Journal of Applied Pharmaceutical Science Vol. 5 (10), pp. 142-146, October, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.501024
ISSN 2231-3354 (cc) BY-NC-SA

The effect of different grades polymer blends on release profiles of diclofenac sodium from hydrophilic matrices

Sachin S. Mitkare[1*], Dinesh M. Sakarkar[2]

[1]Department of Pharmaceutics, School of Pharmacy, SRTM University, Nanded-431606, M.S. India.
[2]Department of Pharmaceutics, S.N. Institute of Pharmacy, Pusad-445204, M.S. India.

ARTICLE INFO

Article history:
Received on: 21/07/2015
Revised on: 12/08/2015
Accepted on: 30/08/2015
Available online: 28/10/2015

Key words:
Diclofenac sodium,
Hydrophilic matrix,
Hydroxypropylmethylcellulose,
Sustained release.

ABSTRACT

An attempt was made to design matrix tablet of diclofenac sodium by using various grades of hydroxypropyl methyl cellulose (HPMC E50, E15 and E300LV). The effect of hydrophilic polymers was studied on release characteristics of the diclofenac matrix tablet. Dicalcium phosphate and magnesium stearate were used as an excipients. Tablets were prepared by direct compression method. The *in vitro* dissolution test carried out for 12 hrs using USP dissolution apparatus II at 50 rpm in 900ml phosphate buffer pH 6.8. Statistically significant difference was found among the drug release profile from different matrices. The tablet evaluation parameters of hardness, friability, thickness, content uniformity were founded within the limit. At a fixed polymer level, drug release from the higher viscosity grades E50 was slower as compared to the lower viscosity grades (E300LV and E15). Tablet prepared with HPMC E50 is more release retardant. As the drug to polymer ratio increased drug release decreased. The dissolution study revealed that maximum retardation of the drug was obtained by highest viscosity grade HPMC at higher concentrations. The release of the model drug from these HPMC matrix tablets was prolonged.

INTRODUCTION

Diclofenac sodium is a non-steroidal anti-inflammatory agent, which is commonly used for rheumatoid arthritis as long-term therapy. The biological half-life of diclofenac sodium is about 1-2 hrs; therefore to maintain a therapeutic drug blood level, it requires multiple dose. After long-term and frequent administration of diclofenac sodium, it gives adverse side effects like gastrointestinal disturbances, peptic ulceration, and perforation (Scholer *et al.,* 1986; Lin *et al.,* 1991). Diclofenac sodium is one of the most useful NSAIDs agents. It is a practically insoluble in an acidic solution (pKa 4.0), but get dissolved in intestinal fluid and water (Bravo *et al.,* 2004). The conventional tablets make the drug immediately available for absorption in the upper GI tract resulting local GI toxicity varying from minorgastric discomfort to ulceration and bleeding of the mucosa (Carson *et al.,* 1990 and Sivakumar *et al.,* 2010). It is well documented that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but it is probably also due to direct contact of the drug with the mucosa (Carson *et al.,* 1990). In addition, due to the rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times a day is required in maintenance therapy that influences patient compliance. Sustained release formulations of diclofenac sodium are thus supposed to promote patient compliance and to reduce upper GI toxicity to some extent. Diclofenac sodium is well absorbed in the colon (Bjamason *et al.,* 1991) and thus colon-specific release of this drug can be used for the treatment of widespread inflammatory bowel diseases. The matrix tablet by direct compression can be formulated with technological simplicity. As compared to other controlled release systems, matrix tablets required fewer unit operations, less equipments, reduced number of personnel and processing time, enhanced product stability and production rate. Hydroxypropylmethylcellulose is a swellable and hydrophilic polymer, widely used in solid dosage form. Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs (Gleiter *et al.,* 1985). It is very suitable to use HPMC as release retardant material in matrix tablets (Heng *et al.,* 2001 and Lee *et al.,* 1999).

* *Corresponding Author*
E-mail: sachinpharma08@gmail.com

© 2015 Sachin S. Mitkare and Dinesh M. Sakarkar. This is an open access article distributed under the terms of the Creative Commons Attribution License - NonCommercial-ShareAlikeUnported License (http://creativecommons.org/licenses/by-nc-sa/3.0/).

MATERIALS AND METHODS

Diclofenac sodium was received as a gift sample from the Wockhardt research center, Aurangabad. Hydroxypropyl-methylcellulose E50, E15, E300LV purchased from Merck Pvt. Limited, Mumbai. All the other excipients and chemicals were of analytical grade and procured from S D Fine Chemical, Mumbai.

Method of tablet preparation at different ratio

All the material containing diclofenac sodium, filler (ditab), lubricant (magnesium stearate), and flow promoter (aerosil) passed through sieve # 60, triturated and mixed in mortar and pestle. This mixture was then compressed in the 12 station compression machine (Karnavati, India), by using 9mm punch. The all formulations batches and their codes mentioned in table1.

Evaluation of powder characteristics SR matrix tablets (IP, 1996; Liberman and Lachman , 1991)

Bulk density

Bulk density was determined by placing the drug excipients blend into a graduated cylinder and measuring the volume and weight by using the following formula.

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk Volume of the powder}}$$

Tapped density

Tapped density was determined by USP method II tablet blend was filled with 100 ml graduated cylinder of tap density tester which was operated for a fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by the following formula.

$$D_t = \frac{M}{V_b}$$

Where, D_t = Tapped density; M = Weight of powder taken; V_b = Tapped volume.

Angle of repose

Tablet blend was poured from funnel, to form the heap of powder. Height (h) & diameter (D) of powder were measured. The repose angle θ was calculated by the following formula.

$$\text{Tan}\theta = \frac{h}{r}$$

Where, θ = angle of repose; h = height of the cone; r = radius of the cone

Carr's index

It is an indirect method of measuring powder flow from bulk densities was developed by Carr. The compressibility of the granulations was determined by the following formula (Tetsuo *et al.*, 2005).

$$Carr's\ index\ (\%) = \frac{Tapped\ \ density - Bulk\ density}{Tapped\ density} \times 100$$

Evaluation of tablet (I.P., 1990; Liberman and Lachman, 1991; Tetsuo *et al.*, 2005)

Weight variation

Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablets was calculated.

Thickness

Thickness and diameter of tablets were determined by using calibrated Vernier caliper. 20 tablets from each batch were selected randomly, and their average thickness was measured.

Hardness

The Hardness was measured by using the Pfizer hardness tester, for each batch three tablets were tested.

Friability

For each formulation, the friability of 20 tablets was determined using the Roche friabilator (Lab Hosp). This test subjects a number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of reweighed 20 tablets was placed in Roche friabilator, which was then operated for 100 revolutions for 4 minutes. The tablets were then dusted and reweighed.

Drug content uniformity

Five tablets were weighed individually, and these tablets were crushed in a mortar. Drug equivalent to 10 mg of powder was taken, to this 10 ml of distilled water was added. The absorbance was measured at 276 nm after suitable dilution using double beam UV visible spectrophotometer. The drug content was determined.

***In vitro* drug dissolution studies** (Ming-Thau *et al.*, 1992 and Samanta *et al.*, 2010)

In vitro drug release study for the prepared matrix tablets was conducted for a period of 12 hrs using a six-station USP type II (paddle) apparatus at 37°C and 50 rpm speed. The dissolution studies were carried out for 12 hrs in the distilled water. 0.1N HCl and phosphate buffer pH 6.8, Sampling were done after every 1hr interval; samples of 10ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. The release rates from these hydrophilic polymeric matrices were conducted in a medium of by changing the pH by starting with a tablet in HCl solution (pH 1.2) for 2 hrs. Then, the tablets were immersed in a phosphate buffer (pH 6.8) for 8 hrs. The sample solutions were analyzed for diclofenac sodium by UV-absorbance at 276nm using a spectrophotometer. The cumulative percentage of drug release was calculated.

RESULTS AND DISCUSSION

Drug polymer interaction study

Compatibility of excipients with diclofenac sodium was studied by Fourier Transform Infrared Spectroscopy (Shimadzu).

The FT-IR spectra of all the combinations containing drug and polymer shows same or slightly shift in peak values which revealed that all polymers used are compatible with drug, as shown in fig. 1.

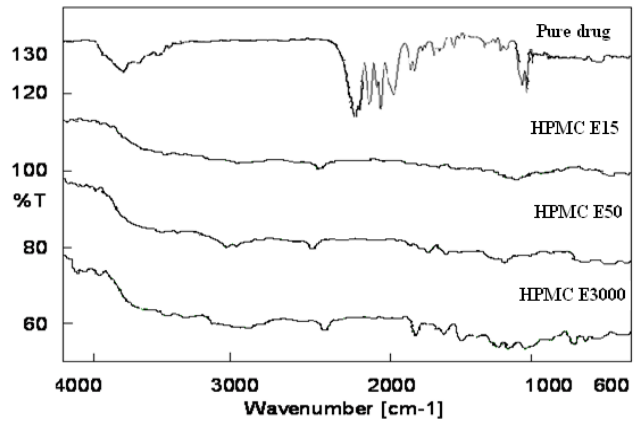

Fig. 1: FT- IR Spectra of API and excipients.

Evaluation of powder characteristic of SR tablets

The powders prepared for compression of tablets were evaluated for their flow properties. The powder characteristic indicates good flowability with an angle of repose value ranging from 25-30 i.e. (<30). The angle of repose of all formulations was found to be the range of 23.10 ± 0.750 to 28.38 ± 0.12. The bulk density of all the formulations showed acceptable range. The bulk density of these powders was found to be in the range of0.424 ± 0.06 to 0.630 ± 0.02gm/cm^3 for all formulations. The measured tapped density was in the range of 0.440 ± 0.06 to 0.870 ± 0.05gm/cm^3 for all formulations. Carr's index of powder was found the range of 09.00±0.02 to 20.00± 0.02 for all formulations. These values indicate that the prepared powder exhibited good flow properties. The result mentioned in the table 2.

Characterization of SR tablets

The weights of the tablets of all formulations found with low standard deviation values, representing uniformity of weight. The difference in weight was within the range of 5% complying with Pharmacopeial specification (Indian Pharmacopoeia). The weight variation deviation of different formulations was found to be between 3.102 to 4.584. The hardness for different formulations was found to be between 4.8±0.22 to 6.6± 0.16 kg/cm^2. It was indicated satisfactory mechanical strength. The diameter and thickness of all the formulations were found in the range of 9.10 ± 0.03 to 9.18 ± 0.05 mm and 3.23 ± 0.04 to 3.43±0.02 mm respectively. The friability of all formulations was found to be between 0.46 ± 0.04 to 0.65 ± 0.06%. The tablets compressed were stable and having better physical characteristics. The percentage drug content for different tablet formulation varied from 95.32 ± 0.03 to 99.32 ± 0.03 was found to be within limits which indicate uniform drug distribution in all formulations, the limit (85% to 115%) of % drug content allowed by I.P., the result of tablet characterization is mentioned in the table 3.

***In vitro* drug dissolution studies of diclofenac sodium**

In the formulation T_1 (1:1), T_2 (1:2) and T_3 (1:3) shows drug release 102.16%, 85.77% and 81.33% respectively in 12 hrs, shown in Fig.2. As the concentration of polymer increased drug release decreased. T_4 (1:1) released 101.24% drug in 7 hrs. T_5 (1:2), T_6 (1:3) gives drug release 86.69%, 80.51% respectively at the end of 12 hrs, shown in Fig.3. Whereas in the formulation of T_7 it shows 105.16% drug release in only 6 hrs at lower concentration, i.e. (1:1), while T_8 (1:2), T_9 (1:3) gives drug release 100.28%, 93.04% respectively at the end of 12 hrs, shown in Fig.4. Results of cumulative percentage drug release are shown in table 4. Comparative graph of drug release through all the formulations is shown in Fig.5.

Table 1: Composition of matrix tablet of diclofenac sodium (250mg).

Ingredients	**T_1**	**T_2**	**T_3**	**T_4**	**T_5**	**T_6**	**T_7**	**T_8**	**T_9**
Diclofenac sodium	50	50	50	50	50	50	50	50	50
HPMC E50	50	100	150	-	-	-	-	-	-
HPMC E15	-	-	-	50	100	150	-	-	-
HPMC E300LV	-	-	-	-	-	-	50	100	150
Dicalcium phosphate (Ditab)	147	97	47	147	97	47	147	97	47
Magnesium stearate	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1
Drug: Polymer (ratio)	**1:1**	**1:2**	**1:3**	**1:1**	**1:2**	**1:3**	**1:1**	**1:2**	**1:3**

(All ingredients are taken in mg per tablet)

Table 2: Comparative study of powdered characteristics for formulation

Batch Code	**Angle of repose (θ)**	**Bulk Density (g/cm^3)**	**Tapped Density(g/cm^3)**	**Carr'sIndex (IC)**
T_1	25.71 ± 0.21	0.568 ± 0.02	0.870 ± 0.05	16.00 ± 0.02
T_2	27.57 ± 0.08	0.621 ± 0.04	0.725 ± 0.07	09.00 ± 0.02
T_3	28.38 ± 0.12	0.530 ± 0.02	0.561 ± 0.03	17.32 ± 0.03
T_4	24.04 ± 0.340	0.468 ± 0.02	0.641 ± 0.02	13.60 ± 0.12
T_5	23.10 ± 0.750	0.521 ± 0.04	0.561 ± 0.03	14.00 ± 0.02
T_6	27.99 ± 0.57	0.630 ± 0.02	0.461 ± 0.03	20.00 ± 0.02
T_7	24.04 ± 0.340	0.432 ± 0.02	0.661 ± 0.02	19.00 ± 0.02
T_8	28.10 ± 0.750	0.424 ± 0.06	0.440 ± 0.06	14.00 ± 0.14
T_9	25.99 ± 0.47	0.588 ± 0.03	0.490 ± 0.01	12.18 ± 0.02
Broad Range	23.10 ± 0.750 to 28.38 ± 0.12	0.424 ± 0.06 to0.630 ± 0.02	0.440 ± 0.06 to 0.870 ± 0.05	09.00 ± 0.02 to 20.00 ± 0.02

Mean ± SD (n=3).

Table 3: Physico-chemical characterization of diclofenac sodium tablets.

Batch Code	Weight variation		Hardness (kg/cm^2)	Diameter (mm)	Thickness (mm)	Friability (%)	Assay (%)
	Average Weight (mg)	Highest (%) deviation					
T_1	249	4.215	6.3 ± 0.35	9.18± 0.05	3.33 ± 0.01	0.54 ± 0.02	97.02 ± 0.02
T_2	251	3.816	5.6 ± 0.12	9.11 ± 0.03	3.34 ± 0.09	0.63 ± 0.05	98.42 ± 0.03
T_3	250	4.105	5.2 ± 0.16	9.13 ± 0.08	3.43 ± 0.02	0.56 ± 0.04	99.13 ± 0.05
T_4	251	3.543	5.5 ± 0.26	9.14 ± 0.04	3.23 ± 0.04	0.53 ± 0.03	99.32 ± 0.03
T_5	250	4.520	6.6 ± 0.16	9.17 ± 0.02	3.30 ± 0.01	0.65 ± 0.06	97.32 ± 0.04
T_6	248	4.584	4.9 ± 0.26	9.12 ± 0.03	3.37 ± 0.09	0.55 ± 0.02	96.51 ± 0.04
T_7	253	3.102	6.2 ± 0.16	9.15 ± 0.04	3.36 ± 0.01	0.57 ± 0.02	95.32 ± 0.03
T_8	249	3.942	5.9 ± 0.26	9.14 ± 0.02	3.29 ± 0.03	0.60 ± 0.05	98.32 ± 0.04
T_9	251	3.586	4.8 ± 0.22	9.10 ± 0.03	3.40 ± 0.05	0.46 ± 0.04	97.51 ± 0.04

Mean ± SD (n=3).

Table 4: Dissolution profile of DCF- HPMC E50, HPMC E15 and HPMC E300LV.

Time (hrs)	%Cumulative release								
	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9
0	00	00	00	00	00	00	00	00	00
1	23.68	19.67	16.43	40.21	22.59	23.31	47.49	22.59	20.46
2	32.38	23.67	20.43	51.83	33.09	32.37	55.88	27.68	24.65
3	40.38	32.73	27.68	59.87	40.73	43.61	68.61	32.43	35.66
4	51.64	43.61	40.71	72.61	51.63	48.75	82.10	38.62	40.42
5	58.96	48.76	45.48	80.70	56.06	55.35	89.12	45.20	46.63
6	63.77	55.35	49.90	89.16	60.15	58.71	105.16	52.86	50.70
7	69.31	57.64	55.06	101.24	66.05	60.28		60.19	56.93
8	74.87	60.65	57.71		72.33	66.18		68.24	64.99
9	80.87	68.35	61.02		75.72	68.49		73.08	73.06
10	88.42	73.54	65.53		80.21	72.60		84.41	81.14
11	96.55	81.27	73.24		82.91	76.72		92.88	87.09
12	102.16	85.77	81.33		86.69	80.51		100.28	93.04

Mean ± SD (n=3)

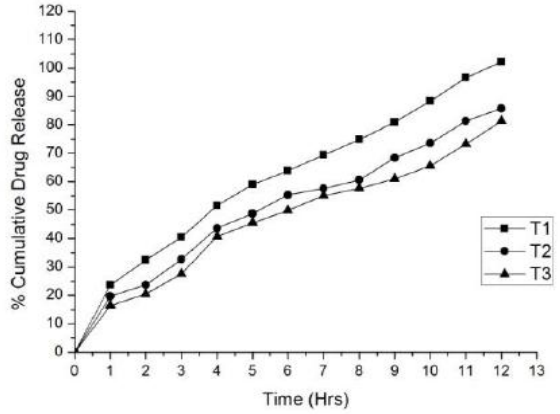

Fig. 2: Comparative dissolution study of DCF- HPMC E50.

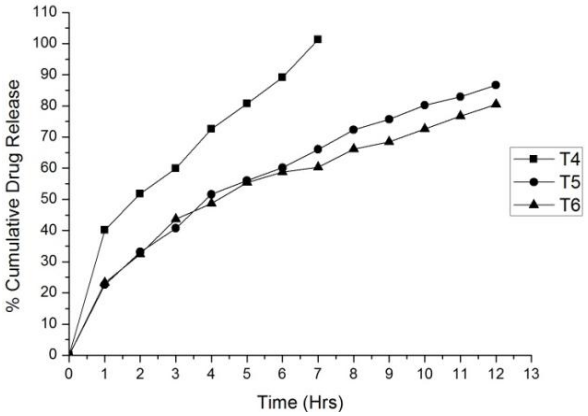

Fig. : 3 Comparative dissolution study of DCF- HPMC E15.

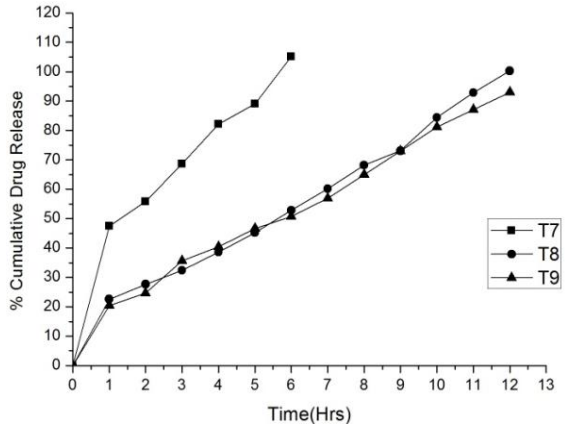

Fig. 4: Comparative dissolution study of DCF- HPMC E300LV.

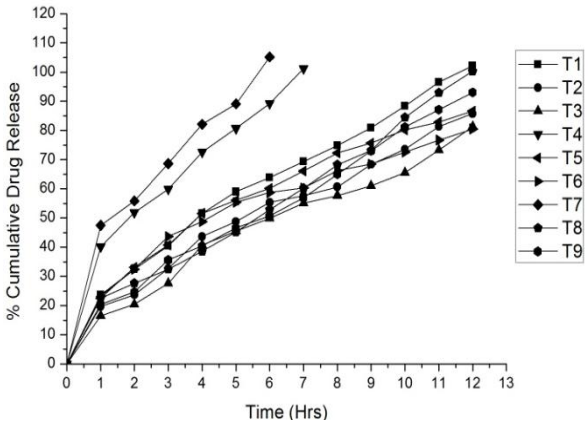

Fig. 5 : Comparative dissolution study of all formulation.

At fixed drug to polymer ratio it was found that a formulation containing HPMC E50 is more release retardant than HPMC E15 and HPMC 300LV. Formulation T_3 (containing E50 1:3) retarded drug release more, while formulation T_7 (containing HPMC E300LV 1:1) was less release retardant. HPMC E50 was significantly more successful at retarding drug release than HPMC E15 and HPMC E300LV; it might be due to its high viscosity. Drug release retard found in order $T_3>T_2>T_1>T_6>T_5>T_4>T_9>T_8>T_7$. Among all polymers used HPMC E50 retards drug release more than HPMC E15 and HPMC E300LV. Drug release retard was found in order HPMC E50 > HPMC E15 > HPMC E300LV.

CONCLUSION

From the preformulation and precompression studies, it was concluded that diclofenac sodium suitable drug candidate for the formulation of hydrophilic matrix tablets and the formulated tablets showed compliance for various physiochemical parameters. According to the *in vitro* drug release studies, the decrease in the release rate was observed with an increase in the viscosity of the polymer. As the drug to polymer ratio increased, more drug gets retarded from tablets. The tablet formed with HPMC E50 controlled drug release more than HPMC E15 and HPMC E300LV. The order of drug release retardation was HPMC E50>HPMC E15>HPMC E300LV.

ACKNOWLEDGEMENT

Author is thankful to Director, School of Pharmacy, Department of Pharmaceutics, Swami Ramanand Teerth Marathwada University, Nanded for providing facilities to carry out the present research work.

REFERENCES

Bjarnason I, Fehilly B, Smethurst P, Menzies I S, Levi A J., Importance of local versus systemic effects of non-steroidal anti-inflammatory drugs in increasing small intestinal permeability in man. Gut, 1991, 32, 275–277.

Bravo SA, Lamas MC, Salomon CJ., Swellable matrices for the controlled-release of diclofenac sodium: formulation and *in vitro* studies. Pharm Dev Technol., 2004, 9(1), 75-83.

Carson J, Notis WM, Orris ES., Colonic ulceration and bleeding during Diclofenac therapy N Engl J Med,1990, 323(2),135-137.

Gleiter CH, Antonin KH, Bieck P, Godbillon J, Schönleber W, Malchow H., Colonoscopy in the investigation of drug absorption in healthy volunteers. Gastrointest Endosc., 1985, 31 (2), 71-73.

Heng PWS, Chan LW, Easterbrook MG, Li X., Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. J Control Release. 2001, 76, 39-49.

Lee BJ, Ryu SG, Cui JH., Formulation and release characteristics of hydroxypropylmethylcellulose matrix tablets containing melatonin. Drug Dev Ind Pharm., 1999, 25 (4); 493-501.

Liberman H, Lachman L, Joseph B., Text book of Pharmaceutical dosage forms; Tablets, Revised & expanded, Volume I, Second edition, 1991, 2-52.

Lin SY, Kao YH., Tablet formulation study of spray-dried sodium diclofenac enteric-coated microcapsules. Pharm Res., 1991, 8, 919-924.

Ming-Thau Sheu, Huei-Lan Chou, Ching-Cheng Kao, Cheng-Hsiung Liu, Theodore D. Sokoloski, Dissolution of diclofenac sodium from matrix tablets. International Journal of Pharmaceutics, 1992, 85 (1-3); 57-63.

Samanta C. Mourao, Cristiane da Silva, Tania M.B. Bresolin, Cristina H.R. Serra, Valentina Porta, Dissolution parameters for sodium diclofenac-containing hypromellose matrix tablet. International Journal of Pharmaceutics, 2010, 386, 1-2: 201-207.

Scholer DW, Ku EC, Boettacher I, Schweizer., A Pharmacology of diclofenac sodium. Am J Med., 1986, 80, (4B), 34-38.

Sivakumar T, Vipul Kumar Shingala, Anoop Kumar Singh, Sudhir Kumar Yadav., Design and characterization of diclofenac sodium tablets containing Mangifera indica resin as release retardant. Int J Pharm Tech Research, 2010, 2, 2107-2111.

Tetsuo Hayashi, Hideyoshi Kanbe, Minoru Okada, Makoto Suzuki, Yasuo Ikeda, Yoichi Onuki, Tetsuo Kaneko, Takashi Sonobe., Formulation study and drug release mechanism of a new theophylline sustained-release preparation. International Journal of Pharmaceutics, 2005, 304 (1–2); 91-101.

The Indian Pharmacopoeia. The Controller of Publication, Govt. of India, Delhi, Edition IV, Vol. 2, 1996, A82-A85

How to cite this article:

Mitkare SS and Sakarkar DM. The effect of different grades polymer blends on release profiles of diclofenac sodium from hydrophilic matrices. J App Pharm Sci, 2015; 5 (10): 142-146.