AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Preparation and Characterization of Diclofenac Sodium Loaded Microsponges for Capsule

Kirti A Londhe[1]*, Sheetal B Gondkar[1], Ravindranath B Saudagar[2]
1. Dept. of Pharmaceutics R.G. Sapkal College of Pharmacy Kalyani Hills, Anjaneri, Nashik-422213. (INDIA)
2. Dept. of Pharmaceutical Chemistry R.G. Sapkal College of Pharmacy Kalyani Hills, Anjaneri, Nashik-422213. (INDIA).

ABSTRACT

Microsponges are tiny, uniform, micro-porous polymeric beads and spherical in shape. It has the interconnected voids. The particle size of it ranges between 5-300µm. The porous surface of non-collapsible structure of microsponges helps to deliver the active ingredient in controlled manner. Diclofenac Sodium is a Non-steroidal anti-inflammatory drug. The plasma half-life of Diclofenac is 1-2 hrs which increases the dosing frequency and this drug also causes the gastrointestinal irritation. Therefore the purpose of present investigation was to design suitable controlled release Diclofenac Sodium microsponges which can reduce the dosing frequency and gastric irritation. In the present work, Diclofenac Sodium loaded eudragit microsponges were prepared using quasi emulsion solvent diffusion method. Different drug: polymer ratios were used to formulate the microsponges. The compatibility of the drug with polymer was established. Surface morphology of the microsponges was examined using scanning electron microscopy. Production yield, loading efficiency, particle size analysis, and in-vitro release studies were carried out. In-vitro release study showed that the release of drug was in controlled manner and it was increased with increase in drug to polymer ratio up to certain limit.

Keywords: Microsponges, Diclofenac Sodium, Eudragit RS100, Controlled release, Quasi-emulsion.

*Corresponding Author Email: kirtialondhe20@gmail.com
Received 07 November 2014, Accepted13 November 2014

Please cite this article as: Londhe KA *et al*., Preparation and Characterization of Diclofenac Sodium Loaded Microsponges for Capsule. American Journal of PharmTech Research 2014.

INTRODUCTION[1, 2, 3]

Many of conventional delivery systems require high concentrations of active agents to be incorporated for effective therapy because of their low efficiency as delivery systems. Thus novel drug delivery systems have been increasingly investigated to achieve targeted and controlled release of drugs. Microsponges are highly crosslinked, patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and recently for oral administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, elegance, flexibility in formulation, reduce side effects and modify drug release profiles. Microsponges are prepared by several methods utilizing emulsion systems as well as by suspension polymerization in a liquid-liquid system. The most common emulsion system used is Quasi-emulsion solvent diffusion method. Diclofenac Sodium is a non-steroidal anti-inflammatory drug. The anti-inflammatory effects of diclofenac are believed to be due to inhibition of leukocyte migration and enzyme cyclooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of diclofenac. Diclofenac is metabolised to 4'-hydroxydiclofenac, 5-hydroxydiclofenac, 3'-hydroxydiclofenac and 4', 5-dihydroxydiclofenac. Chemically it is Sodium 2 -[(2,6-dichlorophenyl)-amino]phenylacetate. Diclofenac sodium is BCS class II drug i.e. high permeability low solubility. The plasma half-life of Diclofenac is 1-2 hrs which increases the dosing frequency. This drug also causes the irritation of gastrointestinal tract. Thus the present study is aimed at developing microsponge based novel drug delivery system containing Diclofenac Sodium. The microsponges of Diclofenac Sodium were prepared and characterized. They were filled in capsule and subjected to *in-vitro* characterization for various attributes.

MATERIALS AND METHODS

Materials

Diclofenac Sodiumwas obtained as gift sample from Kirti Pharma Chem, Sinnar, Nashik. Polyvinyl Alcohol and Triethyl citrate were obtained as gift sample from Glenmark Pharmaceuticals, Sinnar, Nashik. All other chemicals and solvents were of analytical grade.

Drug-Excipient Interactions[4, 5]

The physicochemical compatibilities of the drug and polymer were tested by FT-IR spectrophotometry. FT-IR spectra of the drug alone and drug-polymer physical mixtures (1:1 w/w)

were derived from Alpha T- BRUKER, FT-IR.

Formulation of diclofenac sodium loaded microsponges[6, 7, 8]

The microsponges of Diclofenac Sodium were prepared by using quasi emulsion solvent diffusion technique. The internal phase was prepared by dissolving Drug and polymer in ethanol in the ratio 1:1, 3:1, 5:1, 7:1, 9:1, 11:1, 13:1 followed by addition of triethyl citrate. The internal phase was then poured into aqueous solution of polyvinyl alcohol, the external phase, and kept for continuous stirring and heating. After 3hrs of continuous stirring and heating, the microsponges were formed due to evaporation of alcohol. Then the microsponges were filtered and dried at 40^0c for 12hrs. For this purpose mini magnetic stirrer (DBK instruments) was used. The composition of microsponge formulations are given in table 1.

Table 1: Composition of various microsponge formulations

Ingredients	Ratios (Drug: Polymer)						
	1:1	3:1	5:1	7:1	9:1	11:1	13:1
Diclofenac Sodium (mg)	50	150	250	350	450	550	650
Eudragit RS 100 (mg)	50	50	50	50	50	50	50
PVA (mg)	3	3	3	3	3	3	3
Ethanol (ml)	3	3	3	3	3	3	3
TEC (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
DW (ml)	60	60	60	60	60	60	60

Evaluation of diclofenac sodium loaded microsponges

Particle size determination[8]

Particle size of microsponges was determined using Motic microscope (Motic DMB series). To determine the particle size, small amount of microsponges were taken on glass slide and slide was placed on stage of microscope. Then the coarse and fine adjustment was done to obtain the clear image. The reading of particle size was displayed on the display of computer. Same procedure was repeated for all batches.

Surface Morphology [9, 10]

Scanning electron microscopy of optimized microsponge formulation was carried to determine the surface morphology. The sample was mounted directly onto the SEM sample holder using double sided sticking tape and images were recorded at different magnifications at acceleration voltage of 10 kV using scanning electron microscope (JSM 6930, JEOL/EO Datum Ltd. Japan).

Differential scanning calorimetry[11, 5]

For the structural, crystal and physical state characterization of Diclofenac Sodium, the DSC study was performed for pure drug, and formulation. Accurately weighed sample of drug and

formulation was placed in a sealed aluminium pans before heating under nitrogen flow (20 ml/min) at a scanning rate of 10^0C per min from 25 to 300^0C. An empty aluminium pan was used as a reference.

Loading efficiency and Production yield[7, 12]

Loading efficiency

Diclofenac Sodium microsponges equivalent to 10 mg of the drug was taken in a 10 ml volumetric flask. 5 ml methanol was added and shaken for about half an hour and the volume was made up to 10 ml with methanol. 0.1 ml of the solution was taken and diluted to 10 ml with methanol. The absorbance of the resulting solution was measured at 275nm and the content of Diclofenac Sodium was calculated. The loading efficiency (%) of the microsponges was calculated by using following formula.

$$\textbf{\textit{Loading efficiency}}\ (\%) = \frac{DCact}{DCtheo.} \times 100 \text{---------- (1)}$$

Where, DC act = Actual drug content in microsponges

DC theo. = Theoretical drug content.

Production yield

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the weight of the microsponge obtained.

$$\textbf{\textit{Production yield}}\ (\%) = \frac{Wpr}{Wth} \times 100 \quad \text{----------(2)}$$

Where, W pr = Practical mass of Microsponges

W th = Theoretical mass (Polymer + Drug).

Porosity[13, 14]

Porosity of microsponges was calculated by using following equation.

$$\textbf{\textit{Porosity}}\ (\%) = \frac{Bulk\ volume - True\ volume}{Bulk\ volume} \times 100 \text{---------- (3)}$$

To measure the bulk volume, weighed amount of microsponges was poured into 1 ml pipette and the bulk volume was noted to nearest graduated unit. True volume was determined by liquid displacement method.

In-vitro Drug Release Study[15, 16]

The *in vitro* drug release study of microsponges (equivalent to dose of Diclofenac Sodium filled in capsule)and plain drug filled in capsules werecarried out inthe USP Dissolution apparatus type II(Electrolab TDT 08L). Phosphate buffer pH 6.8 was used as dissolution medium. Temperature was maintained at 37^0C ± 0.5^0C and paddle was rotated at the speed of 50 rpm.Drug release was monitored for 30 min, 1, 2, 3, 4, 5, 6, 7, 8^{th} hr. 5ml of sample was withdrawn at each time intervals

and sink condition was maintained by replacing an equal amount of fresh dissolution medium. Samples were filtered and analyzed by UV-Visible spectroscopy (Jasco V 630) at 275nm.Dissolution rate was studied for all formulations in triplicate.

Dissolution kinetics[17]

The dissolution profile of optimized formulation was subjected to various models such as Zero order kinetics (percentage drug release against time), First order kinetics (log percentage drug unreleased against time), Higuchi (percentage drug released against square root of time), Korsemeyer-Peppas (log percent drug released against log of time) and Hixson-Crowell **(**cube root of cumulative percentage of drug remaining against time) to assess the kinetics of drug release from prepared Diclofenac Sodium loaded microsponges.

Stability Studies[18]

Stability study of optimized formulation was carried out to point out any chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized Diclofenac Sodium loaded microsponge formulation was assessed at $25^0c\pm2^0c$/ 60% ±5% RH as per ICH Guidelines. The powder of microsponge formulation equivalent to 50 mg of Diclofenac Sodium was packed with aluminium strip and stored for 6 months. Sample was analyzed after 3 months and 6 months for drug content and *in-vitro* dissolution profile**.**

RESULTS AND DISCUSSION

In the present work, FT-IR spectra of Diclofenac Sodium and physical mixture of drug and polymer were examined. In FT-IR spectra of drug, the major peaks at 3018.36 cm^{-1}(Aromatic C-H stretching), 1449.60 cm^{-1} (C=C stretching), 1691.30 cm^{-1} (C=O stretching), 1561.69 cm^{-1}, 1505.98 cm^{-1} (N-H bending), 748.11 cm^{-1} (C-Cl), 1181.32 cm^{-1}, 1291.33 cm^{-1}, 1398.75 cm^{-1} (C-N) were seen. All these peaks were present in physical mixture of drug and polymer. This is an indication of no drug-polymer interaction and hence it can be said that the polymer is compatible with the active pharmaceutical ingredient. The FT-IR spectra of drug and drug with polymer are shown in Figure. 1 and 2. Particle size analysis showed that the mean perimeter was found to be in the range of 12.4 to 36.4 µm. Mean particle size of formulations 1:1 to 13:1 is given in table2. The SEM Micrograph of the microsponges at 200X and 100µmshowed the porous surface of microsponge and it is shown in Figure. 3. DSC thermograph of Diclofenac Sodium is shown in Figure. 4 which shows melting endotherm at 286.19^0c i.e. melting point and crystalline state of drug. DSC thermograph of microsponge (11:1) formulation is shown in Figure. 5. Thermograph

showed melting endotherm at 237.11^{0}c indicates that drug was embedded in matrix of polymer used. Loading efficiency of microsponges was increased with increase in concentration of drug in drug: polymer ratio. Maximum loading efficiency was found for 11:1 drug: polymer ratio. Results obtained from calculation are shown in table 2.Maximum production yield was found for batch containing 11:1 drug: polymer ratio. The porosity of microsponges was decreased with increase in concentration of drug in drug: polymer ratio. Maximum porosity i.e. 67.75% was found for 1:1 ratio of drug: polymer and minimum porosity i.e. 52.08% was found for 13:1 ratio of drug: polymer. Results obtained from calculation are shown in table 2. The release profiles obtained for the microsponges are presented in Figure. 6. Release study has shown that drug release from the microsponges was in controlled manner as compared to pure drug and it was increased with increase in concentration of drug in drug: polymer ratio upto certain limit i.e. 11:1 ratio of drug: polymer.Drug release for 13:1 ratio of drug: polymer was found to be fairly similar to that of 11:1 ratio of drug: polymer. So it can be postulated that there was not considerable change in release pattern after increasing concentration of drug in drug: polymer ratio. Hence 11:1 proportion of drug: polymer should be an ideal and optimized ratio for considering drug release.The pure drug filled in capsules has shown 40.72% drug release within 30 min and 91.57% drug release within first 4 hours. Maximum drug release i.e. 98.29% upto 8 hours was found for formulation containing 11:1 ratio of drug: polymer which indicates that microsponges has shown better controlled release up to 8 hours for release of 98.29% of drug. The present study of dissolution was analyzed by PCP Disso Version 3 software to study the dissolution kinetics. The R^2 values for various release models are 0.9839 for Zero order, 0.9871 for First order, 0.9700 for Higuchi, 0.9931 for Korsemeyer-Peppas and 0.9861for Hixson-Crowell kinetics. The results showed that the optimized batch followed korsmeyer- peppas model kinetics. The R^2 value of korsmeyer-peppas model was found close to one.The Drug Release Kinetics for best fitting optimized batch was calculated and it is shown in table 3. The release exponent n = 0.7 indicates that it is following non -Fickian release (anomalous), this means that drug release followed controlled release mechanism. Optimized formulation was subjected to stability studies as per ICH guidelines. Parameters such as drug content and in-vitro drug release were measured before and after 3 and 6 months of stability. Results of stability studies are shown in table 4. Physical appearance of optimized formulation was unaffected or did not show any significant change. Results of stability studies has shown that there is no significant change in above mentioned parameters upto 6 month period of given temperature and humidity conditions during stability studies. Thus, it can be proved from the stability studies that the prepared formulation was stable up to 6 month period.

Table 2: Evaluation of Microsponges

Parameters	Formulations						
	1:1	3:1	5:1	7:1	9:1	11:1	13:1
Mean perimeter (µm) ± SD	12.10 ± 0.015	13.34 ± 0.040	13.23 ± 0.031	12.38 ± 0.026	21.44 ± 0.040	29.45 ± 0.051	36.43 ± 0.038
Loading efficiency % ± SD	93.14 ± 0.036	93.64 ± 0.040	94.52 ± 0.032	94.72 ± 0.031	96.83 ± 0.035	98.92 ± 0.030	98.91 ± 0.026
Production yield %	55.32	63.51	71.66	52.48	51.08	84.85	81.43
Prosity % ± SD	67.72 ± 0.031	62.75 ± 0.051	59.07 ± 0.031	57.12 ± 0.076	56.73 ± 0.042	54.77 ± 0.025	52.10 ± 0.020

Table 3: Drug release kinetics for optimized batch

Sr. No.	Model Fitting	R^2 Value	N	K
1.	Korsmeyer- peppas	0.9931	0.7437	2.1411

Table 4:Stability study of optimized formulation

Sr. No.	Stability Parameters	Before Stability Testing	After Stability Testing	
			3 Months	6 Months
1.	Drug Content (%) ± SD	98.91 ± 0.026	98.60± 0.031	98.45± 0.025
2.	*In-vitro* drug release study (%) ± SD	98.29 ± 0.012	98.20± 0.036	98. 15± 0.031

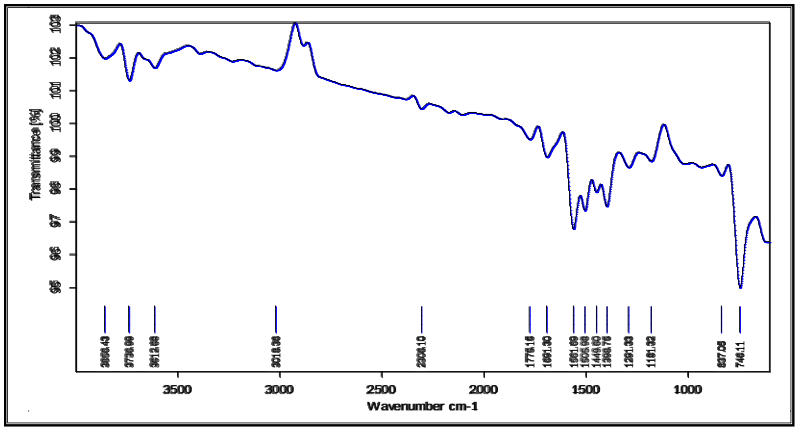

Figure. 1: FTIR spectrum of Diclofenac Sodium

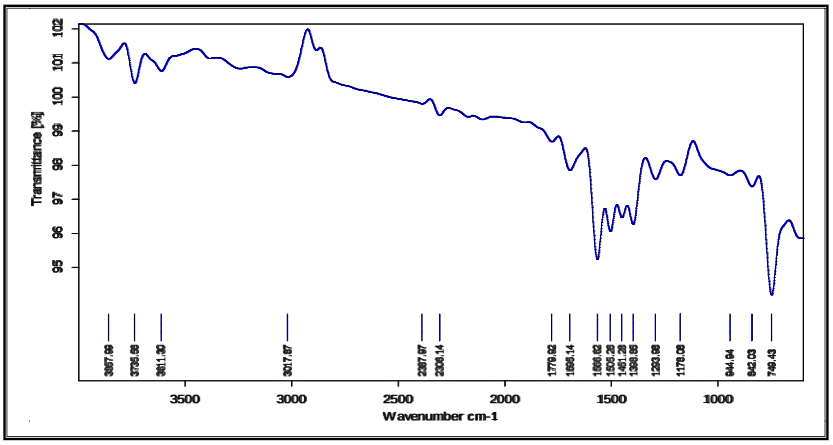

Figure. 2: FTIR spectrum of Diclofenac Sodium and polymer'sphysical mixture

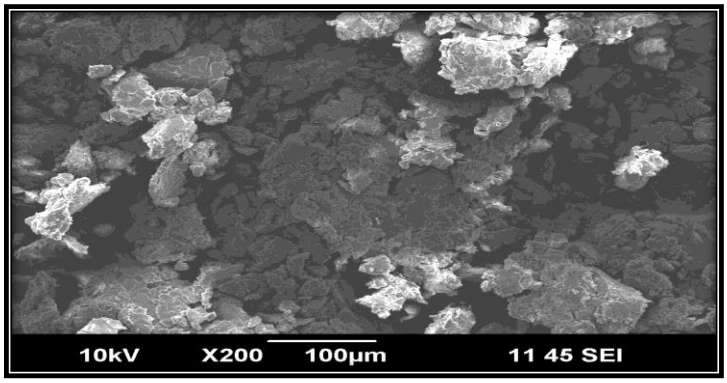

Figure. 3: SEM photograph of microsponge formulations

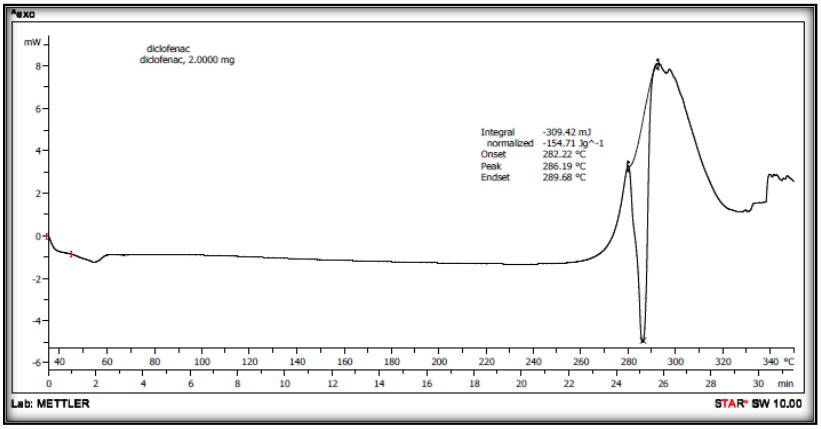

Figure. 4: DSC Thermograph of Diclofenac Sodium

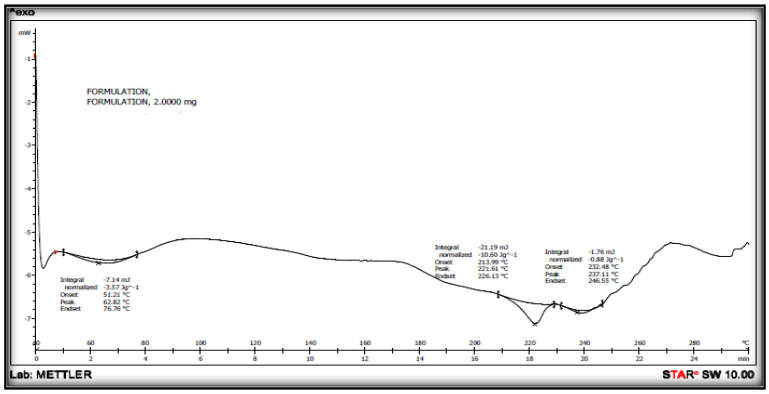

Figure. 5:DSC Thermograph of MS (11:1) Formulation

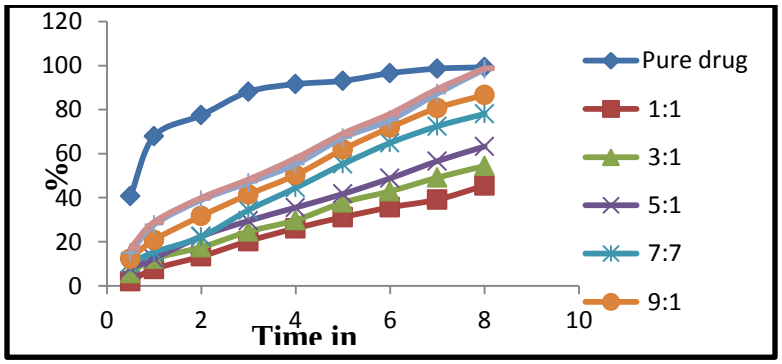

Figure. 6: Comparative in-vitro drug release profile of different ratios of microsponges

CONCLUSION

From all the results obtained after various evaluations, it can be considered that the microsponges can be formulated using quasi emulsion solvent diffusion technique. Formulation containing lowest concentration of eudragit RS 100 showed excellent results. Thus, this study presents a new approach for the preparation of modified microsponges with prolonged release characteristics. The prepared microsponges exhibited characteristics of an ideal delivery system.

REFERENCES

1. Pradhan SK. Microsponges as the Versatile Tool for Drug Delivery System. International Journal of Research in Pharmacy and Chemistry 2011; 1(2): 243-244.
2. Yerram C, Shaikh F, Rubia Y, Amaravathi V, Mahitha B, Aruna U. Microsponges: A Novel Drug Delivery System for Controlled Delivery of Topical Drugs. International Journal of Pharmaceutical Research and Analysis 2012; 2(2): 79-80, 84-85.
3. Mandava SS, Thavva V. Novel Approach: Microsponge Drug Delivery System. International Journal of Pharmaceutical Sciences and Research 2012; 3(4): 967.
4. Pavia DL, Lampman GM, Kriz GS, Vyvyan JR. Spectroscopy. New Delhi: Cengage Learning; 2007: 37-40.
5. Sabyasachi M, Santanu K, Somasree R, Biswanath SA. Development and Evaluation of Xanthan Gum-Facilitated Ethyl Cellulose Microsponges for Controlled Percutaneous Delivery of Diclofenac Sodium. Acta Pharm 2011; 61: 257-270.
6. Gonul N, Comoglue T, Baykara T. The effects of Pressure and Direct Compression on Tableting of Microsponges. International Journal of Pharmaceutics 2002; 242: 191-195.
7. Karthika R, Elango K, Ramesh K, Rahul K. Formulation and Evaluation of Lornoxicam Microsponge Tablets for the Treatment of Arthritis. International Journal of Pharmaceutical Innovations 2013; 3(2): 29-40.
8. D'souza JI, More HN. Topical Anti-Inflammatory Gels of Fluocinolone Acetonide Entrapped in Eudragit Based Microsponge Delivery System. Research Journal of Pharmacy and Technology 2008; 1(4): 502-506.
9. Jain V, Singh R. Development and Characterization of Eudragit Rs 100 Loaded Microsponges and its Colonic Delivery using Natural Polysaccharides. Acta Poloniae Pharmaceutica Drug Research 2010; 67(4): 407-415.
10. Amrutiya N, Bajaj A, Madan M.Development of Microsponges for Topical Delivery of Mupirocin. American Association of Pharmaceutical Scientists 2009; 10(2): 402-409.

11. Mahajan AG, Jagtap LS, Chaudhari AL, Swami SP, Mali PR. Formulation and Evaluation of Microsponge Drug Delivary System using Indomethacin. International Research Journal of Pharmacy 2011; 2(10): 64-69.
12. Saboji JK, Manvi FV, Gadad AP, Patel BD. Formulation and Evaluation of Ketoconazole Microsponge Gel by Quasi Emulsion Solvent Diffusion. Journal of Cell and Tissue Research 2011; 11(1): 2691-2696.
13. Subrahmanyam CVS. Textbook of Physical Pharmaceutics. 2nd ed., Delhi: Vallabh Prakashan; 2008: 213 & 218.
14. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 6th ed., Wolters Kluwer; 2011: 461.
15. Jain V, Singh R. Dicyclomine-loaded Eudragit®-based Microsponge with Potential for Colonic Delivery: Preparation and Characterization. Tropical Journal of Pharmaceutical Research 2010; 9(1): 67-72.
16. Baykara T, Comoglu T, Gonul N. Preparation and In Vitro Evaluation of Modified Release Ketoprofen Microsponges. IL Farmaco 2003; 58: 101-106.
17. Costa P, Lobo JM. Modeling and Comparison of Dissolution Profiles. European Journal of Pharmaceutical Sciences 2001; 13: 123-133.
18. ICH Harmonized Tripartite Guideline, International Conference on Harmonization. Stability testing of new drug substances and products Q1A (R_2) and Evaluation for stability data Q1E. Current step version, 6 February 2003.