HARNESSING DESIGN EXPERT FOR PIROXICAM NANOSPONGES FORMULATION AND ITS EVALUATION

Priyanka A. Bobade*[1], Kiran B. Dhamak[2], Vikas D. Kunde[3], Vinayak M. Gaware

1. Department of Quality Assurance, PRES's College of Pharmacy (For Women), Chincholi, Nashik
2. Department of Quality Assurance, PRES's College of Pharmacy (For Women), Chincholi, Nashik
3. Department of Pharmaceutics, PRES's College of Pharmacy (For Women), Chincholi, Nashik

Corresponding Author: Dr. Kiran B. Dhamak
PRES's College of Pharmacy (For Women), Chincholi
Sinnar, Nashik

Abstract

An Innovative idea for a medication delivery system is the nanosponges. In order to improve the drug's bioavailability and release it in a controlled and sustained manner, the current study set out to create and characterize the best stable nanosponges of piroxicam using the emulsion solvent diffusion method. The emulsion solvent diffusion method was utilized to prepare the nanosponge, employing distinct drug-polymer ratios such as ethyl cellulose, polyvinyl alcohol, and dichloromethane. FTIR, or Fourier transform infrared spectroscopy, was used to estimate Piroxicam's compatibility with polymers. Preformulation parameters were assessed for the prepared nanosponges. All batches of the nanosponges formulations were assessed for entrapment efficiency and production yield. The drug and other excipients do not interact chemically or physically, according to the results of the FTIR analysis. Several mathematical models were fitted to the in vitro release study data. In conclusion, the formulation and evaluation of Piroxicam nanosponges present a promising strategy for overcoming the limitations associated with poorly soluble drugs.

Keywords: *Piroxicam, Nanosponges, Polymer, NSAID, Emulsion solvent diffusion*

INTRODUCTION

A new class of materials known as nanosponges is composed of tiny particles with chambers that are only a few nanometers across and can contain a wide range of chemicals. These particles have the ability to convey hydrophilic and lipophilic compounds, as well as to increase the solubility of molecules that are not very water soluble. According to preliminary trials, this

method may be up to five times more effective than conventional methods at delivering breast cancer drug. Nanosponges are microscopic structures that resemble mesh and have the potential to revolutionize the treatment of numerous diseases. [1] [2]

The nanosponge has a naturally degradable polyester scaffold structure serving as its backbone, and it is roughly the size of a virus. With the help of tiny molecules known as cross-linkers, which have a preference for particular polyester segments, the long polyester strands are mixed in solution. The polyester segments are cross-linked to create a spherical shape with numerous pockets, or cavities, for storing medicines. Because the polyester degrades reliably in the body, the medication can be delivered according to a predetermined schedule. [3]

The drug molecules are contained within the center of the encapsulating nanoparticles, or nanosponges. The three types of nanoparticles encapsulating, complexing, and conjugating can be distinguished based on how they associate with medications. Nanosponges and nanocapsules serve as symbols for the first type. Drug molecules are carried by sponge-like nanoparticles called alginate nanosponges, which have numerous holes and resemble sponges.

ADVANTAGES

1. Boost the drugs water solubility in aqueous solutions.
2. Drug molecules can be released by nanosponges in a predictable manner.
3. Microorganisms cannot pass through the nanosponges minuscule 0.25 µm pore size, which makes them function as self-sterilizers.
4. The drug delivery systems utilizing nanosponges are non-toxic, non-mutagenic, and non-irritating.
5. The body may eliminate poisonous and venomous substances with the aid of nangsponges.[7]
6. The medicine delivery technique of nanosponges minimizes adverse effects.
7. Improve and strengthen formulation stability. The adaptability of the Lessen the frequency of doses.
8. Increased adherence from patients.
9. Complexes of nanosponges are stable at temperatures up to 130 °C and over a broad pH range (Le. 1-11). [8][9]
10. Nano sponges show good compatibility with nearly all of the formulation's ingredients and vehicles.

DISADVANTAGE

1. While nanosponges can encapsulate small molecules, they are not appropriate for bigger compounds.
2. Occasionally, there may be dose dumping. [10]

MATERIALS AND METHODS

Piroxicam was obtained as Gift sample. Polyvinyl alcohol, Ethyl cellulose and Dichloromethane were obtained from Molychem Pvt. Ltd.,Mumbai.

METHODS:

Production of nanosponges by emulsion solvent diffusion method involves varying the ratio of ethyl cellulose and speed of rotation. Two phases that is the dispersed phase and the continuous phase are prepared separately. The dispersed phase is prepared by dissolving ethyl cellulose and the piroxicam in 20 ml of dichloromethane.200 mg of polyvinyl alcohol is dissolved in 100 ml of water by using a magnetic stirrer (continuous phase).Then dispersed phase was added drop wise in the continuous phase. The mixture is continuously stirred for 4 hours using a magnetic stirrer at different RPM as per formulation batches. The nanosponges formed were collected by filtration and dried in oven at 40°c for about 24 hours. The nanosponges were then kept in the vacuum desiccators to remove the residual solvent till further use.[54]

METHODOLOGY

1. Preformulation study:

A. Drug Characterization

i. **Colour:** A little amount of Piroxicam was taken in butter paper and examined under well lighted area.
ii. **Odour:** Small amount of Piroxicam sample was smelled to get the odour.
iii. **Appearance:** A pinch of Piroxicam was taken between two fingers and appearance was observed.

B. Determination of melting point:

The sample's melting point serves as the initial indicator of its purity. Melting point of Piroxicam was performed by open capillary method. Piroxicam was taken in a glass capillary whose one end was sealed by flame. The capillary was then placed inside the melting point apparatus and melting point was noted.

C. Solubility study:

The solubility of Piroxicam was determined in various solvents. In a test tube 10 ml of required solvent was transferred and 20 mg of Piroxicam was added to the solvent. The mixture was then sonicated for 10min and observation was done for the particles remain if any.

D. UV-visible spectrophotometric analysis:

UV spectroscopy: The UV spectrum of Piroxicam was obtained. Shimadzu, A11454500 Spectrophotometer and spectra manager software was used for analysis. Methanol was used as solvent to prepare dilutions.

Method: 10 mg of Piroxicam was dissolved in 10 ml of solvent (methanol) to produce 1000 µg/ml. From this prepared solution 0.2 ml of sample was taken and further diluted with methanol up to 10ml to produce 20 µg/ml sample and spectra was observed.

Calibration Curve preparation:

Solution A: From stock solution 1ml of sample was withdrawn and diluted up to 10ml with solvent (methanol) to produce 100 µg/ml.

Dilutions: From solution A 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml solution were withdrawn and diluted up to 10ml with solvent (methanol) to produce 5 ppm, 10 ppm, 15 ppm, 20 ppm and 25 ppm and absorbances were measured at 325 nm.

E. FT-IR of Piroxicam:

The IR spectrum of Piroxicam was recorded on Perkin Elmer Spectrum one. Spectrum was recorded by using potassium bromide (KBr) as blank, at a resolution of 4 cm over a range 400-4000 cm. The peaks in the spectrum of Piroxicam were compared with the principle peaks of the IR spectrum reported in the monograph.

2. Drug excipient compatibility study:

Drug excipient compatibility studies represent an important phase in drug development. Drug substances are usually combined with the excipients which serve different and specialized purpose. Excipients are pharmacologically inert, but given the right conditions they can undergo chemical reactions and physical interactions with drug molecules under favorable environmental conditions. Compatibility test on drug excipient have been used to approve or reject excipients for use in pharmaceutical formulation. The API alone and with individual excipients were taken in different ratios and mixed well. Passed through sieve, the blend was filled into the glass vials and kept in stability chamber at 40± 2°C/75 ± 5%RH.

3. Preparation of nanosponges by Emulsion solvent diffusion method

4. Factorial Design model:-

In order to formulate stable nanosponges, 3^2 full factorial design was applied to the formulation that showed the satisfactory results to see the effect of varying the concentrations of variables such as Speed of rotation (X1) and Concentration of polymer (Ethyl cellulose) (X2) on responses like particle size and entrapment efficiency. The levels of two factors were selected on the basis of studies carried out before implementing the experimental design. .[62]

Table No.1: Factorial design for Nanosponges

Factor	**Levels**		
Independent variables	**Lower level**	**Medium level**	**Higher level**
Speed of rotation	1400	1600	1800
Drug: Ethyl cellulose ratio	1:1	1:1.5	1:2
Responses			
Particle size (nm)	Lowest		
Entrapment efficiency (%)	Highest		

5. Evaluation procedures:

1. Physical examination:[63]

i. **Color:** A little quantity of nanosponges was taken on a glass slide and examined in well lighted area.

ii. **Odor:** Adequate quantity of nanosponges was smelled to get the odour.

iii. **Appearance:** Quantity of nanosponges was taken in between two fingers and appearance was experienced.

2. Practical yield :[64]

The practical yield of nanosponges was determined using the weight of the dried finished product with respective to the initial weight of the drug and polymer used to make the nanosponges. The following equation was used to determine the practical yield.

$$\text{Practical yield} = \frac{\text{Practical weight of nanosponges}}{\text{Theoretical weight of (Drug + Polymer)}} \text{ X 100}$$

3. Entrapment efficiency:

To calculate the entrapment efficiency accurately weighed quantity of nanosponges (10 mg equivalent of piroxicam) with 5 ml of methanol in a volumetric flask was shaken for 1 min using

vortex mixer. The volume was made up to 10 ml with methanol. Then the solution was filtered, diluted and the concentration of piroxicam was determined spectrophotometrically at 325 nm.

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \text{ X 100}$$

4. In vitro release study: [65]

Drug release was determined by dialysis method. 100 mg of each formulation was poured into dialysis bags and put into 25 ml phosphate buffer (pH 6.8 pH) and stirred (100 rpm, room temperature). At predetermined time intervals, 1 ml of aliquot was taken and then substituted by fresh phosphate buffer. Finally, suitable dilution was made with methanol and the amounts of released piroxicam in phosphate buffer were measured by spectrophotometer at 325 nm. Aliquots withdrawn were assayed at each time interval for the drug released at λ max of 325 nm using UV-Visible spectrophotometer by keeping methanol as blank and the amount of released drug was estimated by the standard curve.

5. Particle size determination:[66]

The average mean diameter and size distribution of loaded nanosponges was determined by Dynamic Light Scattering method using Malvern zeta sizer at 25°c. The dried nanosponges were dispersed in water to obtain proper light scattering intensity for piroxicam nanosponges.

6. Determination of zeta potential:[67]

Zeta potential is a measure of surface charge. The surface charge (electrophoretic mobility) of nanosponge can be determined by using Zeta sizer (Malvern Instrument) having zeta cells, polycarbonate cell with gold plated electrodes and using water as medium for sample preparation. It is essential for the characterization of stability of the nanosponges.

RESULT & DISSCUSION

1. Preformulation study:

A. Drug Characterization:

Drug characterization parameters such as colour, odour and appearance were analysed for the procured drug samples and the results were shown in table 2.

Table No.2: Drug characterization parameters

Colour	Off-White

Odour	Characteristic
Appearance	Fine powder

B. Determination of melting point:

The melting point of Piroxicam was found to be in the range of **196-198** **ºC** which comply with reported melting point of Piroxicam.

C. Solubility study:

The solubility study of Piroxicam was carried out by using different solvent systems as per the literature. The solubility results were shown in table 3.

Table No.3: Results for solubility study

Sr.no	Solvent	Observation
1.	Methanol	Soluble
2.	Dimethyl sulfoxide	Soluble
3.	Dichloromethane	Soluble
4.	Water	Insoluble

D. UV-visible spectrophotometric analysis:

The UV-visible spectrophotometric analysis was carried out by using Shimadzu, A11454500 Spectrophotometer and spectra manager software was used for analysis. Methanol was used as solvent system for determination of λ_{max}. 20 µg/ml of Piroxicam sample was used and λ_{max} was found as 325 nm. The spectra for results were expressed in figure.

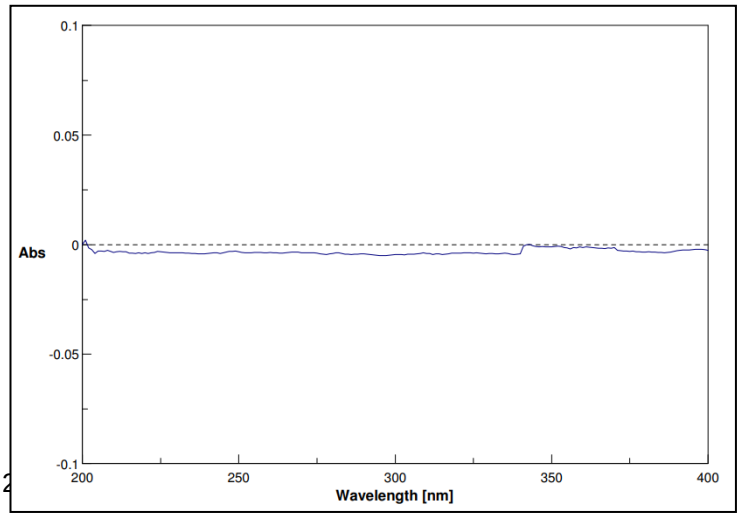


Fig. No.1: Blank in Methanol

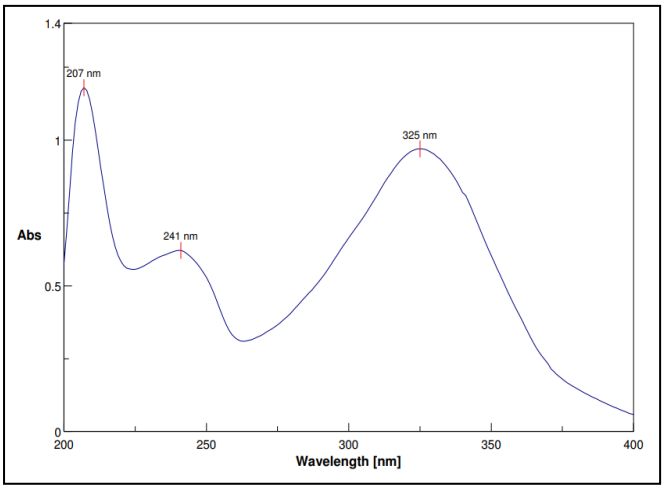


Fig. No.2: 20 PPM solution of Piroxicam in Methanol

Calibration curve for Piroxicam in methanol:

Table No.4: Calibration curve for Piroxicam

Sr.no.	Concentration (ppm)	Absorbance
1.	5	0.2335
2.	10	0.4558
3.	15	0.7224
4.	20	0.9703
5.	25	1.1488

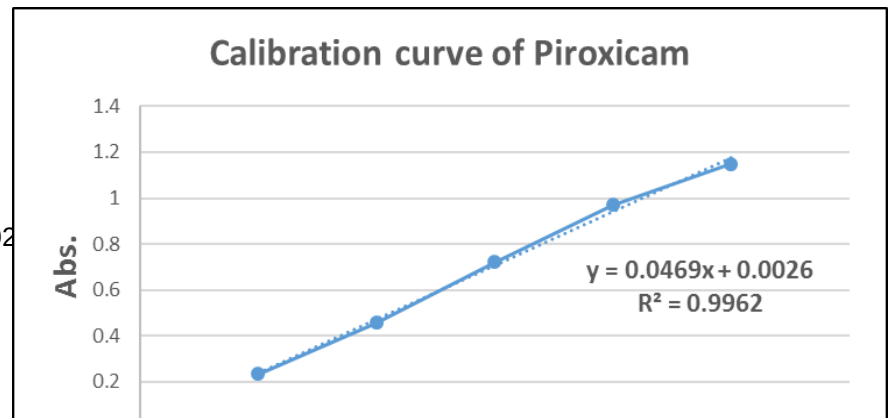


Fig. No.3: Calibration curve for Piroxicam

The calibration curves were linear and obeyed Beer-Lambert's law in the concentration range 5-25 µg/ml. The correlation coefficient values were 0.9962 indicating excellent linearity of the data.

E. FT-IR of Piroxicam:

The IR spectrum of Piroxicam was recorded by using FTIR spectrometer. IR spectra was shown in figure 4. Characteristic functional groups were observed in FTIR spectrum as shown in table 5.

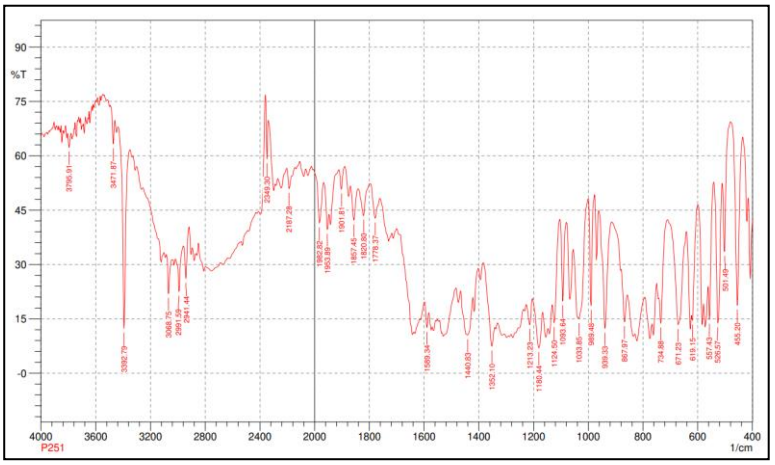


Fig. No.4: IR of Piroxicam

Table No.5: IR frequencies of Piroxicam functional group

Functional group	Observed Frequency	Reported Frequency
O-H Stretching (Alcohol)	3471.87	3550-3200

N-H Stretching (Aliphatic amine)	3392.79	3400-3300
C-H Stretching (Aromatic)	2991.59, 2941.44	3000-2800
C=C Stretching (Cyclic alkene)	1589.34	1650-1566
C-N Stretching (Amide group)	1440.83	1500-1400
S=O Stretching (Sulphonamide)	1352.1	1370-1335

2. Drug excipient compatibility study:

The FTIR Spectra of Piroxicam in pure form and their physical mixture was observed, the result showed that there was no interaction between drug, polymer and excipients. IR spectra for compatibility study were shown in figure 5, 6, 7 and their respective functional group detection data were shown in 6.

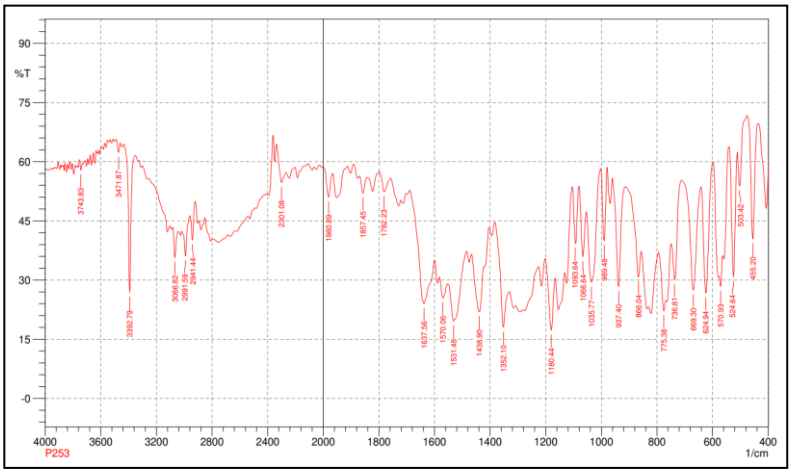


Fig. No.5: Compatibility IR for Piroxicam: Polyvinyl alcohol

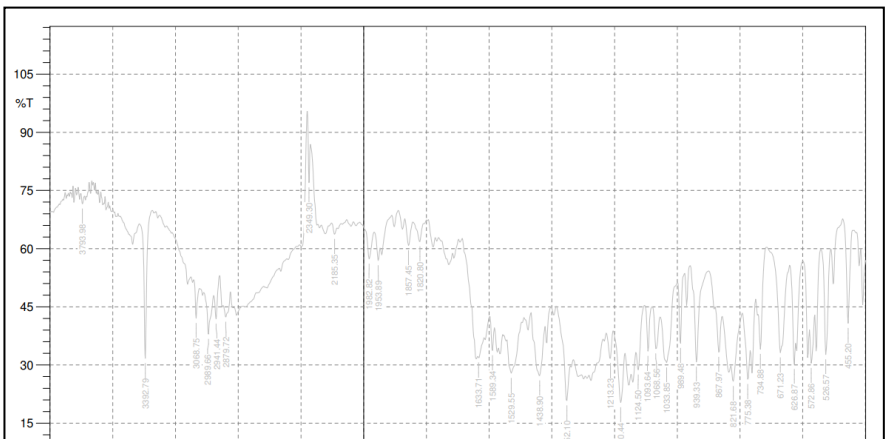


Fig. No.6: Compatibility IR for Piroxicam: Ethyl cellulose

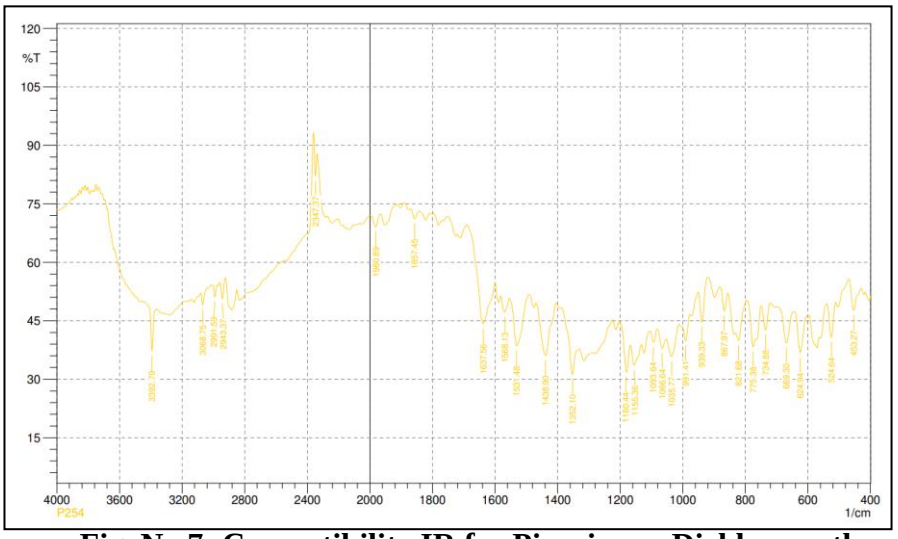


Fig. No.7: Compatibility IR for Piroxicam: Dichloromethane

Table No.6: Drug excipient compatibility

Ingredient	**Initial observation**	**Condition**
		40°C/75% RH (Accelerated)
		1 month
Piroxicam	White	NCC
Piroxicam : Polyvinyl alcohol	White	NCC
Piroxicam : Ethyl cellulose	White	NCC

Piroxicam : Dichloromethane	Transparent	NCC

NCC (No conformational change) in physical appearance from initial description, RH (Relative Humidity). It can be seen from the above data that Piroxicam combination was stable with all the excipients used for formulation and development.

3. Formulation of Piroxicam loaded Nanosponges:

Table No.7: Formulation ingredients and its roles

Sr.no	Ingredients	Role
1.	Piroxicam	Anti-inflammatory
2.	Polyvinyl alcohol	Stabilizing agent
3.	Ethyl cellulose	Polymer
4.	Dichloromethane	Solvent for polymer
5.	Distilled water	Dispersion medium

Formulation strategy:

Table No.8: Formulation strategy

Sr.no.	Ingredients/ Parameters	Batches								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Piroxicam (mg)	100	100	100	100	100	100	100	100	100
2.	Polyvinyl alcohol (mg)	200	200	200	200	200	200	200	200	200
3.	Ethyl cellulose (mg)	100	100	100	150	150	150	200	200	200
4.	Speed of rotation (RPM)	1400	1600	1800	1400	1600	1800	1400	1600	1800
5.	Dichloromethane (ml)	20	20	20	20	20	20	20	20	20
6.	Distilled water (ml)	100	100	100	100	100	100	100	100	100

4. Evaluation of formulated batches:

a. Physical evaluation:

All prepared batches were examined for physical evaluation parameters such as colour, odour and appearance. The results for all the batches were mentioned in table 9.

Table No.9: Physical evaluation of Nanosponges

Batches	Colour	Odour	Appearance
F1	Off-white	Characteristic	Fine particles
F2	Off-white	Characteristic	Fine particles
F3	Off-white	Characteristic	Fine particles
F4	Off-white	Characteristic	Fine particles
F5	Off-white	Characteristic	Fine particles
F6	Off-white	Characteristic	Fine particles
F7	Off-white	Characteristic	Fine particles
F8	Off-white	Characteristic	Fine particles
F9	Off-white	Characteristic	Fine particles

b. Determination of practical yield:

Practical yield of the formulated Piroxicam nanosponges were calculated using the formula and results were mentioned in table 10.

Table No.10: Determination of percent practical yield

Batches	Practical mass (Nanosponges) mg	Theoretical yield (Drug + Polymer) mg	% Practical yield
F1	150.32	200	75.16
F2	156.44	200	78.22
F3	171.26	200	85.63
F4	193.15	250	77.26
F5	206.1	250	82.44
F6	210.9	250	84.36

F7	210.36	300	70.12
F8	234.57	300	78.19
F9	237.96	300	79.32

c. Determination of Entrapment efficiency:

The entrapment efficiency was found to be highest for F9 formulation which is 94.16 and the lowest entrapment of drug was found for F1 formulation. This might be due to the fact that the variation in entrapment efficiency was due to the changes in the polymer concentration. The prepared nanosponges possess high drug entrapment efficiency and were found to be in the range of 80.35% - 94.16%.

Table No.11: Determination of percent Entrapment efficiency

Batches	Entrapment efficiency (%)
F1	80.35
F2	84.88
F3	87.63
F4	85.58
F5	88.65
F6	90.05
F7	90.35
F8	92.88
F9	94.16

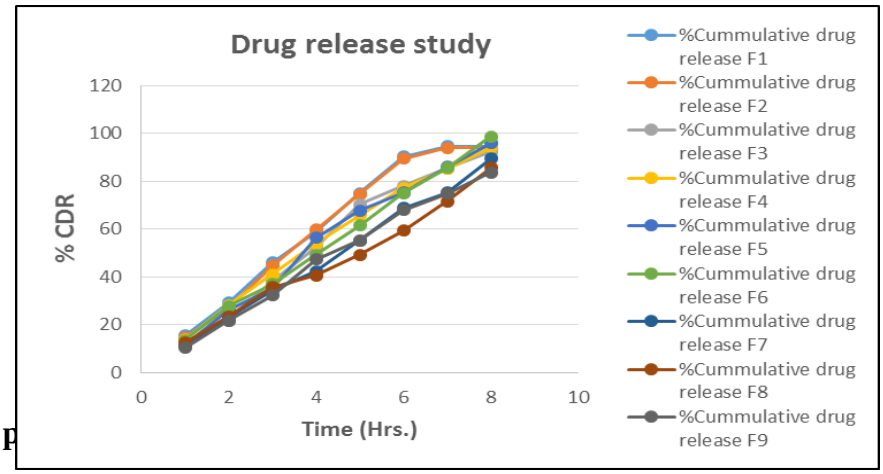
d. In vitro dissolution study:

In vitro drug release study of the prepared Piroxicam nanosponges was carried out using dialysis bag diffusion method. Amount of drug released in different time intervals were observed. The percent cumulative drug release for all the batches were found in the range of 83.57 – 98.75 %. As the concentration of polymer in nanosponges increases percent cumulative drug release also increases with decrease in time. On the basis of in vitro dissolution data, it was found that F6

batch was having highest percent cumulative drug release that is 98.75 % with respective to other batches. The results were expressed in table 12 and figure 8.

Table No.12: Determination of % drug diffusion

Time (Hrs.) ↓ / Batches →	% Cumulative Drug Release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	15.46	14.58	12.45	13.68	11.28	13.45	11.38	12.45	10.35
2	29.27	27.14	21.69	28.16	26.16	27.69	23.16	23.36	21.69
3	45.99	44.68	38.24	41.05	35.05	37.04	34.35	35.67	32.28
4	58.77	59.78	52.27	54.06	56.36	49.27	42.46	40.72	47.41
5	75.15	74.58	70.39	65.78	67.78	61.59	55.28	49.16	55.25
6	90.26	89.46	78.13	77.28	75.28	75.13	68.78	59.25	68.03
7	94.66	93.92	85.34	85.06	86.06	85.64	75.25	71.67	74.92
8	-	-	92.16	94.15	95.96	98.75	89.36	85.61	83.57



5. Optimization of p

To study the effect of independent variables on responses Design Expert 7.0 software was used. Experimental design layout developed for 9 possible batches of piroxicam loaded nanosponges. Out of the various models such as Linear, 2FI, Quadratic and Cubic which fit well was suggested by software and was tested for analysis of variance (ANOVA).

Table No.13: The layout of Actual Designs

Runs	Factor1	Factor 2	Response 1	Response 2
	A: Speed of rotation (RPM)	B: Ethyl cellulose (mg)	Particle size (nm)	Entrapment efficiency (%)
1	1600	100	210.9	84.88
2	1800	200	201.7	94.16
3	1600	200	268.9	92.88
4	1400	150	304.5	85.58
5	1400	200	315.2	90.35
6	1800	100	195.4	87.63
7	1800	150	135.3	90.05
8	1600	150	245.7	88.65
9	1400	100	254.3	80.35

Results for Particle size:

Model Graphs for Particle size:

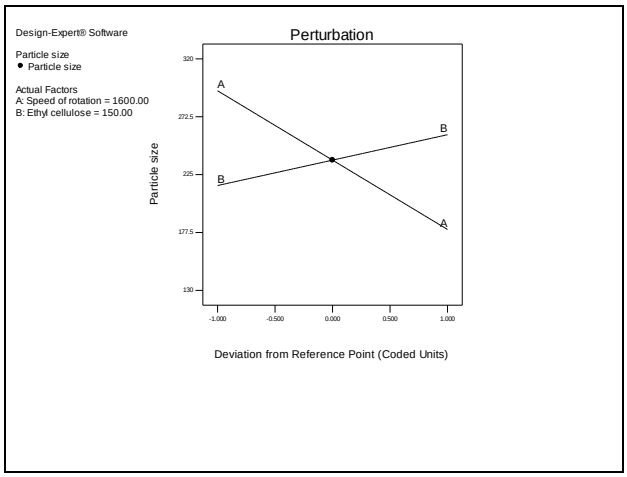


Fig. No.9: Effect of Speed of rotation and ethyl cellulose on Particle size

Conclusion: Speed of rotation and ethyl cellulose concentration are having impact on particle size of nanosponges. As the speed of rotation increases the particle size of nanosponges get decreases and as the concentration of ethyl cellulose in increases particle size of nanosponges also get increases.

Results for Entrapment efficiency:

Model Graphs for Entrapment efficiency:

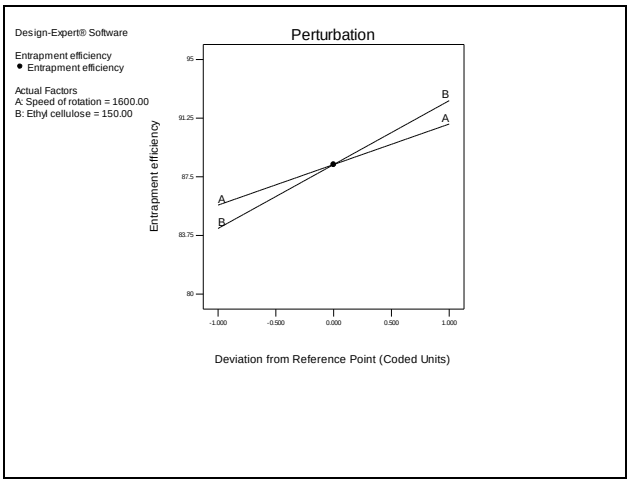


Fig. No.10: Effect of Speed of rotation and ethyl cellulose on Entrapment efficiency

Conclusion: Speed of rotation and ethyl cellulose concentration are having impact on entrapment efficiency of nanosponges. As the speed of rotation increases the entrapment efficiency of nanosponges get increases and as the concentration of ethyl cellulose increases entrapment efficiency of nanosponges also get increases.

Table No.14: Summary for effect of independent variable on responses

Sr. No.	Independent variables	Particle size	Entrapment efficiency
1	Speed of rotation (RPM)	Inversely proportional (As speed of rotation increases particle size decreases)	Directly proportional (As speed of rotation increases entrapment efficiency increases)
2	Concentration of Ethyl cellulose (mg)	Directly proportional (As Conc. of ethyl cellulose increases particle size increases)	Directly proportional (As Conc. of ethyl cellulose increases entrapment efficiency increases)

Conclusion: On the basis of data obtained from evaluation of batches as well as factorial design model study F6 batch was selected as optimized batch which was having low particle size, high entrapment efficiency and sustained release of drug till 8 hrs.

Result for particle size:

The particle size is one of the most important parameter for the characterisation of nanosponges. The average particle sizes of the prepared Piroxicam nanosponges were measured using Malvern zeta sizer. Result was mentioned under figure 11.

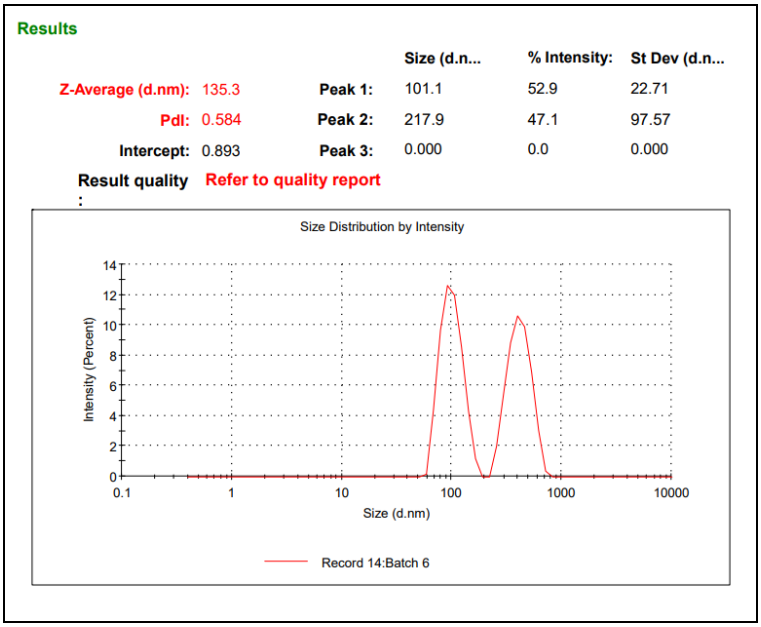


Fig. No.11: Particle size analysis for optimized batch (F6)

Result for Zeta potential:

Zeta Potential was determined using Malvern zeta-sizer instrument. Zeta potential analysis is carried out to find the surface charge of the particles to know its stability during storage. The magnitude of zeta potential is predictive of the colloidal stability. Nanosponges with zeta potential value greater than +20 mV or less than -20 mV typically have high degrees of stability. For Piroxicam nanosponges zeta potential was found to be -20.3mV with peak area of 100% intensity.

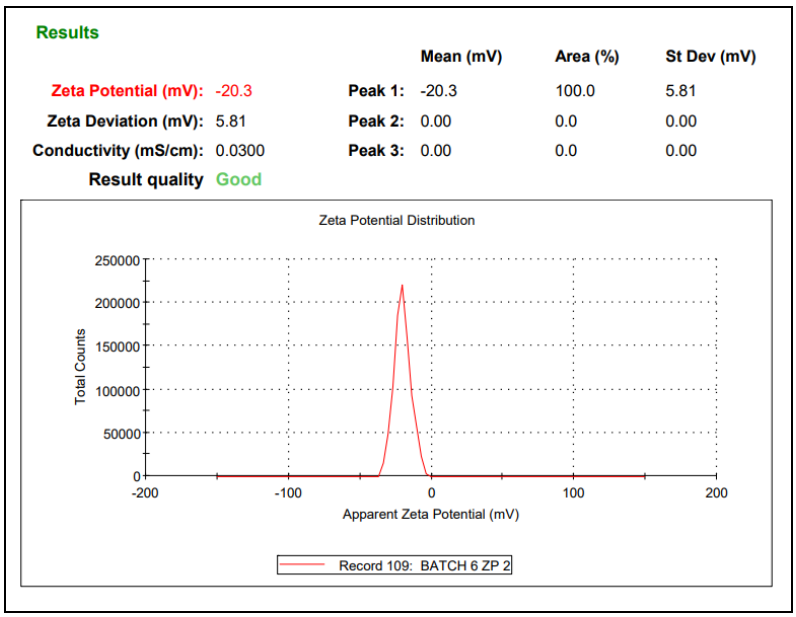


Fig. No.12: Zeta potential analysis for optimized batch (F6)

CONCLUSION

In the current study, a novel approach to improve the drug Piroxicam's bioavailability and solubility was presented. This would enable a sustained delivery of the medication to the intended site, helping to treat various anti-inflammatory treatments associated with arthritis disease. Using varying concentrations of ethyl cellulose and polyvinyl alcohol, an emulsion solvent diffusion method was used to create the nanosponges. There was no incompatibility between the drug and the excipients, according to FTIR studies. Formulation F6 was found to have the highest percent cumulative drug release after in vitro data analysis. F6 was selected as optimized batch with low particle size, high entrapment efficiency and sustained release till 8 hrs. The nanosponges demonstrated a sustained drug release profile, high encapsulation efficiency, and uniform particle size all of which are essential for sustaining therapeutic drug levels for a prolonged amount of time. To further confirm the efficacy and safety of piroxicam nanosponges, in vivo investigations and clinical trials ought to be the main areas of future research. The development of Piroxicam nanosponges has resulted in a noteworthy progress in drug delivery systems and presents a promising avenue for augmenting the effectiveness of anti-inflammatory treatments.

REFERENCE

1. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, Vallero R. Ultrasound-assisted synthesis of Cyclodextrin-based nanosponges. EP 1 786 841 B1; 2007.
2. David F. Nanosponge drug delivery system more effective than direct injection. 01.06.2010, accessed on 20.12.2011.
3. Liang L, De-Pei L, Chih-Chuan L. Optimizing the delivery systems of chimeric RNA DNA oligonucleotides beyond general oligonucleotide transfer. Eur. J. Biochem., 2002; 269: 5753-5758.
4. J.A. Girigoswami A, K. Girigoswami Versatile applications of nanosponges in biomedical field: a glimpse on SARS-CoV-2 management BioNanoScience., 2022; 12(3):1018-1031.
5. F. Trotta, M. Zanetti, R. Cavalli Cyclodextrin-based nanosponges as drug carriers Beilstein). Org. Chem., 2012; 8: 2091-2099.
6. Kaivalya R, Prasad D, Sudhakar M, Bhanja SB, Tejaswi M, "A Review on Nansponges." IJRSR, 2020; 11(1):36878-36884.
7. Thakre AR. Gholse YN, Kasliwal RH. Nanosponges: a novel approach of drug delivery system. J Med Pharm Allied Sci., 2016; 78:103-11.
8. Rita L Amit T, Chandrashekhar G. Current trends in B- cyclodextrin based drug delivery systems. Int J Res Ayurveda Pharm., 2011;2:1520-6.
9. Ahmed RZ. Patil G, Zaheer Z. Nanosponges-a completely new nano-horizon: pharmaceutical applications and recent advances. Drug Dev Ind Pharm., 2013;39:1263-72
10. Singh D. Soni GC, Prajapati SK. Recent advances in nanosponges as drug delivery system: a review. Eur J Pharm Med Res., 2016; 3:364-71.
11. Kaur G., Aggrawal G., Nanosponges: New Colliodal Drug Delivery System for Topical Delivery. 2015; 5(1), 53-57.
12. Kamal S., Sarabjeet S., Ajay A., Sanju N., Transdermal Gel: An Alternative Vehicle for Drug Delivery. International Journal of Pharmaceutical Chemicals and Biological Science., 2013; 3(3):495-503.
13. Rathod J., and Mehta P., A Review on Pharmaceutical Gel. ActaScientifica International Journal of Pharmaceutical Science. 2015; 1(1): 33-47.
14. Sharma R, Pathak K. Nanosponges: Emerging drug delivery system. Pharma Stud., 2010; 33-5.

15. Lala R, Thorat A, Gargote C. Current trends in ß- cyclodextrin based drug delivery systems. Int J Res Ayur Pharm., 2011; 2(5): 1520-1526.
16. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, Vallero R. Ultrasound-assisted synthesis of Cyclodextrin-based nanosponges. EP 1 786 841 B1; 2007.
17. S. Anandam, S. Selvamuthukar. Optimization of microwave-assisted synthesis of cyclodextrin nanosponges using response surface methodology. Journal of Porous Materials., 2014;21(6):1015-1023
18. Y. Dai, Q. Li, S. Zhang, S. Shi,Y. Li, X. Zhao, et al.Smart GSH/pH dual-bioresponsive degradable nanosponges based on ß-CD-appended hper-cross-linked polymer for triggered intracellular anticancer drug delivery. . Drug Deliv. Sci. technol., 2021; 64.
19. Tiwari K, Bhattacharya S. "The Ascension of Nanosponges as Drug Delivery Carrier: Preparation, Characterization and Applications." Journal of Materials Science: Materials in Medicine, 2022: 33 (28):1-21.
20. Srinivas P., Reddy A. J., Formulation and Evaluation of Isoniazid Loaded Nanosponges for Topical Delivery, Pharmaceutical Nanotechnology, 2015; 68-73.
21. Swaminathan S., Pastero L., Serpe L., Trotta F., Cyclodextrin-Based Nanosponges Encapsulating Camptothecin, Physicochemical Characterization, Stability & cytotoxicity, European Journal of Phramaceutic and Biopharmaceutics, Elsevier science Direct., 2010; 193-201.
22. J. Guo, Y. Xiao, Y. Lin, J. Crommen, Z. Jiang Effect of the crosslinker type on the enantioseparation performance of ß- cyclodextrin functionalized monoliths prepared by the one-pot approach J. Chromatogr. A, 2016; 1467: 288-296.
23. T. Girek, W. Ciesielski Polymerization of ß-cyclodextrin with maleic anhydride along with thermogravimetric study of polymers J. Inclusion Phenom. Macrocycl. Chem., 2011; 69 (3):445-45.
24. Amber V, Shailendra S, Swarnalatha S. Cyclodextrin based novel drug delivery systems. J Incl Phenom Macrocycl Chem, 2008; 62:23-42
25. Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an updated review. AAPS PharmSciTech., 2005;6:E329-57
26. Rajeswari C, Alka A, Javed A, Khar R K. Cyclodextrins in drug delivery: an update review. AAPS pharmSciTech, 2005; 6(2):E329-E357.
27. Pawar YA, Naik AK, Jadhav KR. "Nanosponges. A Novel Drug Delivery System. Asian Journal of Pharmaceutics, 2016; 10 (4): 56-63.

28. Singh D, Soni GC, Prajapati SK. “Recent Advances in Nanosponges as Drug Delivery System: A Review.” EJPMR, 2016; 3 (10): 364-371.
29. Sharvari M. Ksshirsagar, Nisha Shrestha, Thomas Kipping, Ajay K. Banga. Formulation development of tazarotene-loaded PLGA nanoparticles for follicular delivery in the treatment of inflammatory skin diseases. European Journal of Pharmaceutics and Biopharmaceutics., 2024; 200.
30. Medipalli Viswaja, D. V. R. N. Bhikshapathi, Mamatha Palanati, A. Kiahore Babi, Arjun Goje. Formulation and Evaluation of Ibrutinib Nanosponges Incorporated Tablet. Int J App Pharm, 2023; 15(2): 92-97.
31. Dalia A. Gaber, Mahasen A. Radwan, Danah A. Alzughaibi, Jenan A. Alails, Rafa S. Aljumah, Reema M. Alogla, Sara A. Alkhalifah and Siham A. Abdoun. Formulation and evaluation of Piroxicam nanosponge for improved internal solubility and analgesic activity.Drug Delivery, 2023; 30:1.
32. Falgun A. Dabhi, Vrushti D. Shah and Bhavin D. Pandya. A Review on Nanosponges: an ascendance of potential nanocarrier for emerging drug delivery, Ejpr, 2023; 10(5): 134-147.
33. Praveen Gujjula, Angala parameswari. Development and evaluation of nanosponges-based buccal tablets for delivery of quercetin using box-behnken design. International Journal of Applied pharmaceutics 2023; 15(3).
34. Shabaraya, AR, Sumana G, Vineetha K. Formulation and Evaluation of Nanosponges-loaded Gel of Lornoxicam for Topical Delivery. International Journal of Drug Delivery Technology: 2022; 12(2):634-639.
35. Silpa GS, Deepa Manohar R, Mathan S, Shaiju S Dharan. Formulation and Evaluation of Nanosponges Loaded Hydrogel Using Different Polymers Containing Selected Antifungal Drug. J. Pharm. Sci. & Res. 2021; 13(2):101-111.
36. Mohammad Javed Ansari. Formulation and in vitro evaluation of topical nanosponges-based gel containing butenafine for the treatment of fungal skin infection.saudi pharmaceutical jounal., 2021;29:467-477.
37. Manisha B. Balwe, Madhura T. Deshmukh, Abhijeet N. Khopade, ajkumar V. Shete. Formulation and characterization of griseoflvin loaded nanosponge. Bull. Env. Pharmacol. Life Sci., 2021; 10(4):135-149.

38. Brunda S. Suresh V Kulkarni, Manjunath K and Pushpalatha D. Formulation and evaluation of oxiconazole nitrate loaded nanosponges. World Journal of Advanced Research and Reviews, 2021; 11(03):028-040.
39. R. Gangadhara", K. P. Satheesh', N. Devanna, L. Sasikala and Vandavasi Koteswara Rao³. Formulation and Invitro Characterization of ketorolac loaded Nanosponges. IJRPC 2021; 11(3): 99-103.
40. Pushpalatha D, Abdul Waris Khan, Manjunath K and Brunda S. Formulation and evaluation of lovastatin loaded nanosponges. WJARR 2021; 11(3):041-056.
41. Samia M.Omar, Fares Ibrahim, Aliaa Ismail. Formulation and evaluation of cyclodextrin-based nanosponges of griseofulvin as pediatric oral liquid dosage form for enhancing bioavailability and making bitter taste. Saudi Pharmaceutical Journal, 2020; 28(3):349-361.
42. Bhalekar Rohini V, Nagoba Shivappa N, Shaikh Nasheer S & Swami Avinash. B. Formulation and evaluation of nanosponges hydrogel for topical drug delivery containing griseofulvin. IJMPS 2020; 10(2): 57-70.
43. Balaji Maddiboyina, Arthapu Hari Krishna, Makkena Ramya Sri, Pasupuleti Bhuvana Kalyani, Shaik Jabeena, Shaik Sharmila, Vankudavatu Lakshmi bai. Preparation and evaluation of ibuprofen in-situ periodontal gel. IJAMSCR 2020; 8(1): 67-75.
44. Khanderao Rajaram Jadhav, Shivraj Popat Jadhav, Deepak Devidas Sonawane. Formulation and Evaluation of nanosponges based topical gel preparation of fluconazole. IJPPR 2020; 19(3).
45. Rahul S. Solunke, Uday R. Borge, Krishna Murthy, Madhuri T. Deshmukh, Rajkumar V. Shetes. Formulation and Evaluation of Gliclazide Nanosponges. International Journal of Applied Pharmaceutics. 2019; 11(6).
46. Sneha R. Jagtap, Omprakash G. Bhusnure, Imran N. Mujewar, Sachin B. Gholve, V.B. Pancha bai. Nanosponges: A Novel Trend for Targeted Drug Delivery. Journal of Drug Delivery and Therapeutics, 2019; 9(3): 931-938.
47. Dingwoke John Emeka Francis, Felix Sunday Yusuf. Development and evaluation of nanosponges loaded extended release tablets of lansoprazole. Universal Journal of Pharmaceutical Research, 2019; 4(1): 24-28.
48. Monica R. P. Rao, Jagruti Chaudhari, Francesco Trotta, and Fabrizio Caldera. Investigation of Cyclodextrin-Based Nanosponges for Solubility and Bioavailability Enhancement of Rilpivirine. AAPS PharmSciTech 2018.

49. Priyanka D, Sindhu S, Saba Maanvizhi. Design Development and Evaluation of Ibuprofen Loaded Nanosponges for Topical Application. International Journal of ChemTech Research, 2018; 11(2): 218-227.
50. Subhash Chandra Bose PENJUR, Nagaraju RAVOURU, Saritha DAMINEN, Sailakshmi BNS2, Srikanth Reddy. Formulation and Evaluation of Lansoprazole Loaded Nanosponges. Turk J Pharm Sci 2016; 13(3): 304-310.
51. Geeta Aggarwal, Manju Nagpal and Gurpreet Kaur. Development and Comparison of Nanosponge and Niosome based Gel for the Topical Delivery of Tazarotene. Pharmaceutical Nanotechnology, 2016; 4: 213-228.
52. Pande j.Amadcep s. controlled release in Topical Drug Delivery System: A Research. International Journal of Pharm. Resource and Allied Science. 2018; 12(3): 367-382.
53. Aldawsari M., Design and Formulation of a Topical Hydrogel Intergrating Lemongrass loaded Nanosponges with an Enhanced Antifungal Effect; in vitro /in vivo evaluation. International Journal of Nanomedicine 2015; 10: 893-902.
54. Aritomi H, Yamasaki Y, Yamada K, Honda H and Khoshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated micro sponges prepared by dry impact blending method. Journal of Pharmaceutical Science and Technology, 1996; 56(1): 49-5
55. https://pubchem.ncbi.nlm.nih.gov/compound/Piroxicam
56. https://en.wikipedia.org/wiki/Piroxicam
57. https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/piroxicam
58. Raymond C., Rowe Paul J., Weller, “Handbook of Pharmaceutical Excipients,” Fourth Edition, 237,491.
59. https://en.wikipedia.org/wiki/Ethyl_cellulose
60. https://en.wikipedia.org/wiki/Dichloromethane
61. https://en.wikipedia.org/wiki/Polyvinyl_alcohol
62. Raghavendra Kumar Gunda, J. N. Suresh Kumar, Ajay Babu , formulation development and evaluation of lamotrigine sustained Release tablets using 32 Factorial design, International Journal of pharmaceutical science and research, 2015; 6(4): 1746-1752.
63. Indian Pharmacopeia (2007)-Volume2, 44-45.
64. Swaminathan S. Linda P. Loredana 5, Francesco T, Pradeep V. Dinc A Michele T, Gianpaolo Z, Roberta C. Cyclodextrin-based nanosponges encapsulating camptothecin

Physicochemical characterization stability and cytotoxicity. Eur J Pharm Biopharm 2010; 74(2): 193-201.

65. Raja NV, Kumar G, Anusha K. Fabrication and evaluation of ciprofloxacin loaded nanosponges for sustained release. International Journal of Research in Pharmaceutical and Nano Sciences. 2013; 2(1):1-9.
66. Renuka Sharma, Roderick BW, Kamia Pathak, Evaluation of kinetics and mechanism of drug release from econazole nitrate nanosponge loaded carbapol hydrogel. Ind Pham Edu Res., 2011; 45(1): 25-31.
67. Swaminathan S. Pradeep V. Trutta F. Cavalli R. Nanosponges encapsulating dexamethasone for ocular delivery; formulation design, physicochemical characterization, salety and corneal permeability. J Biomed Nanotechtal 2013; 963: 999-1007.