is used to determine the particle size based on the principle of dynamic light scattering. Polydispersity index (PDI) shows distribution of the particles within sample. Lower value of PDI indicates monodisperse nature of the sample and higher value of PDI shows wider particle size distribution with polydisperse nature of sample.

X-ray diffraction study[16, 25]

X-ray diffractometer is used to detect the formation of inclusion complex in the solid state. Diffraction pattern of individual component, uncomplexed Nanosponges and inclusion complex is different. Crystalline material shows sharp peak in their diffraction pattern as compared to amorphous form. The complex formation may be indicated by

disappearance or shifting of the parent peak in diffraction pattern. When drug molecule is loaded into nanosponge, the crystalline nature of drug may be changed which is clearly observed in their diffraction pattern as disappearance or shifting of the sharp peak.

Fourier transform-infrared spectroscopy (FT-IR)[1, 2, 26]

The interaction between drug and polymer can be studied by IR spectroscopy. It is used to determine the presence of functional group which is unique characteristics of individual material. To understand the interaction FT-IR spectra of nanosponge, drug and drug loaded inclusion complex was taken. If the spectra of pure drug and drug loaded nanosponge differs largely then it is said to be there is interaction between drug and polymer used. It is one of the preformulation test to choose suitable polymer for selected drug candidate.

Differential scanning calorimetry (DSC)[4, 5]

It is used to predict any physiochemical interaction between the excipients in the formulation. It is one the tool to select chemically compatible material. If there is any interaction between the materials in the formulation then it is indicated in thermogram by appearance of one or more new peak or disappearance of one or more peaks corresponding to those of the material.

Loading efficiency[4, 6, 7]

It is used to determine the drug loading capacity into the nanosponges. In this method weighed amount of loaded nanosponge complex were dissolved in suitable solvent and then it is sonicated. The resultant solution was analysed by UV spectrophotometer or by HPLC method. The drug loading capacity is calculated by using given formula,

$$\text{Loading Capacity} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Applications of Nanosponges

Nanosponges are used as drug carriers in pharmaceutical formulations. It solves the problems like drug insolubility, instability and permeation. Generally, BCS class-II and class-IV drugs are loaded into the nanosponges to increase the solubility and stability of the drugs.

Solubility improvement[24, 27]

The presence of cross linking and Nano-cavities in structure allows variety of drug molecules for complexation and get solubilised in the cavities. The increased drug solubility was obtained because of decreased drug crystallanity. Formation of water-soluble complex is critical parameter which is mostly depends on the molecular dimension and conformation. It also enhances the permeability of poorly water-soluble drugs by increasing their solubility.

Sustained drug release[28]

Repeated administration of the dosage form is one of the major drawbacks of most conventional dosage form. To overcome this problem drug molecule is loaded into the nanosponge which releases the drug slowly over time.

Carrier for various molecules[10, 11, 12]

It is used as a carrier for delivery of various molecules like enzymes, proteins, peptides and biocatalyst. Delivery of such molecules via other systems creates a major problem of stability. This carrier system delivers such macromolecules across the biological membrane and targets them at site specific.

Delivery of gases[10]

Recent studies shows that Cyclodextrin based nanosponges were used for delivery of various gases which is used for diagnostic as well as treatment of various diseases. Oxygen loaded nanosponge has the ability to store and supply oxygen over time in condition called hypoxaemia.

Treatment of cancer[4, 9]

Chemotherapy of cancerous cells by using nanosponges as a drug carrier gives advantages over

traditional dosage form is that it delivers the drug at tumour site in large amount. Chemotherapy of cancer by other dosage forms kills the normal cells as well, so this problem can be overcome by means of nanosponges.

Antiviral applications[11, 12]

Many of the antiviral drugs such as zidovudine, saquinavir, acyclovir and interferon are delivered through nanosponges in the treatment of various diseases like HIV, HBV and HSV. It is also used to target the viruses that cause respiratory tract infections namely respiratory sinctial virus, influenza virus and rhinovirus.

Topical drug delivery[20, 21, 24]

The various categories of drugs including local anaesthetics, antibiotics and antifungal agents can be easily loaded into nanosponges for topical delivery. Major advantages of nanosponges as drug carrier for topical application are it reduces the side effects like skin irritation and rashes and provides sustained drug release at the targeted site.

Industrial uses[1, 2, 3]

The water used in pharmaceutical, electronic and number of power plants should be free from pollutants. It is used for purification of water by removal of dissolved organic matter from the water.

II. CONCLUSION

Nanosponges are novel drug carriers to improve the solubility and stability of drug molecules.[30] Both lipophilic and hydrophilic drugs can be loaded into nanosponges which releases the active molecule at targeted site in a controlled manner and thus improves bioavailability.[31]

The spherical shape and smaller particle size of the nanosponge allow delivering the drugs via oral, parenteral and topical route which improves the patient compliance. Side effects of the conventional dosage forms can be overcome by means of nanosponges.[3, 4]

III. REFERENCES

[1]. Shringirishi M, Prajapati SK, Alok M, Yadav P, Verma A. Nanosponges: a potential nanocarrier for novel drug delivery-a review. Asian Pacific Journal of Tropical Disease 2014; 4:519-526.

[2]. Shastrulagari S, Kranthy KP. Nanosponges - Novel emerging drug delivery system: a review. International journal of pharmaceutical sciences and research 2015; 6(2):529-540.

[3]. Bachkar BA, Gadhe LT, Mahajan N, Battase P, Wagh R. Nanosponges: a potential nanocarrier for targeted drug delivery. World Journal of Pharmaceutical Research 2014; 4(3); 751-768.

[4]. Gursalkar T, Bajaj A, Jain D. Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta Pharm. 2013; 63: 335–358.

[5]. Tamkhane V, Sharma PH. Nanosponge - A Novel Drug Delivery System. Journal of Current Pharma Research 2014: 4(3):1186-1193.

[6]. Ramnik S, Nitin B, Jyotsana M, Horemat SN. Characterization of Cyclodextrin Inclusion complexes –A Review. Journal of Pharmaceutical Sciences and Technology 2010; 2(3):171-183.

[7]. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. Nanosponges: a novel class of drug delivery system-review. Journal of Pharmacy and Pharmaceutical Sciences, 2012; 15(1): 103-111.

[8]. Nilesh J, Ruchi J, Navneet T, Brham PG, Deepak Kumar J. Nanotechnology : A Safe and Effective Drug Delivery Systems. Asian Journal of Pharmaceutical and Clinical Research, 2010; 3(3): 159-165.

[9]. Ramnik S, Nitin B, Jyotsana M, Horemat S N. Characterization of Cyclodextrin Inclusion Complexes – A Review. Journal of

Pharmaceutical Sciences and Technology 2010; 2(3): 171-183.

[10]. Rajeswari C, Alka A, Javed A, Khar RK. Cyclodextrins in drug delivery: an update review. AAPS pharm Sci Tech, 2005; 6(2): E329-E357.

[11]. Khalid AA, Pradeep RV, Francesco T, Roberta C. Cyclodextrin-based nanosponges for delivery of Resveratrol: In Vitro characterisation, stability, cytotoxicity and permeation Study. AAPS PharmSciTech, 2011; 12(1): 279-286.

[12]. Patel EK, Oswal RJ. Nanosponge and Microsponges: A Novel Drug Delivery System. IJRPC 2012; 2(2): 237-244.

[13]. Patel SB, Patel HJ and Seth AK. Nanosponge Drug Delivery System: An Overview. Journal of Global Pharma Tech 2010; 2(8):1-9.

[14]. Bolmal UB, Manvi FV, Kotha R, Palla SS, Paladugu A. Recent advances in nanosponges as drug delivery system. International journal of pharmaceutical sciences and nanotechnology 2013; 6(1):1934-1944.

[15]. Lala R, Thorat A, Gargote C. Current trends in β-cyclodextrin based drug delivery systems. International journal of research in Ayurveda and pharmacy 2011; 2(5):1520-1526.

[16]. Tejashri G., Amrita B., Darshana J., Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta Pharmaceutica, 2013; 63(3): 335-358.

[17]. Moya-Ortega M.D., Alvarez-Lorenzo C. Concheiro A., Loftsson T., Cyclodextrin-based nanogels for pharmaceutical and biomedical applications. International Journal of Pharmaceutics, 2012; 428: 152-163.

[18]. Cavalli R., Trotta F., Tumiatti W., Cyclodextrinbased Nanosponges for Drug Delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2006; 56: 209-213.

[19]. Thakre AR, Gholse YN, Kasliwal RH. Nanosponges: A novel approach of drug delivery system. Journal of medical pharmaceutical and allied sciences 2016; 78-92.

[20]. Jilsha G, Viswanad V. Nanosponges: A novel approach of drug delivery system. International journal of pharmaceutical sciences review and research2013; 19(2):119-123.

[21]. Ramnik S, Nitin B, Jyotsana M, Horemat S N. Characterization of Cyclodextrin Inclusion Complexes – A Review. Journal of Pharmaceutical Sciences and Technology, 2010; 2(3):171-183.

[22]. Jenning V, Schafer-Korting M, Gohla S. Vitamin A loaded solid lipid nanoparticles for topical use: drug release properties. Journal of controlled release, 1999; 66: 115-126.

[23]. Orlu M, Cevher E, Araman A., Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. International Journal of Pharmaceutics, 2006; 318:103-117.

[24]. Shankar G, Agrawal YK. Formulation and evaluation of β-cyclodextrin based nanosponges of a poorly water soluble drug. Journal of chemical and pharmaceutical research 2015; 7(4):595-604.

[25]. Tiwari H, Mahor A, Dixit ND, Kushwaha M. A review on nanosponges. World journal of pharmacy and pharmaceutical sciences 2014; 3(11): 219-233.

[26]. Mahajan AG., Jagtap LS. Chaudhari AL., Swami SP. Formulation and Evaluation of Microsponge Drug Delivery System using Indomethacin. International Research Journal of Pharmacy, 2011; 2(10): 64-69.

[27]. Cavalli R, Ansari K.A, Vavia P.R. Nanosponges formulations as oxygen delivery systems. International journal of pharmaceutics 2010; 402: 247-254.

[28]. Sharma R., Roderick B., and Pathak K., Evaluation of kinetics and mechanism of drug

release from Econazole nitrate Nanosponges loaded carbopol Hydrogel. Indian J of Pharma Edu and research, 2011; 45(1): 25-31.

[29]. Ansari K. A, Torne S. J, Vavia P. R, Trotta F, Cavalli R. Paclitaxel loaded nanosponges: in-vitro characterization and cytotoxicity study on MCF-7 cell line culture. Current Drug Delivery. 8(2): 2011; 194-202.

[30]. Vyas S.P., Khar R.K. Targeted and Controlled Drug Delivery- Novel Carrier Systems. Molecular Basis of Targeted Drug Delivery. CBS Publishers and Distributors. New Delhi. 2008: 38- 40.

[31]. D'souza J. I. The Microsponge Drug Delivery System: For Delivering and Active Ingredient by Controlled Time Release. Pharma info.net 2008; 6(3): 62.

Cite this article as :

G. J. Dhumal, A. S. Kulkarni, K. K. Bandal, R. H. Dambe, V. R. Thorat, T. T. Patil, K. K. Dhayagonde, "NANOSPONGES : A New Approach for Drug Delivery System", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 9 Issue 6, pp. 170-178, November-December 2022. Available at doi : https://doi.org/10.32628/IJSRST229617
Journal URL : https://ijsrst.com/IJSRST229617