Cyclodextrin Based Nan sponges: A Propitious Platform for Enhancing the Solubility of Poorly Water-Soluble Drug.

[1]Sadhana Dhanraj Mane,[2] DR.A.H Hosmani, [3]Megha Mane, [4]Vinanti Mudgal,[5] Prajkta Waghmare

[1] Reserch student, [2]Assistant professor
Department of pharmaceutics
Government College of Pharmacy, Karad, Maharashtra, India

***ABSTRACT*: The low aqueous solubility of many useful drugs is a current issue in the pharmaceutical industry. Before a new drug can be approved for the market, it must undergo extensive research and testing. The aqueous solubility of a drug is one of the factors that determine its efficacy because it is not easily absorbed by the body. The hydrophobic nature of the drug contributes to its low aqueous solubility. To overcome the challenge of drug insolubility, many methods have been developed. Because cyclodextrins are nontoxic to humans, cyclodextrin-based nanosponges have been used in pharmaceutical and biomedical applications. The use of beta-cyclodextrin as a drug carrier to improve the solubility of poorly soluble drug is the focus of this paper. Under an optical microscope, the product obtained in these conditions has a peculiar morphology; it is made up of spheroidal particles with regular dimensions smaller than 5 microns. The individual particles' spherical shape is a requirement for the polymer to be used in advanced and innovative pharmaceutical applications.**

Index term: Beta-cyclodextrin, Cyclodextrin-based carbonate nanosponge, Cyclodextrin-based carbamate nanosponges, Cyclodextrin-based ester nanosponges.

1. INTRODUCTION:

The major challenges faced by drug development industry are; low solubility and low permeability and sustained release technology for reducing irritation of a wide range of APIs thereby increasing patient compliance and result. Enhanced formulation stability ensuring long term product efficacy and extended shelf life. Also targeting the drug delivery has long been a problem for medical researchers perhaps how to get them to the right place in body and how to control the release of the drug to prevent overdose. The development of new and complex molecules called nanosponges has the potential to solve these problems. Nanosponges are new class of materials, made of microscopic particles with few nanometres' wide cavities, in which large variety of substance can be encapsulated. These particles can transport both lipophilic and hydrophilic substances while also increasing the solubility of poorly water-soluble molecules. The nanosponges delivery system is a one-of-a-kind technology for controlling the release of topical drugs, extending drug release and drug form retention on the skin. Anaesthetics, antifungals, and antibiotics are examples of drugs that are easily formulated into topical nanosponges. When the active ingredient enters the skin, it may cause a rash or other serious side effects. This technology, on the other hand, allows for increased solubility and a more uniform, sustained release rate, reducing irritation while maintaining efficiency. [1]

Even when a substance has interesting pharmacodynamic properties, its solubility is a factor that prevents its use in therapy. As a result, new strategies for improving the solubility and kinetics of active ingredient release are being researched more and more. Various formulation approaches, such as the use of cosolvents, surfactants, particulate systems, and complexes, are used in the pharmaceutical industry to improve solubility. One of the most incredibly interesting approaches is the use of inclusion complexes (active ingredient and cyclodextrin). Cyclodextrins (CD) are non-reducing cyclic oligosaccharides with a truncated cone structure formed by 6-8 glucose molecules bonded with a 1,4-a-glucosidic bond. The glucose molecule's functional groups are arranged in such a way that the molecule's surfaces are polar while its internal cavity is lipophilic. Nanosponges are typically made from beta-cyclodextrin because it has the highest complexing ability and stability with crosslinking agents of the three cyclodextrins (alpha, beta, and gamma). Beta-CD has interesting properties that can be tuned to form nanochannels in which drugs can be incorporated, as well as its complex network. Moreover, cavity dimension, low production cost, and higher productivity rates are some of the benefits provided by beta-CD for the preparation of nanosponges. Beta-CD is more water soluble (1.85g per 100cm3) than alpha-CD (14.5g per 100cm3) and gamma-CD (23.2g per 100cm3). Furthermore, beta-CDNS may represent a new avenue for controlling the amount of dosage frequency and the delivery site of antivirus delivery.

These complexes can be used in pharmaceutical technology to increase the speed of dissolving, drug solubility, mask unpleasant taste, or convert liquid substances into solids. [2]

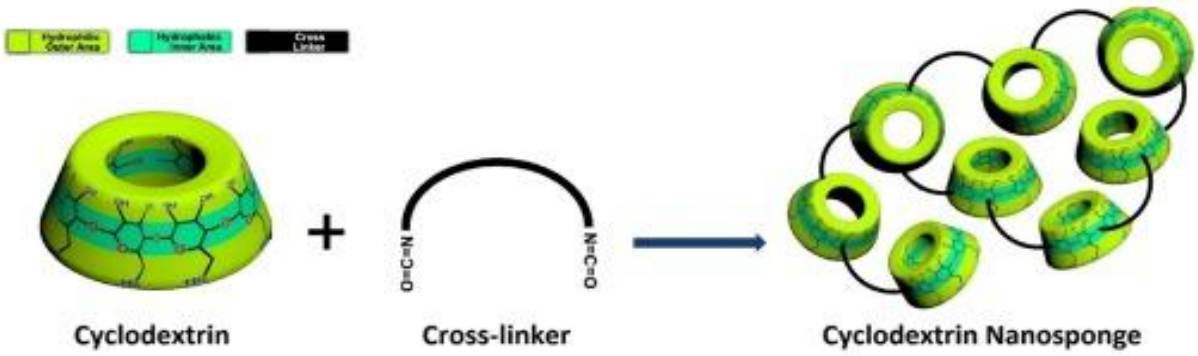


Fig- cyclodextrin based nanosponges. [3]

2. Characteristics features of nanosponges-

1) Nanosponges exhibit a range of dimension (1nm or less) with tuneable polarity of the cavities.
2) They could be either para-crystalline or in crystalline form, depending on the process conditions.
3) Crystal structure of nanosponges play a very important role in their complexation with drug. The drug loading capacity of nanosponges mainly depends on the degree of crystallisation.
4) They are nontoxic, porous particles insoluble in most organic solvent and stable at high temperature up to 300^0c.
5) Nanosponges as formulation are stable over the ph. range of 1to 11 and temperature up to 130^0c.
6) They form clear and opalescent suspension in water and can be regenerated by simple thermal desorption, extraction with solvents, by the use of microwave and ultrasounds.
7) They can be targeted to different sites due to their ability to be linked with different functional groups. Chemical linkers enable nanosponges to bind preferentially to the target site. They form inclusion and non-inclusion complex.

3. Advantages of nanosponges

1. This technology provides entrapment of active contents and less harmful Side effects since smaller quantities of the drug have contact with healthy tissue.
2. Non-irritating, non-toxic.
3. Drug is protected from degradation.
4. Excipients are biodegradable and scale-up for commercial production is easier.
5. Therapeutically, it provides faster onset of action and formulation are cost effective.
6. Particles can be made smaller or large by varying the proportion of cross-linker to polymer.

4. OBJECTIVES:

1. Increase the solubility of the drug.
2. To control the release of drug.
3. To characterise the nanosponges for physical and chemical properties.
4. To improve the efficacy, drug loading capacity and biocompatibility of drug by formulating in nanosponges.
5. To minimize the toxicity and increase the stability of drug by encapsulating in nanosponges system.

5. Types of beta-cyclodextrin based nanosponges;

TYPES OF NANOSPONGES	CROSSLINKERS	METHOD	ENCAPSULATED DRUG
Cyclodextrin carbonate nanosponge	Diphenyl carbonate, carbonyl diimidazole, dimethyl carbonate	Solvent extraction, thermal desorption	L-DOPA, telmisartan, curcumin, reservertol, tamoxifen,itraconazole

Cyclodextrin carbomate nanosponges	Hexamethylene diisocynateand toluene diisocynate	Solvent method	Steroids, dyes and naringin, dextromethorphan
Cyclodextrin anhydride nanosponges	Pyromellitic dianhydride,	Solvent method	Ibuprofen doxorubicin, meloxicam, acetylsalicylic acid and strigolactones
Epichlorohydrin cyclodextrin nanosponges	epichlorohydrin	Solvent method	Creatinine, cilazapril captopril andenalpril

Depending on the crosslinker used, there are several types of cyclodextrin nanosponges:

1) Cyclodextrin-based carbamate nanosponges: In the presence of DMF solution, CDs are reacted with suitable diisocyanates such as hexamethylene diisocyanate (HDI) and toluene-2,4-diisocyanate (TDI) at 70 °C for 16 to 24 hours under a nitrogen atmosphere. By thoroughly washing with acetone, residual DMF is removed, and powder of the crosslinked polymer is obtained. These nanosponges can bind to organic molecules and have been widely used in water purification. Nitrophenol, for example, is removed from its water solution even at very low concentrations. Organic molecules have a loading capacity ranging from 20 to 40 mg per cm3. Nanosponges have the ability to remove up to 84 percent of dissolved organic carbon (DOC) from waste water. They are used to remove undesirable taste and odorous compounds from water because of this property. CD-based carbamate nanosponges have successfully removed compounds such as geosmin and 2-methylisoborneol. [4]

2) Cyclodextrin-based carbonate nanosponges: Nanosponges improve the wetting and solubility of these poorly water-soluble drugs in particular. Carbonate nanosponges have no discernible effect on water surface tension. They are non-hygroscopic and retain their crystal structure during moisture absorption and desorption. (3) A distinguishing feature of CD-based carbonate nanosponges is that their ability to improve solubility is highly dependent on crystallinity. For example, crystalline nanosponges improve the solubility of the well-known anticancer drug dexamethasone fourfold, whereas amorphous nanosponges improve the solubility of the widely used antiviral compound acyclovir twice as much. [5]

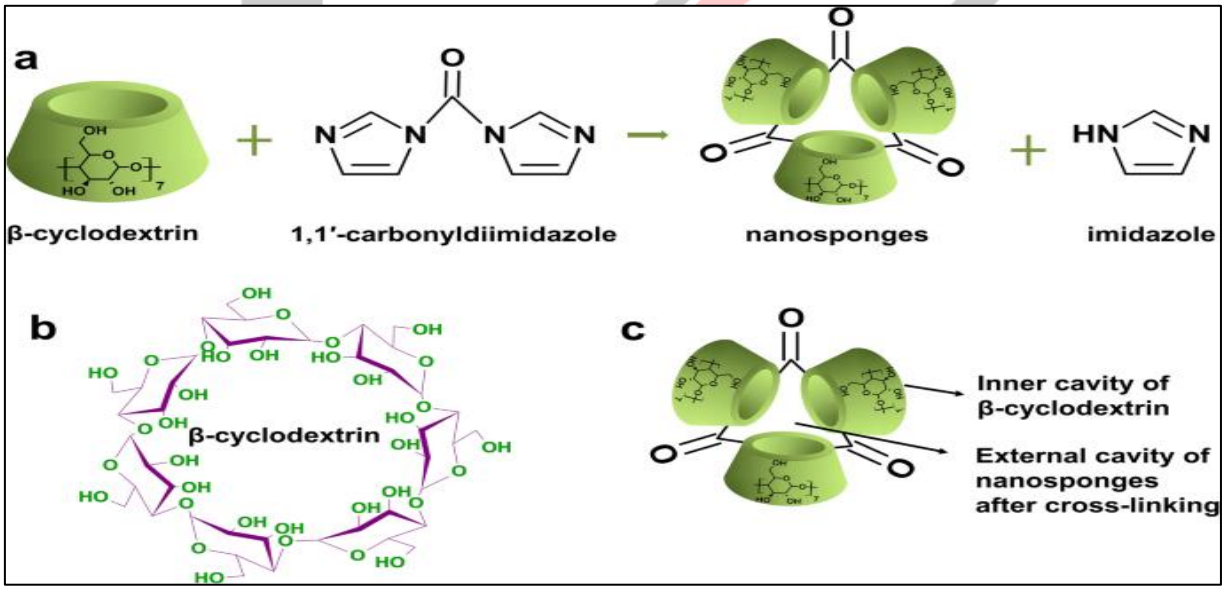
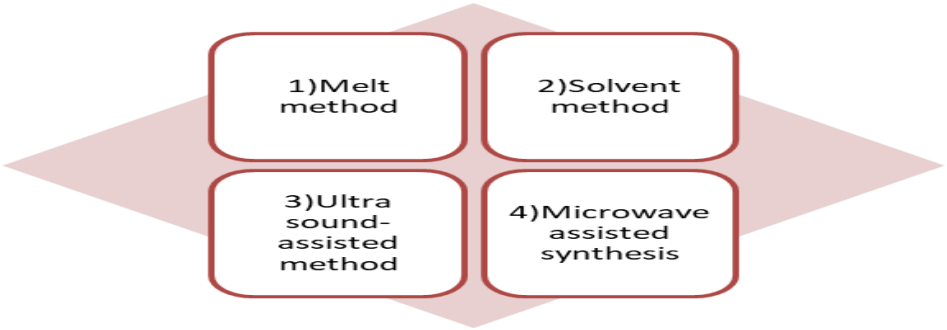


FIG.2-Beta-cyclodextrin carbonate nanosponges [6]

3) Cyclodextrin-based ester nanosponges:For the fabrication of these nanosponges, a suitable dianhydride, such as pyromellitic anhydride, is used as a crosslinking agent. The exothermic crosslinking reaction is very fast (completed in a few minutes) and takes place at room temperature, with the CD and dianhydride dissolved in DMSO in the presence of an organic base such as

pyridine or triethylamine (to accelerate the reaction in a forward direction). Because it contains a polar free carboxylic acid group, this type of nanosponge can host both apolar organic molecules and cations at the same time. [7]

6. Method of preparation of cyclodextrin nanosponges-



1) Melt method: In a nutshell, the crosslinking agent is melted with cyclodextrin, and all components are homogenised and heated at 1000 degrees Celsius with magnetic stirring for 5 hours. The matrix above is then allowed to cool. Bathing is done frequently to remove by products and unreacted components.

2) Solvent evaporation technique: The fusion step is avoided in the solvent evaporation method, and solvents such as dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) are used to solubilize the cross-linking agent. Polymer is mixed with solvent (polar aprotic), and the resulting mixture is placed in a cross-linker solution and refluxed for 1–48 hours. The product is made by adding cold solution to a large surplus of distilled water. Finally, filtration is performed to recover the final product, which is purified for extended periods of time using Soxhlet extraction. By using either a non-inclusion or inclusion mechanism, spherical and solid nanostructures with high water solubility are produced. High pressure homogenization, in which a water suspension of prepared nanosponges is homogenised at a constant speed, can reduce the size of nanosponges. [6,7,8]

3) Ultrasound-assisted fabrication: in this method cyclodextrins are first reacted with crosslinking agents without the use of solvents under ultrasound. Anhydrous-CD and DPC are placed in a vial and sonicated for 5 hours in an ultrasound bath that has been pre-filled with water (at 90°C). In addition, the crystallisation and purification steps are identical to those used in solvent evaporation and melt technique.

4) Microwave assisted synthesis: Microwave irradiation is the simplest method for synthesising cyclodextrin based nanosponges, and it significantly reduces reaction time. The nanosponges that results have a higher crystallisation degree. Microwave assisted fabrication showed a reduction in reaction time when compared to the traditional melt method. Particle homogeneous distribution and crystallinity were produced as a result of the process. [9]

7. Drug loaded into blank nanosponges: By dispersing the active moieties within the drug dispersion and then freeze drying them, the active moieties are entrapped into the nanopores of blank nanosponges. Another method for loading active moieties into nanosponges that has been reported is solvent evaporation, which uses organic solvents suitable for dissolving the active moiety. Finally, the prepared active moiety dispersion is triturated with nanosponges until the solvent evaporates.

8. Application of beta-CD nanosponges: Solubility enhancement through the use of cyclodextrin nanosponges One of the most pressing issues in the pharmaceutical industry is increasing the solubility of active ingredients that have low solubility in aqueous fluids such as physiological liquid. New strategies, such as cyclodextrin-based nanosponges, are being investigated to improve the solubility of poorly soluble drugs.

Many drugs' low water solubility is one of the most significant barriers to their development. The formulation of poorly water-soluble drugs constitutes a problem that is difficult to solve. Many technological approaches have been investigated. The ability of cyclodextrins to form inclusion complexes with various molecules is widely used in the pharmaceutical field as a strategy to increase the aqueous solubility and, consequently, bioavailability of lipophilic drugs. For hydrophilic or moderately polar drugs this approach is less effective, and consequently cyclodextrin derivatives have been investigated. Nanosponges can improve the wetting and solubility of molecules with very poor solubility in water. Around 40% of new drugs are poorly soluble in water, limiting their clinical application. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Many formulation and bioavailability problems can be solved by enhancing the solubility and dissolution rate of a substance, and nanosponges can greatly enhance the drug solubility.

Some examples of improving the solubility of drug:

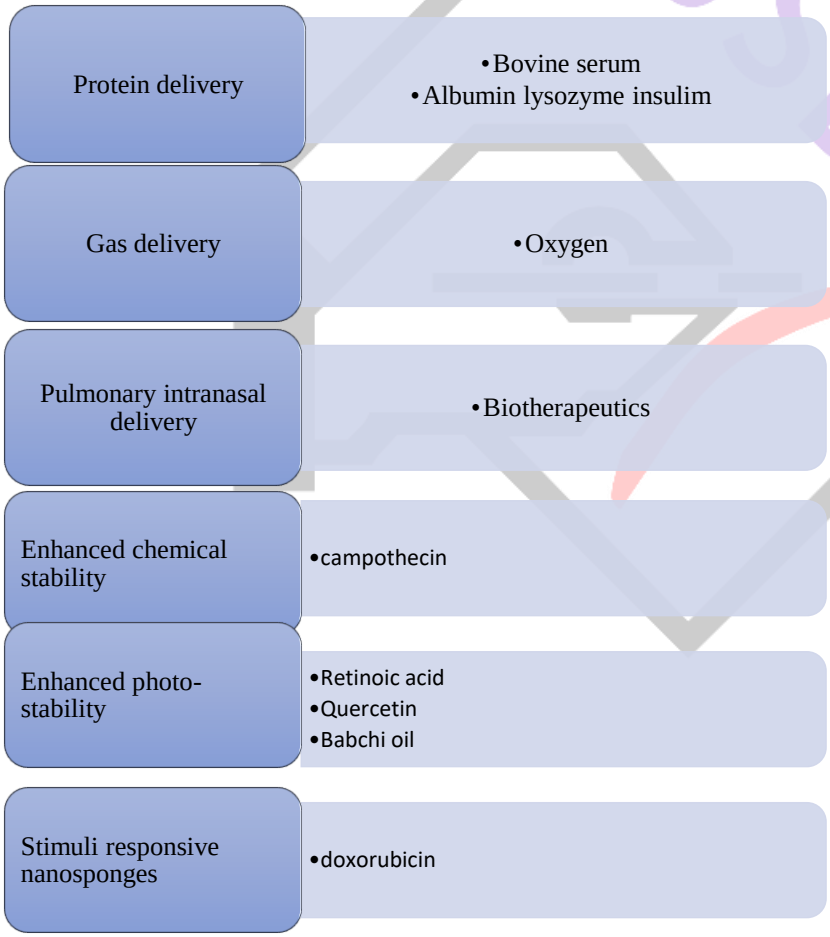
a) β-CD nanosponges were used to overcome low solubility of Dexibuprofen which may increase bioavailability and therapeutic action. [10]

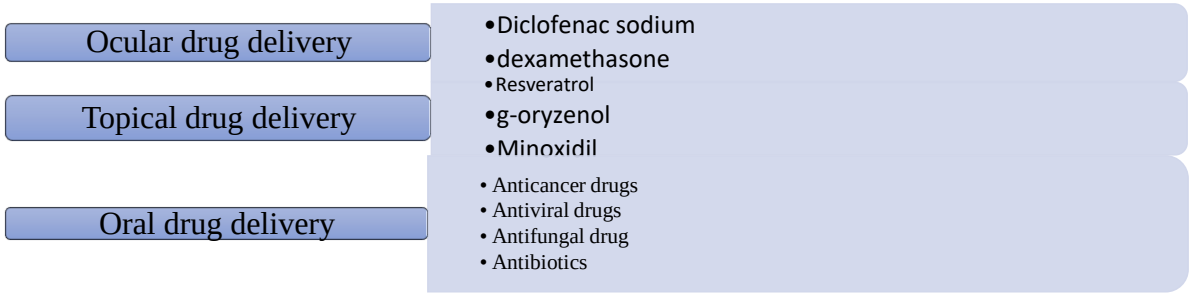
b) The solubility of kynurenic acid was significantly increased with nanosponge (111.1 µg/ml) compared to free kynurenic acid (16.4 µg/ml) and β-cyclodextrin (28.6 µg/ml). High drug loading (19.06%) and encapsulation efficiency (95.31%) were achieved with NS. The particle size and zeta potential of kynurenic acid loaded nanosponge was around 255.8 nm and -23 mV respectively. Moreover, higher solubilization of kynurenic acid loaded nanosponge produced better antioxidant activity compared to free kynurenic acid. [11]

c)A carbonate nanosponge based on cyclodextrin (CD) was used to improve ibuprofen solubility and dissolution. Solvent and ultrasound assisted methods were used to prepare nanosponges using two CDs (β-CD and 2-hydroxypropyl-β-CD (2HP-β-CD)) and a cross-linker (CL) diphenyl carbonate (DPC) in varying molar ratios. Nanosponges were studied for solubilizing efficiency and phase solubility. [12]

d)Rilpivrine is a BCS class II antiretroviral drug used to treat HIV infection. Because of its low aqueous solubility (0.0166 mg/ml) and dissolution rate, the drug's bioavailability is low (32%). The goal of this study was to use beta-cyclodextrin-based nanosponges to improve rilpivrine solubility and dissolution. These nanosponges are biocompatible nano porous particles with a high loading capacity that can form supramolecular inclusion and non-inclusion complexes with hydrophilic and lipophilic drugs to improve their solubility. To make nanosponges, beta-cyclodextrin was crosslinked with carbonyl diimidazole and pyromellitic dianhydride. [13]

e) Ellagic acid (EA) is a polyphenolic compound found naturally in a variety of fruits. It has anticancer, antimutagenic, and antioxidant properties. Its low oral bioavailability and therapeutic potential are attributed to its low aqueous solubility and permeability in the GI tract, permanent binding to DNA and proteins of cells, and first pass metabolism. Ellagic acid solubilization efficiency and release control have been improved using cyclodextrin-based nanosponges. [14]





CONCLUSION- Cyclodextrin nanosponges have unique properties in terms of encapsulation, biocompatibility, and solubilization capacity with respect to various types of molecules. It is possible to conclude that cyclodextrin-based nanosponges are a novel class of biocompatible, versatile crosslinked polymer that significantly improves the solubility and performance of their parent cyclodextrin. The particle size and release rate can be modulated to better suit the application by adjusting the polymer to cross-linker ratio. They have the potential to improve the aqueous solubility of lipophilic drugs while also protecting the active moieties from physiological degradation.

REFRENCE:

[1] G. Utzeri, M. Matias P, D. Murtinho, Valente A J M, "Cyclodextrin based nanosponges: overview and opportunities". J frontiers in chemistry, vol. 10, March2020.

[2] K. Sunil, D. Pooja, R.Rekha, "Cyclodextrin Nanosponges: A promising approach for modulating drug delivery". Colloid science in pharmaceutical nanotechnology, December2019.

[3] S. Atul, D. Bhushan, K. Darshana, J. Mrunal, "Cyclodextrin-based nanosponges: A critical review". J carbohydrate polymer, Vol.173, pp.37-49, May 2017.

[4] G. Tejashri, B. Amrita, J. Darshan, "Cyclodextrin based nanosponges for pharmaceutical use". Acta pharmaceutica, Vol.63, pp.335-358, September 2013.

[5] R. Cavalli, F. Trotta, W. Tumiatti, "Cyclodetrin based nanosponges for drug delivery". J of inclusion phenomenon macrocyclic chemistry. Vol.56, pp.209-213, March 2006.

[6] G. Yasayan, B. Saritroglu, E. Tatar, "Fabrication and characterisation studies of cyclodextrin-based nanosponges for sulfamethoxazole delivery". J incl phenom macrocycl chem. Vol.97, pp.175-186, June 2020.

[7] L. Rita, T. Amit, G. Chandrashekhar, "Current trends in b-cyclodextrin based drug delivery system". International J of research in ayurveda and pharmacy. Vol.2, pp.1520-1526, May 2011.

[8] F. Trotta, W. Tumiatti, "Cross-linked polymers based on cyclodextrin for removing polluting agent". United states patent application US. Vol.10, pp.510-792, April 2002.

[9] F. Trotta, R. Cavalli, "Characterisation and application of new hyper crosslinked cyclodextrin". J composite interfaces. Vol.16, pp.39-48, February 2009.

[10] C. Sai, P. Priti, J. Kisan, G. Gajendra, K. Vilasrao. "Cyclodextrin based nanosponges: a propitious platform for enhancing drug delivery. J Expert opinion on drug delivery. Vol.11(1), pp.111-120, January 2014.

[11] S. Anandam, S. Selvamuthukumar. "Cyclodextrin based nanosponges to enhance the dissolution profile of quercetin by inclusion complex formation". J Particulate science and technology. Vol.34(3), pp.341-346, December 2015.

[12] K. Qandeel, A. Mahmood, M. Muhammad, B. Fakhra, M. Nadia, R. Mubashar, "Novel β-cyclodextrin nanosponges by chain growth condensation for solubility enhancement of dexibuprofen: characterisation and acute oral toxicity studies. J of drug delivery science and technology. Vol.61, February 2021.

[13] D. Nilesh, C. Fabrizio, B. Federia, C. Clavdio, P. Alberto, C. Roberta, D. Chiara, T. Francesco. "Evaluation of solubility enhancement, antioxidant activity and cytotoxicity studies of kynurenic acid loaded cyclodextrin nanosponges". J carbohydrate polymer. Vol.224, pp.115-168, November 2019.

[14] S. Qurat, L. Sumera, I. Qozi, A. Hafsa, S. Muhammad, H. Amjad, A. Muhmmad, S. Nadeem, A. Nasir. "Solubility and dissolution rate enhancement of ibuprofen by cyclodextrin based carbonate nanosponges". Pakistan j of pharmaceutical sciences. Vol.34(3), pp.1045-1055, May2021.

[15] P. Rao, J. Chaudhari, F. Trotta, F. Caldera. "Investigation of cyclodextrin based nanosponges for solubility and bioavilability enhancement of rilpivirine". AAPS pharmscitech. Vol.19(5), pp.2358-2369. July2018.

[16] M. Fatma, R. Sabrin, I. Mohamed. "Cyclodextrin based nanosponges for improvement of solubility and oral bioavailability of ellagic acid. Pakistan journal of pharmaceutical science". Vol.31, pp.2069-2076, September2018.

[17] M. Preeti, W. Balaji, W. Pravin, "Cyclodextrin based nanosponges: A multinational drug delivery system and its biomedical application". Current drug delivery. Vol.18, pp.1467-1493, April2022.

[18] A. Khalid, V. Pradeep, T. Francesco, C. Roberta. "Cyclodextrin-based nanosponges for delivery of resveratrol; in vitro characterisation, stability, cytotoxicity and permeation study". American association of pharmaceutical science. Vol.12, pp.279-286. March2011.

[19] A. Vishwakarma, P. Nikam, R. Mogal, S. Talele. "Nanosponges; A benefication for novel drug delivery". International journal of pharmatech reserch. Vol.6, pp.11-20. March2014.

[20] S. Prathima, K. Sreeja. "Formulation and evaluation of voriconazole loaded nanosponges for oral and topical delivery. International journal of drug development and research. Vol.5, pp.206-211, March2013.