IJAPB International Journal of Advances in Pharmacy and Biotechnology

Journal homepage: http://ijapbjournal.com/

Research Article

Design, Fabrication and Evaluation of Ketorolac Tromethamine Loaded Microsponge Based Colon Targeted Tablet

Rehan Uddin[1], Vipul Sansare[2*]

[1]*Department of Pharmaceutics, Sir Madanlal Institute of Pharmacy, Etawah, Uttar Pradesh, India, 206001.*
[2*]*Department of Pharmaceutics, Indira Institute of Pharmacy, Sadavali, Ratnagiri, Maharashtra, India, 415804..*

ARTICLE INFO

Article history:
Received 05 April 2020
Received in revised form 16 April 2020
Accepted 17 April 2020
doi.org/10.38111/ijapb.20200602002

Keywords:
Inflammatory bowel diseases, Ketorolac tromethamine, Microsponges, Colon targeted system.

ABSTRACT

The present study was aimed to formulated ketorolac tromethamine (KTM) loaded microsponge based colon targeted tablet for treatment of inflammatory bowel diseases. The Eudragit S-100 polymeric microsponges were utilized for delivery of drug. The drug loaded microsponges were fabricated by quasi-emulsion solvent diffusion technique and were evaluated with respect to particle size, production yield, entrapment efficiency, surface morphology and micromeritics properties. Which were revealed good production yield, drug entrapment efficiency and spherical morphology. The microsponge based tablet (MBT) was prepared by direct compression using lactose and evaluated with respect to drug content and *in-vitro* drug release kinetics. The MBTs showed desirable amount of drug (90-95 %) and drug release profile up to 10 hrs. The drug release from MBT was followed zero order kinetics with diffusion-controlled mechanism. Thus, present study could be novel approach for colon targeted delivery of KTM.

1. Introduction

Inflammatory bowel diseases (IBD) is chronic intestinal disorders mainly occurs in two forms i.e. Crohn's disease (CD) and ulcerative colitis (UC). CD majorly affects the ileum and colon whereas UC may affect the entire colon.[1-2] The conventional oral drug delivery for treatment and management of IBD is less effective due to very less extent of administered drug actually reach at site of action. The colon targeted drug delivery (CTDD) useful for delivery of maximum extent of administered drug in colon. Thus, it is desirable for effective treatment and management of various disease conditions associated with colon such as irritable bowel syndrome, colon cancer and IBD. These systems prevent release of drug in the stomach and small intestine and initiate maximum extent of drug release upon entry into the colon. Several novel approaches have been investigated to achieve colon specific drug delivery.

Microsponges are cross-linked, porous, non-collapsible, polymeric microspheres that can entrap wide range of drugs.[4] These systems have been widely investigated for topical and oral administration of various drugs. Microsponges have capability to encapsulate relatively more amount of drug and improving stability of encapsulated drug. Thus, protects the encapsulated drug from physical and environmental degradation. In addition to this the encapsulated drug in polymeric microsponge releases in controlled manner thus it is possible to modify drug release profile using microsponge system which makes its suitability as drug carrier. Due to sponge like texture of microsponges, it has unique dissolution and compression properties. They are highly effective, non-toxic, non-mutagenic and improve patient's compliance. Various biocompatible polymers such as Eudragit, polystyrene, ethyl cellulose have been investigated to prepare microsponge. [5]

Microsponge based system was widely investigated for colon targeted delivery of various drugs. Comoglu *et al*., 2003[6] have prepared ketoprofen microsponges. Orlu *et al*., 2006[7] have investigated microsponge as a system for CTDD of flurbiprofen. Authors have reported zero order drug release profile of microsponge based tablet up to 15 hrs. Jain *et al*., 2010[8] have formulated dicyclomine encapsulated microsponge for CTDD. Jain *et al*., 2011[9] have fabricated paracetamol encapsulated microsponges for colon specific administration. Karthika *et al.,* 2013[10] have formulated lornoxicam loaded microsponge based colon targeted tablet. Kumari *et al*., 2017[11] have fabricated prednisolone loaded microsponges for CTDD. Othman *et al*., 2017[12] have formulated 5-fluorouracil loaded microsponges for treatment of colon cancer. Authors have reported more cytotoxic efficacy of drug loaded microsponges over free drug. Janakidevi *et al*.,

* *Corresponding author.* Tel.: +91-8692930764.
E-mail address: avipulsansare@gmail.com.

2018[13] have fabricated mesalamine loaded microsponge for CTDD for treatment of IBD. Janakidevi *et al*., 2018[14] have formulated diclofenac sodium loaded microsponge for CTDD for treatment of IBD.

Ketorolac tromethamine (KTM) is non-selective COX inhibitor classified under pyrrolo-pyrrole group of non-steroidal anti-inflammatory drugs. The chemical name of KTM is 5-benzoyl-2,3-dihydro-pyrrolizine- 1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).[15] This analgesic compound is used for the treatment of local disorders of colon like IBD and also has short biological half-life. The release of KTM in upper GIT causes gastric and duodenal toxic effects. Thus, colon specific drug delivery is desirable to deliver maximum extent of KTM at site of action with reduced toxic effects.

In the view of above-mentioned merits of microsponges for CTDD of analgesic drugs, the present study was started with aim to fabricate microsponge for colon targeted delivery of KTM.

2. Materials and Methods

Materials

Ketorolac tromethamine was kindly gifted by Symed Laboratories, Hyderabad, India. Eudragit S-100 was gifted by Evonik Pharma, Mumbai, India. Polyvinyl alcohol, ethanol and dichloromethane were purchased from SDFCL, Mumbai, India. Other chemicals, reagents and solvents were purchased locally.

Methods

Preparation of KTM loaded microsponges

The KTM loaded polymeric microsponges were fabricated by quasi‑emulsion solvent diffusion technique using various ratios of Eudragit S‑100 polymer.[16-17] The internal phase was prepared by dissolving weighed quantities of Eudragit S−100 and dibutyl phthalate in ethanol: dichloro-methane (1:1). Dibutyl phthalate was included in formulation to improve the plasticity of the polymer. Further KTM was dissolved in prepared polymeric solution through ultrasonication at 35 °C. This mixture was then injected into an aqueous solution of PVA with continuous stirring rate 500 rpm for 60 min. The microsponges were formed due to the evaporation of volatile solvent from the system. Prepared microsponges were then filtered, washed with distilled water and finally subjected to drying at 40 °C for 12 h in hot air oven. The prepared microsponges then weighed to determine production yield. The various formulation batches of microsponges were prepared by varying drug: polymer ratios as per **Table 1.**

Table 1: Composition of KTM microsponge batches (**F1-F5**).

Ingredients	F1	F2	F3	F4	F5
KTM: Eudragit S-100 (mg)	1:1	1:2	1:3	1:4	1:5
Ethanol: Dichloromethane (ml)	5	5	5	5	5
Dibutylphthalate (% w/v)	1	1	1	1	1
Polyvinyl alcohol (% w/v)	0.05	0.05	0.05	0.05	0.05
Water (ml)	100	100	100	100	100

Evaluation of KTM Loaded microsponge

Production yield: The production yield of KTM loaded microsponges was estimated by formula mentioned below.[18]

$$Production\ yield = \frac{Practical\ mass\ of\ microsponges}{Theoretical\ mass\ (polymer + drug)} \times 100$$

Actual drug content and drug encapsulation efficiency: The actual amount of drug encapsulated in microsponges is useful parameter to estimate weight of microsponges require for compression of each tablet. For determination of drug content, the accurately weighed quantity (10 mg) of drug loaded microsponges was kept in 100 ml PBS (pH 7.4) for 15 hrs with continuous stirring. After 15 hrs the medium was filtered through 0.45 µm membrane filter and analyzed for drug content using ultraviolet‑visible (UV) spectrophotometer at 322 nm. The drug content and encapsulation efficiency were calculated using following equations.[18]

$$Actual\ drug\ content = \frac{M_{act}}{M_{ms}} \times 100$$

$$Encapsulation\ efficiency = \frac{M_{act}}{M_{the}} \times 100$$

Where, M_{act} is actual KTM content in weighed quantity of microsponges, M_{ms} is weighed quantity of microsponges and M_{ther} is theoretical content of KTM in microsponges.

Particle size analysis: Particle size analysis of prepared microsponges was measured by using Zetasizer Nano ZS. Microsponges were dispersed in double distilled water containing stabilizer for measurement of particle size. The analysis was carried out at room temperature, keeping the angle of detection at 90°.

Assessment of surface morphology: Surface morphology of KTM loaded microsponges was studied using scanning electron microscope (FEI Quanta 250, USA). Samples were mounted on aluminum stub with carbon adhesive tape and sputter coated by means of palladium prior to assessment.

Micromeritic properties: The drug and blend of drug with excipients were evaluated for micromeritics properties like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. Bulk density was determined by placing 5 gm of microsponges into a graduated cylinder and by measuring the volume. Tapped density was calculated by placing 5 gm of the microsponges in a graduated cylinder and tapping it for 100 times. The calculated values of all are highlighted in Table 4.

Angle of repose: Angle of repose is the most common method used for assessing the flow property of material. It is angle between the horizontal surface and the slope of cone of solid dropped from some elevation. Angle of repose f microsponge blend was determined using funnel method.

Briefly 5 gm of microsponges were allowed to pass through a funnel that was raised vertically until a maximum cone height, 'h' was obtained. The radius of heap, 'r', was measured and angle of repose 'θ' was calculated using the following formula.[11]

$$\theta = tan^{-1}\frac{h}{r}$$

Carr's Index and Hausner's ratio: The Carr's Index provides information regarding ease with which a powder material can be induced to flow. It is a one-point determination. The Carr's Index and Hausners ratio were calculated using the following formula:[11]

$$Carr's\ index = \frac{Tapped\ density - bulk\ density}{Tapped\ density} \times 100$$

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Preparation of KTM microsponge based colon targeted tablet

The prepared drug loaded microsponges were formulated as tablets by "Direct compression method". All the ingredients were weighed accurately and mixed thoroughly. The lubricated blend was then compressed using 8 mm flat face punch.[7] The composition of different formulations used in the study is represented in **Table 2.**

Evaluation of KTM microsponge based colon targeted tablet

The tablets of KTM microsponges were evaluated with respect to weight variation, hardness, thickness, diameter, friability, drug content and *in-vitro* drug release kinetics. [19]

Table 2: Formulation of KTM microsponge based tablets **(TF1-TF5)**.

Ingredients	TF1	TF2	TF3	TF4	TF5
KTM microsponges (mg)	42.5	64	89	112	138
Lactose (mg)	150.5	129	104	81	55
Magnesium stearate (mg)	3	3	3	3	3
Kollidon K90 (mg)	4	4	4	4	4

Weight variation and Hardness: For the weight variation test, 20 tablets were randomly selected from each batch and weighed using sensitive balance. The weight of individual tablets was compared with average weight. Hardness of tablets was estimated using Monsanto hardness tester. For this purpose 3 tablets were randomly selected from each batch and hardness was measured. The results are expressed as mean± SD.

Thickness and diameter: The thickness and diameter of tablet were measured by using vernier calipers. The thickness and diameter of 10 tablets were individually measured and results expresses as mean± SD.

Friability: Friability was determined by Roche friabilator as per Indian Pharmacopoeia. [20] Briefly 10 tablets were weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were individually weighed again and percentage friability was calculated using the following equation:

$$\% friability = \frac{Initial\ weight - final\ weight}{Initial\ weight} \times 100$$

Drug content: Ten tablets were weighed and ground. The weight equivalent to 5 mg of KTM was taken and transferred to a 100 ml standard flask. 25 ml of ethanol and 25 ml of PBS (pH 7.4) were added and stirred for about half an hour and the volume was made up to 100 ml with PBS (pH 7.4). The resulting solution was filtered and analyzed for drug content using ultraviolet‑visible (UV) spectrophotometer at 322 nm after dilution with PBS.

In-vitro drug release kinetics: In vitro drug release kinetics of KTM microsponge based tablets was assessed using USP Type II dissolution apparatus. For assessment of drug release from colon targeted system, it is necessary to conduct experiment using various dissolution medium like simulated gastric fluid (SGF), simulated intestinal fluid (SCF) and simulated colonic fluid. The drug release was first assessed in SGF for 2 hours at 37° ± 0.5°C. Briefly microsponge based tablet was placed in vessel containing 500 ml of pH 1.2 (SGF without enzymes) at 37° ± 0.5°C for 2 hours at 75 rpm. After 2 hours, the pH of medium was adjusted to pH 6.8 (SIF) using 0.5N NaOH, volume was made up to 750 ml and the study was continued for 3 hours. Then, the pH of medium was adjusted to 7.4 with 0.5N NaOH and study continued for next 5 hours. Aliquots were withdrawn at regular time intervals, filtered and analyzed for drug content using UV spectroscopy at 336 nm (pH 1.2) and 322 nm (pH 6.8 and pH 7.4). All dissolution tests were performed in triplicates and results were expressed in the form of mean ± standard deviation.

In order to assess the kinetics of drug release from the microsponge based tablets, models were fitted to the dissolution study data of tablets using non-linear regression analysis. *In vitro* release data was fitted to various release models i.e.: Zero order, First order, Higuchi, Korsmeyer-Peppas and coefficient (R^2) values were calculated. The R^2 values were used as the indicator of the best fit to drug release data for each model.

3. Results and Discussion

Evaluation of KTM microsponges

Production yield: The estimated production yield of all five batches of KTM loaded microsponges were in range from 24.54% to 73.57%. The selected drug: polymer ratios were found to affect the production yield. With increase in drug: Polymer ratio from 1:1 (F1) to 1:5 (F5), the production yield was found to increase. The production yield for formulation batch F1 i.e. drug: Polymer ratio 1:1 was very low, i.e. 24.54% while that with drug Polymer ratio 1:5 (F5) was 73.57%. The drug: polymer can possibly change the rate of diffusion of volatile solvent in aqueous medium while formation of microspheres. The increase in polymer concentration was reported to reduce diffusion rate of volatile solvent to the aqueous phase, which can provides more time for formation of droplet following improved yield.

Actual drug content and drug encapsulation efficiency: The actual amount of drug encapsulated in microsponges was found to be lesser than theoretical amount of drug included in formulation, because drug encapsulation efficiency is less than 100%. The encapsulation efficiencies were in the range of 87.15 – 94.74% as mentioned in Table 3. The less entrapment efficiency of drug is may be due to dissolution of fraction of drug in aqueous phase which eventually loss.

Particle size and surface morphology: The particle size of drug loaded microsponges was found to be in the range of 32.74 - 87.34 µm. The photon correlation spectroscopy revealed that particle size has increased with increase in drug: Polymer ratio. It was because of the fact that with increase in drug: polymer ratio the more amount polymer was available for formation of microsponges which eventually increase polymer wall thickness which led to the more particle size of microsponges. The SEM image of microsponge revealed spherical shape of microsponges (**Fig. 1**).

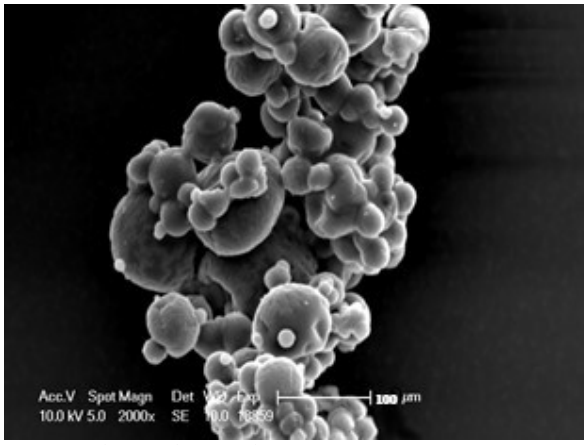

Fig. 1: SEM image of KTM microsponge

Table 3: Product yield, drug content, encapsulation efficiency, particle size of KTM microsponges & Micromeritics properties of KTM microsponges: excipient blend (n=3).

Code	PY*	ADC*	EE*	PS#	BD	TD	CR	HR	AR
F1	24.54±1.79	47.37±0.08	94.74± 0.02	32.74±3.72	0.64±0.02	0.71±0.01	9.85±0.01	1.10±0.02	26.54±1.31
F2	42.85±2.54	31.44±0.06	94.32± 0.01	46.12±5.47	0.58±0.04	0.64±0.01	9.37±0.02	1.10±0.01	22.39±1.8
F3	50.13±2.69	22.57±0.08	90.28± 0.02	63.19±5.89	0.46±0.01	0.51±0.02	9.80±0.02	1.10±0.03	21.27±1.54
F4	67.29±4.56	17.84±0.04	89.2 ± 0.03	68.57±6.75	0.39±0.03	0.45±0.04	13.33±0.04	1.15±0.04	19.26±1.46
F5	73.57±3.89	14.52±0.06	87.15± 0.02	87.34±8.19	0.37±0.02	**0.43±0.03**	13.95±0.03	1.16±0.02	18.13±1.37

PY: Production yield; ADC: Actual drug content; EE: Encapsulation efficiency; PS: Particle size; Bulk density (gm/cm3); Tapped density (gm/ cm3); Carr's index (%); Hausner's ratio; Angle of repose (θ˚)*= %± SD; # = µm

Micromeritic properties: The KTM microsponge based blend was free flowing as indicated by the values of bulk density (0.37 to 0.64 gm/cm^3), tapped density (0.43 to 0.71 gm/cm^3), compressibility index (9.8 to 13.95%) and Hausner's ratio (1.10 to 1.16). Angle of repose ranged from 18.13 to 26.54 θ°. The values are given in **Table 4**.

Evaluation of KTM microsponge based tablet

The KTM microsponge based tablets were compressed by using direct compression technique. The theoretical content of KTM in each tablet was 20 mg and total weight of each tablet was 200 mg. As content of KTM in microsponges has observed to be vary with change in drug: polymer ratio (F1 to F5), the weight of microsponge equivalent to 20 mg of KTM is also varies from F1 to F5 (Table 2). Thus amount of diluent i.e. lactose was change accordingly to adjust weight of tablet up to 200 mg. The prepared microsponge based tablets were evaluated with respect to weight variation, hardness, diameter, thickness, friability and drug content. The mean weight of the core tablet formulations TF1 to TF5 was found to be around 201 mg. The variation in weight was within the range (i.e. < 5%) which complies with the pharmacopoeial specifications.[21] The hardness was found to range in between 4.1 to 4.7 kg/cm^2 revealed acceptable mechanical strength. The friability of the core tablet was in range of 0.68 to 0.81%. The diameter of tablets was in range of 8 to 8.06 mm with thickness 3 to 3.03 mm. The friability of all batches of tablet was in range of 0.25 to 0.47 % indicating good mechanical strength. The drug content of the microsponge based tablet was found to be around 90 – 95% indicating desirable amount of drug loaded in the tablets.

***In-vitro* drug release kinetics**

In vitro drug release kinetics of KTM microsponge based tablets was assessed using USP Type II dissolution apparatus. It was observed that very few amount drug (<7%) was released in the first 5 hr from all batches of tables. After the lag time of 5 hr, the release of drug started at 6th hr in colonic fluid. The less extent of drug release in first 5 hours i.e. in SGF and SIF is due to insolubility of Eudragit S-100 in acidic medium. The polymer selected for fabrication of microsponge exhibit pH dependent solubility and show maximum solubility at pH above 7. Thus less extent of drug release in first 5 hours and maximum extent of drug release in SCF at pH 7.4 due to dissolution of Eudragit S-1. At 6th hr, the percent of drug release from different microsponge based tablet formulations i.e. TF1, TF2, TF3, TF4 and TF5 was observed to be 38.17 ± 0.24%, 39.27 ± 0.34%, 42.19 ± 0.17%, 45.17 ± 0.38%, and 32.47 ± 0.26% respectively.

The overall percent cumulative drug release from all microsponge based tablets at the end of 10 hr was found to be around 94%. Furthermore *In vitro* drug release mechanism was also studied for prepared microsponge based tablets. The obtained data of percent cumulative drug release was treated with zero order, first order, Higuchi and Korsmeyer-Peppas models and R^2 values were calculated for each microsponge based tablet formulation. The R^2 values are represented in table 6. The calculated data suggested that, the release kinetics followed zero order kinetics and the drug release mechanism was observed to be the diffusion mechanism. Thus prepared microsponge based tablets were found to extend drug release.

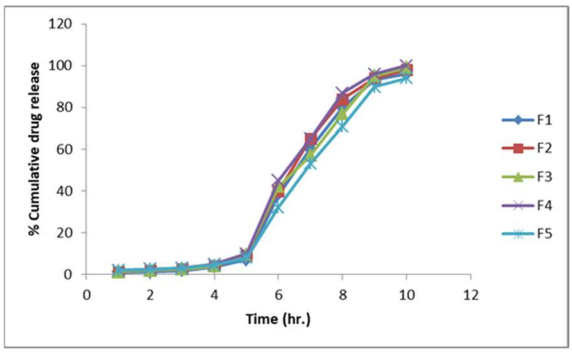

Fig. 2: In-vitro drug release profile of microsponge based tablets

4. Conclusion

The aim of the present was to formulate KTM encapsulated microsponge based colon targeted tablet. The Eudragit S-100 polymeric microsponge revealed acceptable production yield, drug content and drug entrapment efficiency with spherical shape. All batches microsponge based tablets showed minimum extent of drug release in SGF and SIF whereas releases maximum amount in simulated colonic fluid. The drug release profile followed zero order kinetics with diffusion-controlled release mechanism. Thus, microsponge based colon targeted tablet could be novel approach for colon specific delivery of KTM. However, addition studies are required to prove in-vivo efficacy of prepared formulations.

Acknowledgements

Authors would like to say thanks to Saymed Laboratories (Hyderabad, India), Evonik Pharma (Mumbai, India), Department of Pharmaceutics, Bombay college of Pharmacy (Mumbai, India) and Central Institute of Research on Cotton Technology (Mumbai, India) for excellent technical support.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

References

1. Corridoni D, Arseneau KO and Cominelli F. Inflammatory bowel disease. *Immunol Lett*., 2014; 161: 231-235.
2. Goyal N, Rana A, Ahlawat A, Bijjem KR and Kumar P. Animal models of inflammatory bowel disease: a review. *Inflammo pharmacology*., 2014; 22: 219-233.

Table 5: Physical evaluation parameters & Drug release model curve fitting of KTM microsponge based tablet.

Code	Physical Parameters						R^2 value			
	Weight (mg) (n=20)	Hardness (Kg/cm^2) (n=3)	Diameter (mm) (n=10)	Thickness (mm) (n=10)	Friability (%) (n=10)	Drug content (%) (n=10)	Zero order	First order	Higuchi	Korsmeyer-Peppas
TF1	200.02 ± 0.97	4.2 ± 0.17	8 ± 0.18	3.03 ± 0.2	0.42 ± 0.01	95.03 ±0.63	0.9703	0.9331	0.8037	0.854
TF2	201.12 ± 0.94	4.45 ± 0.23	8.04 ± 0.31	3.01 ± 0.3	0.37 ± 0.01	93.5 ± 0.41	0.9612	0.9357	0.8103	0.8672
TF3	200.07 ± 1.27	4.1 ± 0.14	8.06 ± 0.25	3 ± 0.1	0.43 ± 0.02	93.85 ± 0.4	0.9026	0.9402	0.8133	0.8723
TF4	202.06 ± 2.81	4.7 ± 0.27	8 ± 0.13	3.02 ± 0.2	0.25 ±0.01	92.36 ± 0.18	0.9423	0.9268	0.8143	0.8371
TF5	202.03 ± 2.75	4.3 ± 0.18	8.04 ± 0.22	3.01 ± 0.3	0.47 ± 0.03	90.24 ±0.14	0.938	0.9426	0.7933	0.8316

3. Moin A, Deb T, Osmani R, Bhosale R and Hani U. Fabrication, characterization, and evaluation of microsponge delivery system for facilitated fungal therapy. J Basic Clin Pharma., 2016; 7:39-48.
4. Bhatia M and Saini M. Formulation and evaluation of curcumin microsponges for oral and topical drug delivery. *Progress in Biomaterials*., 2018; 7: 239-248.
5. Sansare V. Microsponges: A novel drug delivery system. *Indian J. Res*., 2019; 8(9):1-3
6. Comoğlu T, Gönül N and Baykara T. Preparation and in vitro evaluation of modified release ketoprofen microsponges. *Il Farmaco*., 2003; 58: 101-106.
7. Orlu M, Cevher E and Ahmed A. Design and evaluation of colon specific drug delivery system containing flubriprofen microsponges. *Int. J. Pharm*., 2006; 318: 103-117.
8. Jain V and Singh R. Dicyclomine-loaded Eudragit®-based Microsponge with Potential for Colonic Delivery: Preparation and Characterization. *Trop J Pharm Res*., 2010; 9(1): 67-72
9. Jain V, Singh R. Design and characterization of colon-specific drug delivery system containing paracetamol microsponges. *Arch. Pharm*. Res., 2011; 34: 733-740.
10. Karthika R, Elango K, Kumar R and Rahul K. Formulation and evaluation of lornoxicam microsponge tablets for the treatment of arthritis. *Int. J. Pharma. Innovation*., 2013; 3(2): 29-40.
11. Kumari A, Jain A, Hurkat P, Tiwari A and Jain S. Eudragit S100 Coated Microsponges for Colon Targeting of Prednisolone. *Drug Dev Ind Pharm*., 2017; 44(6): 902-913
12. Othman M, Zayed G, El-Sokkary G, Ali U and Abdellatif A. Preparation and Evaluation of 5-Fluorouracil Loaded Microsponges for Treatment of Colon Cancer. *J Cancer Sci Ther*., 2017; 9: 307-313.
13. Janakidevi S and Ramanamurthy K. Development of Colon-targeted Microsponges for the Treatment of Inflammatory Bowel Disease. *Indian J Pharm Sci*., 2018; 80(4): 604-609.
14. Janakidevi S and Ramanamurthy K. Design of a novel colon targeted microsponges loaded with diclofenac sodium using three different polymers. *Int. Res. J. Pharm*., 2018; 9(4): 10-19.
15. Sharma S, Sharma A, Sara U and Singh S. Chitosan Loaded Ketorolac Tromethamine Nanoparticles for Improved Ocular Delivery in Eye Inflammation. *Indian J of Pharmaceutical Education and Research*., 2018; 52(4 Suppl 2): s202-s209.
16. Moin A, Deb T, Osmani R, Bhosale R and Hani U. Fabrication, characterization, and evaluation of microsponge delivery system for facilitated fungal therapy. *J Basic Clin Pharma*., 2016; 7:39-48.
17. Devrim B and Canefe K. Preparation and evaluation of modified release ibuprofen microspheres with acrylic polymers (Eudragit) by quasi emulsion Solvent diffusion method: effect of variables. *Acta Pol Pharm*., 2006; 63:521-34.
18. Pande V, Kadnor N, Kadam R and Upadhye S. Fabrication and Characterization of Sertaconazole Nitrate Microsponge as a Topical Drug Delivery System. *Indian J Pharm* Sci., 2015; 77(6):675-680.
19. Banker G, Anderson N. The Theory and Practice of Industrial Pharmacy: Tablet. Lachman (3rd eds) Varghese Publishing House, Bombay; 1990, pp. 171-195.
20. Pharmacopoeia I. Govt. of India, Ministry of Health and Family Welfare, Delhi, Ghaziabad,2014. Vol II. 2014;2066.
21. Pharmacopoeia I. a publication of the IP commission. Ministry of Health & Family Welfare Government of India. 2013;3.