

PREPARATION AND CHARACTERIZATION OF MICROSPONGES LOADED WITH KETOPROFEN FOR IMPROVED DRUG DELIVERY

Deepthi Mathew*, Dr. Sunbee Prakash, Dr. Santhosh M. Mathews and Dr. I. John Wesley

¹Research Scholar (Reg No.19120066), JJT University, Rajasthan.²Professor, JJT University, Rajasthan.³Principal, Pushpagiri College of Pharmacy, Tiruvalla.⁴Professor, Ezhuthachen College of Pharmaceutical Sciences.

*Corresponding Author: Deepthi Mathew

Research Scholar (Reg No.19120066), JJT University, Rajasthan.

Article Received on 12/03/2025

Article Revised on 02/04/2025

Article Accepted on 22/04/2025

ABSTRACT

Microsponges are porous, polymeric microspheres that are used chiefly for topical and recently, oral administration. Ketoprofen was used as a model drug for systemic drug delivery of microsponges in the study. Ketoprofen microsponges were prepared by the quasi-emulsion solvent diffusion method with Eudragit RS 100, and afterwards, microsponges were used as different dosage forms. Microsponges can gradually release a certain quantity of medication over time in reaction to various factors. Consequently, the chemical and physical characteristics of the active agents and microsponges must be taken into account during the development process. The dimensions and quantity of interconnect channels in microsponges, along with the drug delivery characteristics, can be influenced by the interaction between their physical properties and the polymer(s) utilized in their preparation. Microsponges have a plastic property that allows for direct compression, resulting in a tablet with greater mechanical strength than a mixture of active agent and polymer alone. There is currently a very promising method for oral medication delivery that increases the rate of poorly soluble drug release by entrapping into microsphere system.

KEYWORDS: Ketoprofen, microsponges, Eudragit, quasi emulsion solvent diffusion method.**INTRODUCTION**

Oral drug delivery systems have evolved significantly over the years to enhance therapeutic efficacy and patient compliance. Conventional drug formulations often face limitations such as poor solubility, limited bioavailability, and undesirable side effects due to fluctuations in plasma drug levels. Advanced drug delivery systems like microsponges have gained prominence to overcome these challenges.

Microsponges are porous, polymeric microspheres that can encapsulate active pharmaceutical ingredients (APIs) and provide controlled drug release. These systems offer advantages such as prolonged drug release, reduced side effects, improved stability, and enhanced patient compliance.

Ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID), is widely used for the treatment of pain, inflammation, and musculoskeletal disorders. However, its conventional oral formulations suffer from gastrointestinal irritation, short half-life, and erratic absorption. Incorporating ketoprofen into a microsponges-based delivery system can mitigate these

challenges by offering controlled release, reduced gastric irritation, and enhanced bioavailability.

The present study focuses on the formulation and characterization of ketoprofen-loaded microsponges and this research aims to evaluate the physicochemical properties, drug release kinetics, and therapeutic potential of the formulated microsponges to establish an effective oral drug delivery system for ketoprofen.

2. METHODS**I. Preformulation Study of Ketoprofen Drug**

Preformulation is the first step in the rational development of a dosage form of a substance and is defined as an investigation of the physical and chemical properties of the drug substance alone and when combined with excipients. This initial learning phase is known as Preformulation. Following is some of the important parameters evaluated during Preformulation studies.

Physicochemical Evaluation of Drug

1. Determination of pH

The pH is the measure of the negative logarithm of hydrogen ion concentration of an aqueous solution. It is one of the most important factors that determine the stand point of solubility, stability, and physicochemical stability of the formulation. The pH of the pure drug was determined by digital pH meter.

2. Determination of Melting point

The temperature at which the first particle of the substance completely melts is regarded as the melting point of the substance. The temperature at which the first particle starts to melt and the last particle completely melts is regarded as the melting range. The melting point of the pure drug was determined by the capillary tube method using Electro Thermal IA 9000 SERIES digital melting point apparatus, and the temperature at which the drug melted was noted as melting point.

3. Determination of Particle size distribution

Particle size distribution is an important factor that determines the number of parameters like dissolution rate, bioavailability, content uniformity, flow properties, texture, and stability of a formulation. The particle size can be analyzed by a number of methods like sieves, microscopic, laser diffraction methods, etc. The particle size was determined by the microscopic method. The stage and the eyepiece micrometer have been calibrated. About 10 mg of the sample was taken in the glass slide, and size analysis was determined for 100 different particles.

4. Compatibility Study of Drug and Excipients

Physical Compatibility Study

Excipients were mixed with Ketoprofen and were kept in stable conditions for one month in 25°C per 60% RH, and 40°C per 75% RH in 2 millimeters glass vial in closed condition.

5. Compatibility study by FTIR spectroscopy

The pellets were prepared by gently mixing 200mg of potassium bromide with 1mg of the sample by using a SHIMADZU FTIR spectrophotometer. A blank was initially taken by KBR only. The prepared pellets were analyzed for the individual drug, Drug and excipients for the microsponges.

II. Method of Preparation

1. Formulation of Microsponge

The microsponges were prepared using the quasi-emulsion solvent diffusion method. It consists of two phases: i) inner organic phase and ii) outer aqueous phase. The microsponges were prepared by using different proportions of polymers (chitosan, Sodium alginate, Eudragit RS 100). The inner organic phase consists of Eudragit RS 100 with a suitable organic solvent. A drug used provided with a solution and dissolved under ultrasonication at 35°C.

The inner phase was then added to the outer phase containing PVA and stirred at room temperature for 3 hours at rpm. After the completion of the reaction, the synthesized microsponge is dried in an air-heated oven at 40°C for 12 hours.

Table No. 1: Different Formulations of Microsponges.

Sl.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Ketoprofen	100	100	100	100	100	100
2	Eudragit RS-100	25	50	75	100	125	150
3	Chitosan	75	50	25	125	100	75
4	Sodium Alginate	75	100	125	25	50	75
5	Polyvinyl Alcohol	1%	1%	1%	1%	1%	1%
6	Acetone(ml)	20	20	20	20	20	20
7	Distilled water(ml)	100	100	100	100	100	100

2. Optimization study

Design, development, and optimization of processes and products using DoE. It is a versatile tool that may be applied to a number of scenarios, including robust design, variable screening, transfer function discovery, optimization, and comparative design.

3. Characterization of the microsponges

The prepared microsponges were characterized for their production yield, entrapment efficiency, morphological studies, drug content, particle size etc.

RESULTS AND DISCUSSION

➤ Preformulation Studies

A preformulation study was performed as per the standard procedure. The results of the study are given below.

● Physical description of API

S. No	Raw material	Colour	Odour	Nature
1.	ketoprofen	White	Odourless	Crystalline powder

Result analysis: The color, odor and the nature of the API was same as that mentioned in the BP and USP.

- Assesment of pH for 1% Ketoprofen dispersion in water.

pH of Ketoprofen in water

S. No.	Solution concentration	pH
1.	1	7.3

Result analysis: The pH of the formulation was found to be 7.3. Ketoprofen is an propionic acid class of NSAID, with pH in the range of 6-7.5 which is neutral in nature.

- Result of Melting point

Melting point of Ketoprofen

S. No.	Reference Range	Observed value
1.	94-96	94

Result analysis: The melting point was checked

with griffin melting point apparatus. The melting point value was found to be same as that mentioned in the monograph.

- Particle size distribution of Ketoprofen

S. No.	Raw Material	Nature of Sample
1.	Ketoprofen	Moderately fine powder

Result analysis: Not less than 95% of the sample mass passed through the sieve 36#, and not more than 40% powder passed through 100#. Hence, the powder was found to be moderately fine, which will have good flow properties suitable for microsphere formulation.

- Compatibility studies by FT-IR

FT-IR spectrum of the drug was used to study the possible interaction between drugs and excipients. The characteristic peaks of the drug with wave number and its corresponding functional group are given below.

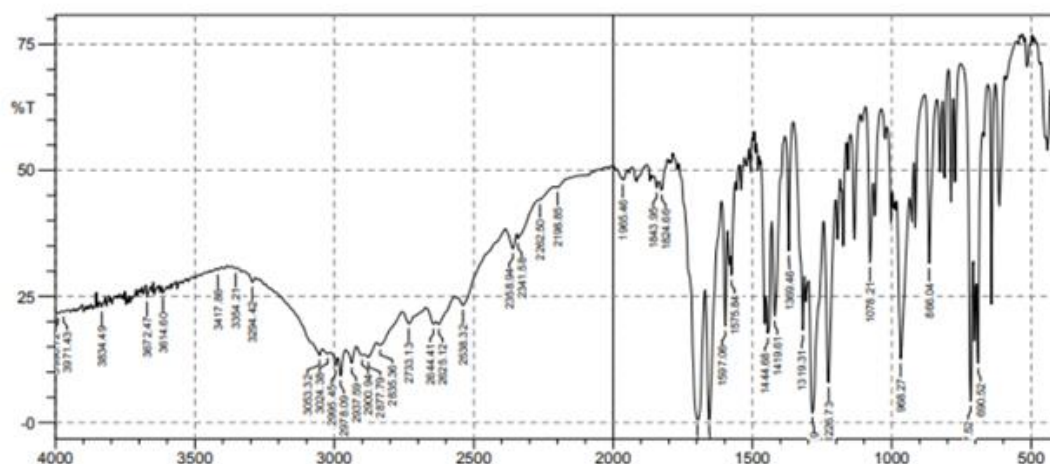


Fig. 1: FTIR spectroscopy for Ketoprofen Pure.

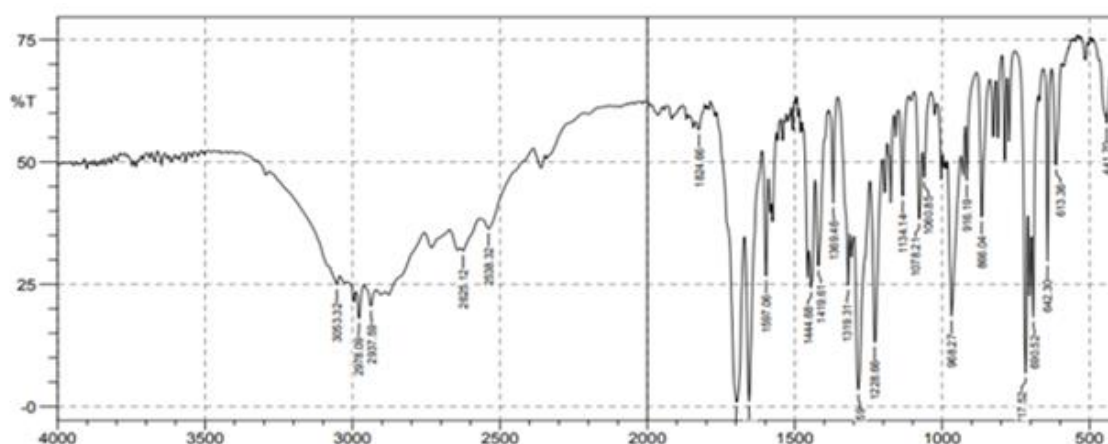


Fig. 2: FTIR spectroscopy of drug and Excipients for microspheres (Polyvinyl alcohol).

Result Analysis: All the important peaks are present in the FTIR spectra of the Drug and excipients. The results of the study indicate the FTIR spectrum of Drug and excipients did not differ with major peaks of

ketoprofen, ie; all the major peaks of the drug appeared on the blend indicate that there is no possible interaction between drug and Excipients.

Results Analysis: The drug ketoprofen and the excipients used for the preparation of Microsponges were subjected to FTIR study for the assessment of the compatibility study. The data shows that all the essential peaks of the drug were present in the prepared Formulations. Therefore, the drug is compatible with all the excipients.

● Formulation of Ketoprofen-Loaded Microsponges

➤ Method of preparation:

Ketoprofen-loaded microsponges were prepared by Emulsion solvent diffusion method using varying concentrations of Eudragit RS100, PVA, and Chitosan Sodium Alginate. The effect of the Eudragit RS100 and stabilizer concentrations on the stability of the microsponges was investigated. Since the formulation involves three polymers (Eudragit RS 100, Chitosan, and Sodium Alginate), the outer aqueous phase will contain Chitosan and Alginate and PVA (polyvinyl alcohol) as a stabilizer.

1. Microsponge Formation:

- ❖ Filter & collect microsponges.
- ❖ Dry at 40°C for 12 hours in an air-heated oven.

Chitosane enhances mucoadhesion and bioavailability. Alginate helps in crosslinking, providing controlled drug

release. Higher Chitosan increases mucoadhesion but may reduce entrapment. Higher Alginate improves sustained release. Stirring speed (600–2000 rpm) affects particle size. Ideal Ratios (Chitosan: Alginate) 1:1 (Equal ratio) produced a balanced encapsulation & release. If the ratio is 1:2 (Higher alginate) produced more sustained release, and if the ratio is 2:1 (Higher chitosan), it produced increased mucoadhesion. The prepared microsponges were subjected to pH, entrapment efficiency, particle size, and SEM. The photographs of prepared microsponges are in the figure given below:

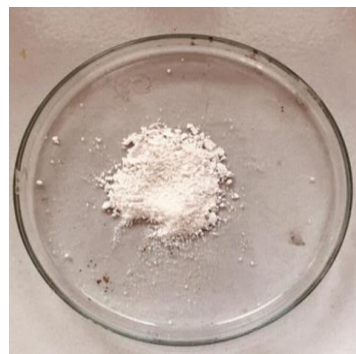


Figure No. 3: Formulated microsponges using drugs and polymers.

● pH analysis of the microsponges

Table No 2: pH, Entrapment Efficiency and Particle Size of the prepared Ketoprofen loaded microsponges.

Formulation Code	pH	Entrapment Efficiency (%)	Particle Size(μm)
F1	6.91 ± 0.01	75.1	126±0.32
F2	6.69 ± 0.01	77.8	130±0.22
F3	7.11 ± 0.03	69.5	109±0.68
F4	6.85 ± 0.02	82.3	108±0.26
F5	6.74 ± 0.01	67.8	122±0.78
F6	6.89 ± 0.02	78.9	121±0.24

Figure No. 2: pH of Different Formulations of Microsponges.

Result analysis: The micro sponge pH was found to be in the range of 6.6–7.1. This is due to the presence of the Excipients used for the preparation of the microsponges. Hence, the formulation has become suitable for oral application. The pH of micro sponge was nearly too neutral.

● Determination of Entrapment Efficiency

The percentage drug entrapment efficiency of ketoprofen microsponges prepared with different formulations of polymers F1, F2, F3, F4, F5, F6 was shown in the Table.

Result analysis: The entrapment efficiency of the formulations was in the range of 69.6 – 82.3. When concentration of polymer is increased, the platform for binding the drug to the core is increasing, and hence greater entrapment efficiency was seen in the F4 and F6 formulations. Formulation F4 was found

to have highest entrapment efficiency. It was shown in the graph.

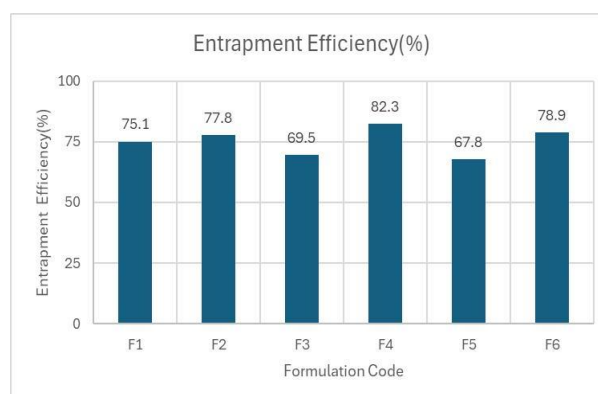


Fig. No 5: Entrapment Efficiency of Micro Sponge.

● Production Yield

The production yield of the micro sponge was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges.

Micro sponges production yield was determined by the formula mentioned below $\text{Production yield (PY)} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer)}}$.

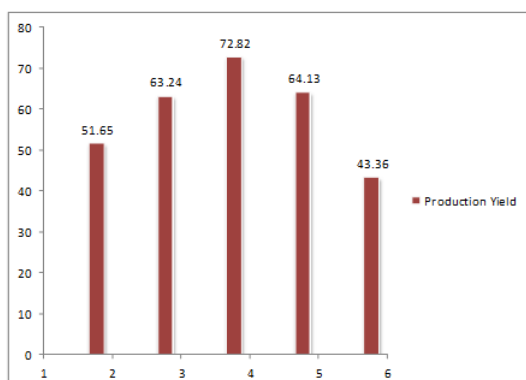


Figure No 6: Production yield of the prepared microsponges.

All batches' production yields were found to fall between 39.78% and 72.82%, given in Table No. It was discovered that the drug-polymer ratio and polyvinyl alcohol concentration had a significant impact on production yield. Additionally, a higher drug polymer ratio led to a relatively low manufacturing yield (39.78) compared to a drug polymer ratio (F6) of 72.82.

● Scanning Electron Microscope (SEM) Study:

The SEM analysis of the prepared Microsponges is revealed at 1400, 2500, and 6600X magnification, respectively. It seemed that the MS was highly porous, finely distributed, and smooth, uniform spheres.

The SEM study reveals the presence of tiny pores in the analyzed formula. The highly porous nature indicates the validity of the method that was used for the formulation of MS, i.e., the QESD method, in which an organic solvent diffuses out of the SP, leaving pores and channels behind it. The so-called “sponge-like” particles are truly evident in the photomicrographs.

The microsponges' SEM images are displayed in fig. The microsponges are spherical and porous, according to SEM photographs. The interior structure was porous with vacuum regions, and no unbroken drug crystals were visible. The solvent's migration from the microsponges' surface created the pores.

Result analysis: SEM micrographs of drug-loaded microsponges were recorded to observe the surface morphology of prepared microsponges. The result showed that the particles have porous surfaces and spherical geometry. The figure given indicates the porous spongy particle in the formulation.

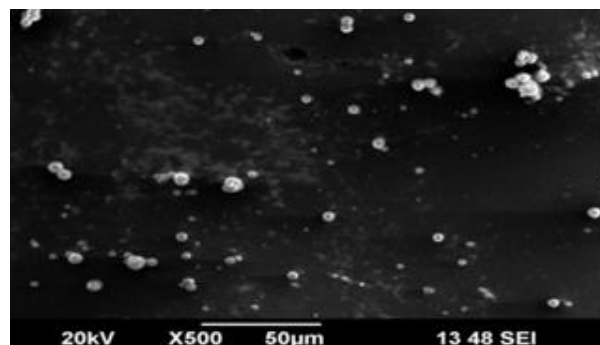


Figure No. 6: Images of microsponges by Scanning Electron microscopy.

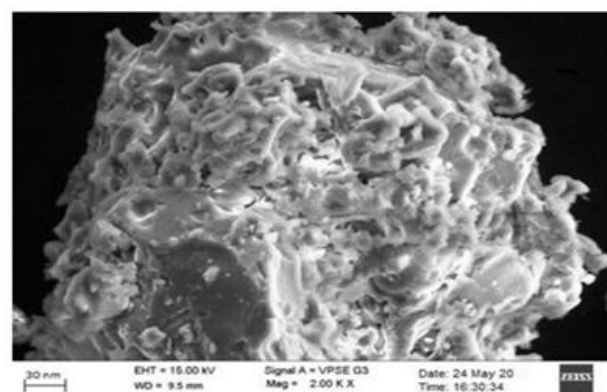


Figure No. 7: Images of prepared microsphere formulation.

● Particle size analysis

Particle size analysis of the formulation was done to estimate the size range of particles in the formulation using a Malvern instrument. The sample was fed into the instrument. A software system attached to this instrument gave the plot for data, showing the size range of different particles present in the formulation.

The Malvern Mastersizer was used to analyze the particle size of the prepared microsponges. To make sure that the light-scattering signal, as measured by the number of particles per second, was within the instrument's sensitivity range, microsponges were dissolved in double-distilled water before the sample was sent through the device. Maintaining a 90° angle of detection, the analysis was performed at room temperature. $d(0.9) \mu\text{m}$ was used to express the average particle size.

Result Analysis

Size distribution data showed that the average particle size of the formulation with a size of $3.2 \mu\text{m}$ (3252nm) was present. The particle size distribution index was found to be 0.378 in formulation, which indicates the size range of particles in formulation was low and uniform. Peak 1 width is given as 484.2d.nm. The range will be $\pm 1/2$ width. The size range of particles in the formulation is between 3494nm and 3010nm. The particle size analysis is given in the figure.

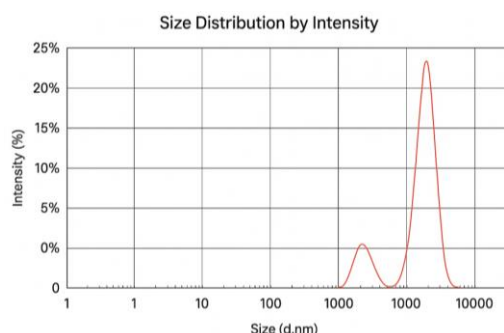


Figure No. 7: Particle Size distribution analysis.

Particle size analysis

The particle size analysis was done for all the batches of microsponges, and the result for the particle size analysis is given in the table. Table No. 4: Particle size of the prepared Ketoprofen loaded microsponges. Microsponge compositions should have an average particle size of 5–300 μm .

● **Drug Content:** A precise weight was assigned to 100 mg of microsponges. They were ground up and extracted using a 100 ml procedure. Using phosphate buffer (pH 7.4) and a UV spectrophotometer, the drug concentration was ascertained by dissolving the formulation in the buffer for a whole day. A sample was then obtained and examined in the UV spectrophotometer. It was discovered that the formulation with the highest medication content was F4. The range of the drug content from F1 to F6 is 80.24 to 94.36%. Table and figure shows drug content of prepared microsponges.

Table No. 3: Drug content of prepared microsponges.

Formulation Code	Drug Content (%)
F1	80.24
F2	82.57
F3	86.44
F4	94.36
F5	91.86
F6	90.24

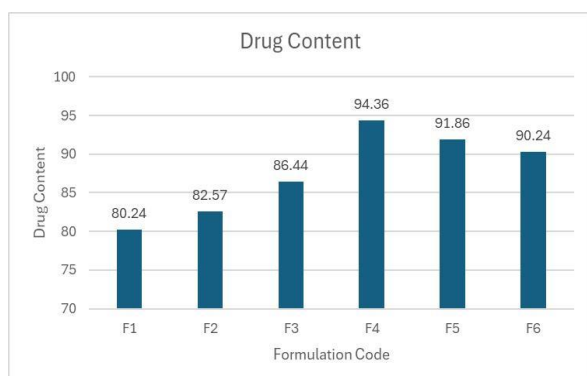


Figure No. 8: Drug content of prepared microsponges.

CONCLUSION

In the current research work, a microsponge containing Ketoprofen was developed and optimized

to reduce the frequency of administration, reducing drug toxicity, improve patient compliance, and reduced cost effect. The study results indicate that microsponge delivery is a promising strategy for prolonged drug release and retention of dosage form on the oral route. The optimized microsponge provides satisfactory release properties prepared with Eudragit R S 100 as a polymer and Polyvinyl alcohol as a stabilizer, along with other ingredients. Based on evaluation parameters, the optimized formulation (F4) can be used once in a day application which is based on the severity of the disease, and age. In conclusion the optimized formulation is suitable for large manufacturing.

REFERENCES

1. Pawan, A.S. and Prashant, P.B., A new era in topical formulations-microsponge drug delivery system. *International Journal of Pharmaceutical Sciences and Research*, 2016; 7(7): 2756.
2. Friberg, C., Genetic studies of psoriasis and psoriatic arthritis. *Inst of Biomedicine. Dept of Medical Genetics*, 2008.
3. Huynh, D. and Kavanaugh, A., Psoriatic arthritis: current therapy and future approaches. *Rheumatology*, 2015; 54(1): 20-28.
4. Venugopal, J. and Prakash, R., Protective effect of COX inhibitors on lipopolysaccharide- induced sickness behaviour or neuroinflammation and oxidative stress on male Wistar rats. *Int J. Pharm. Pharm. Sci*, 2015; 7: 240-245.
5. Pandey, P., Jain, V. and Mahajan, S.C., A review: microsponge drug delivery system. *Int J Biopharm*, 2013; 4(3): 225-230.
6. Jagtap, S.C., Karale, A.A. and Ambekar, A.W., Microsponge: A novel topical drug delivery system. *Journal of drug delivery research*, 2014; 3(4): 1-9.
7. Sen, S., Sharma, A., Kriplani, P. and Guarve, K., Microsponges: A Neoteric Approach for the Effective Management of Osteoarthritis. *Current Rheumatology Reviews*, 2023; 19(4): 385-399.
8. D'souza, J.I. and More, H.N., Topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system. *Research Journal of Pharmacy and Technology*, 1(4), 502-506. PVP k-30 and Hydroxypropyl β - Cyclodextrin *European Journal of Pharmaceutical and Medical Research*, 2008; 4(2): 657-63.
9. Asmita Singh, A.S. and Sudha Rathod, S.R., 2014. Design, development and characterization of liposomal neem gel.
10. Khyade, M.S. and Vaikos, N.P., *Wrightia tinctoria* R. Br.-a review on its ethnobotany, pharmacognosy and pharmacological profile. *Journal of Coastal Life Medicine*, 2014; 2(10): 826-840.
11. Çomoğlu, T., Gönül, N. and Baykara, T., Preparation and in vitro evaluation of modified release ketoprofen microsponges. *Il farmaco*, 2003; 58(2): 101-106.

12. Jain, N., Sharma, P.K. and Banik, A., Recent advances on microsphere delivery system. *International Journal of Pharmaceutical Sciences Review and Research*, 2011; 8(2): 13-23.
13. Jayasawal, P., Rao, N.R. and Jakhmola, V., Microsphere as novel drug delivery system: A review. *Indo Global Journal of Pharmaceutical Sciences*, 2022; 12: 21-29.
14. Singh, C.H., Jain, C.P. and Kumar, B.N., Formulation, characterization, stability and invitro evaluation of nimesulide niosomes. *Pharmacophore*, 2011; 2(3-2011): 131-148.
15. Nokhodchi, A., Jelvehgari, M., Siahi, M.R. and Mozafari, M.R., Factors affecting the morphology of benzoyl peroxide microspheres. *Micron*, 2007; 38(8): 834-840.
16. Killedar, S.G., Bhagwat, D.A., Choudhari, A., Saboji, J.K., Chougule, P.C. and Galatage, S.T., Development and Characterization of Microsphere of Amphotericin B for Topical Drug Delivery. *Research Journal of Pharmaceutical Biological and Chemical Sciences*, 2019; 10(1): 1288-1300.
17. Shaikh, A.A., Chaudhari, P.D. and Lavate, P.K., Central composite design for enhancement of etodolac solubility via inclusion complexation with PVP k-30 and Hydroxypropyl β - Cyclodextrin. *European Journal of Pharmaceutical and Medical Research*, 2017; 4(2): 657-63.
18. Asmita Singh, A.S. and Sudha Rathod, S.R., 2014. Design, development and characterization of liposomal neem gel.
19. Khyade, M.S. and Vaikos, N.P., *Wrightia tinctoria* R. Br.-a review on its ethnobotany, pharmacognosy and pharmacological profile. *Journal of Coastal Life Medicine*, 2014; 2(10): 826-840.