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FORMULATION AND OPTIMIZATION OF SUSTAINED RELEASE TABLETS OF DICLOFENAC SODIUM USING GUAR GUM AS RELEASE MODIFIER

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ABSTRACT

Keywords:

Diclofenac sodium,
guar gum,
sustained release matrix
tablets

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PURPOSE OF STUDY: In the present study, an attempt was made to increase therapeutic effectiveness, reduction in dosing frequency and thus improving patient compliance, by developing sustained release matrix tablets of Diclofenac sodium using guar gum as release modifier.

METHOD: Six batches of sustained release matrix tablets of Diclofenac sodium was prepared by using different drug: polymer ratios viz. 1:1, 1:1.5, 1:2, 1:2.5, 1:3, and 1:3.5 for guar gum. Guar gum was used as matrix forming material, while microcrystalline cellulose as filler to maintain the tablet weight. The tablets were analyzed to determine their hardness, friability, weight variation, and an *In-vitro* release of drug was performed in phosphate buffer saline pH 7.4 for twenty four hours. Swelling study was also carried out to study dispersibility of gums at different concentrations.

RESULTS: All the physical characters of fabricated tablets were within acceptable limits. Results show that as the concentration of gum increases, swelling index also increased proportionally. Batch G6 shows maximum drug release with sustained rate.

CONCLUSIONS: It is clear through the dissolution studies that the release profile of Diclofenac sodium from matrix tablets prepared using guar gum was retarded approximately 24 h. Thus guar gum stands as a good candidate for sustained release formulation.

INTRODUCTION: In recent years the basic aim has been designing of drug products to reduce the frequency of dosing by modifying the rate of drug absorption¹. Regular research is being carried in this field for use of naturally occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration^{2,3}.

Hydrophilic swellable polymers are widely used to control the release of drugs from matrix formulations^{4,5}. Natural polymers are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form. Guar gum, a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of many drugs. Due to specific parameters of structural viscosity, guar gum can be applied in the technology of tablets production. In different formulations guar gum has been used as a binder and disintegrants⁶⁻⁸. Some results also showed that guar gum was used for the formulation of oral controlled release formulations^{9, 10}. Studies also have showed that guar gum can be used for targeted drug delivery system¹¹. Guar gum is hydrophilic polymer, which until recently had been limited for use in gelation, thickening, suspending and as emulsifying agent.

It is essential to develop cost-effective and less tedious procedures for preparation of sustained release formulations on the industrial scale. The most commonly used method for fabricating drugs in a controlled-release formulation is by incorporating them into a matrix containing a hydrophilic rate controlling polymer. Matrix systems are widely used in oral controlled drug delivery because

of their flexibility (which results in obtaining desirable drug release profile), cost effectiveness and broad regulatory acceptance^{13, 14}. Diclofenac Sodium is sodium 2- [(2, 6-dichlorophenyl) - amino] phenyl acetate and is an acetic acid nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It is also used to treat, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis^{15, 16}. The present investigation is aimed to formulate the sustained release matrix tablet of Diclofenac sodium with different concentration of guar gum, using no other varying parameter.

MATERIAL AND METHODS: Diclofenac Sodium was obtained as gift sample from Alchem Laboratories, Baddi, Himanchal Pradesh, India. The Pharmacopoeial grade of Guar gum was obtained from RFCL limited, New Delhi. All materials used were of analytical grade, and procured from commercial sources.

Preparation of SR matrix tablets: According to Table1 sustained release matrix tablets of Diclofenac sodium were prepared by using different drug: polymer ratios viz. 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5 for various batches Batch A, Batch B, Batch C, Batch D, Batch E and Batch F respectively. Guar gum was used as matrix forming material, while microcrystalline cellulose was used as filler to maintain the tablet weight.

All ingredients were passed through a # 20 sieve, weighed and blended. The granules (which were obtained after wet granulation) were compressed using KBr press, with the help of 8mm flat faced punches^{17, 18}. The formulation composition is shown in the following table number 1.

TABLE 1: FORMULATION COMPOSITION OF GUAR GUM MATRIX TABLETS

INGREDIENT	FORMULATIONS					
	BATCH G1	BATCH G2	BATCH G3	BATCH G4	BATCH G5	BATCH G6
Diclofenac sodium	50mg	50mg	50mg	50mg	50mg	50mg
Guar gum	50mg	75mg	100mg	125mg	150mg	175mg
Microcrystalline cellulose	200mg	175mg	150mg	125mg	100mg	75mg
Total weight	300mg	300mg	300mg	300mg	300mg	300mg

Infrared study: All the ingredients were studied for compatibility between them. For that purpose infrared spectra of individual ingredients were compared with infrared spectra of blended powder. The infrared spectra used in that study are illustrated as follows- (cont. on next page).

Evaluation of Fabricated Matrix Tablets:

Weight variation: All prepared matrix tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was also calculated^{19, 20}.

Friability: Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Roche friabilator with triplicate readings^{19, 20}.

Hardness: Hardness of all batches was determined using Digital Force Gauge (Model: EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets^{19, 20}.

Thickness: Thickness was measured by vernier caliper as per USP XXIV monograph. The readings were carried out in triplicate and average value was noted^{19, 20}.

Drug content: The tablets were powdered, and 50 mg equivalent weight of Diclofenac sodium in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 6.6) was added and shaken for 10 min. then, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed at 276 nm using UV- Visible Spectrophotometer (Shimadzu UV- 2450, Japan). The drug content of the each sample was estimated from their standard curve^{21, 22}.

Swelling behavior of sustained release matrix tablets: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a petridish containing pH 7.4 phosphate buffer. At the end of 0.5 h and 1 h, the tablet was withdrawn, dried with tissue paper, and weighed. Then for every 1 h, weights of the tablet were noted, and the process was continued till the end of 8 h. Percentage weight gain by the tablet was calculated by formula;

$$S. I. = \{(M_t - M_0) / M_0\} \times 100,$$

Where, S.I. = swelling index, M_t = weight of tablet at time t (h) and M_0 = weight of tablet at zero time^{23, 24}.

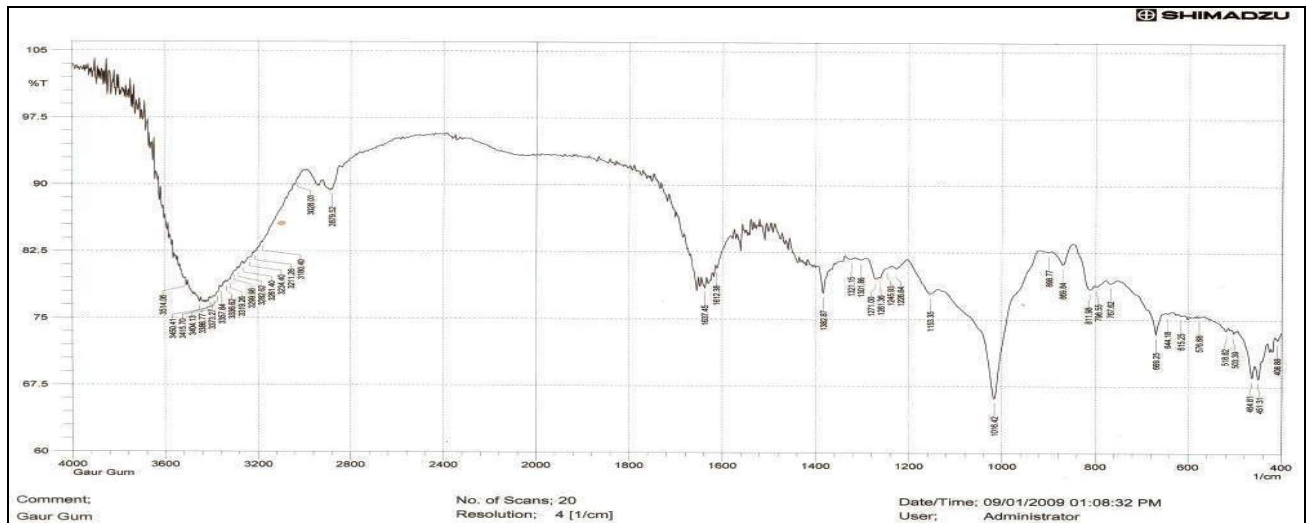


FIG. 1: INFRARED SPECTRUM OF PURE GUAR GUM

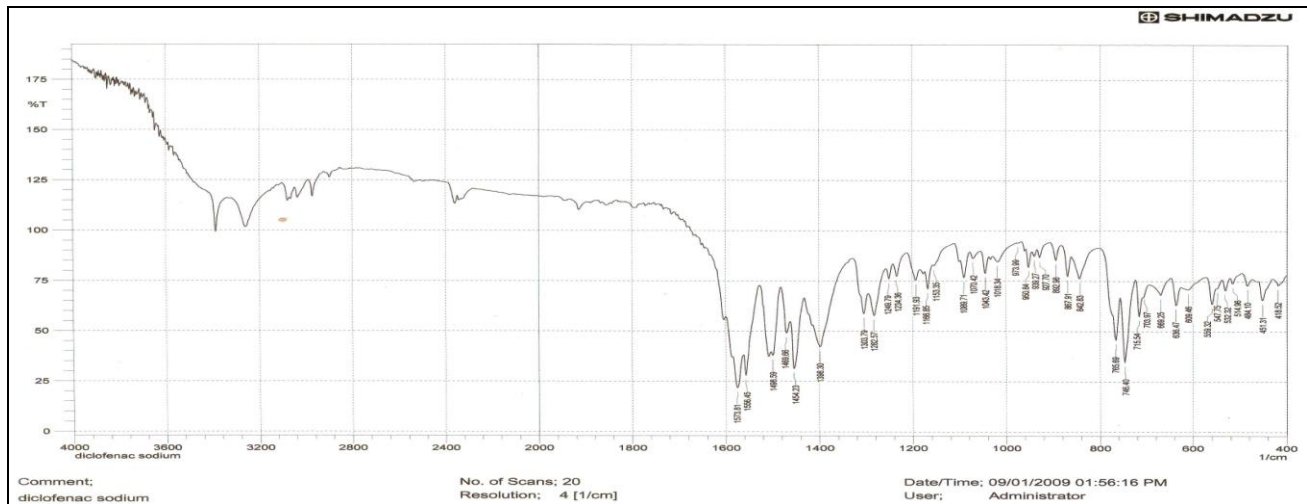


FIG. 2: INFRARED SPECTRA OF PURE DICLOFENAC SODIUM

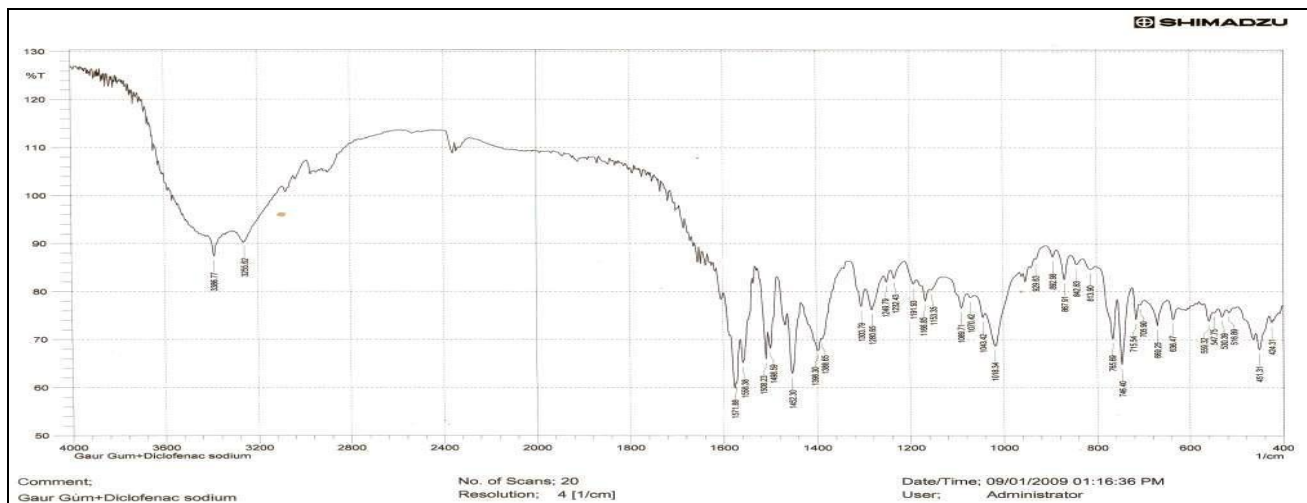


FIG. 3: INFRARED SPECTRUM OF GUAR GUM AND DICLOFENAC SODIUM MIXTURE

In Vitro Drug Release Study: In Vitro Drug release was studied using Lab-India dissolution apparatus, with 900 ml of dissolution medium maintained at $37\pm 1^\circ\text{C}$ for 24 h, at 50 rpm. 5ml of sample was withdrawn after every hour, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically. At a measured wavelength of 276 nm, and cumulative percent drug release was calculated. The study was performed in triplicate and results were recorded^{25, 26}.

The data obtained in the in-vitro dissolution study is grouped according to two modes of data treatment as follows:

1. % Drug release vs time in hrs.
2. Cumulative percentage drug release vs. time in hrs.

RESULTS: Infrared spectra of drug and polymers were used to study the compatibility between them. No change in peak shows that there was no interaction between drug and polymers.

As per Table 2, the formulated matrix tablets met the Pharmacopoeial requirement of uniformity of weight. All the tablets confirmed to the requirement of assay, as per USP. Hardness, percentage friability and thickness were all within acceptable limits^{19, 20}.

TABLE 2: PHYSICAL PARAMETERS FOR FABRICATED GUAR GUM TABLETS

PARAMETER	FABRICATED GUAR GUM TABLET					
	BATCH G1	BATCH G2	BATCH G3	BATCH G4	BATCH G5	BATCH G6
Weight variation(g)	0.301 \pm 0.012	0.303 \pm 0.010	0.302 \pm 0.010	0.301 \pm 0.007	0.299 \pm 0.010	0.299 \pm 0.010
Friability (%)	0.05 \pm 0.007	0.04 \pm 0.010	0.03 \pm 0.010	0.04 \pm 0.010	0.03 \pm 0.007	0.03 \pm 0.010
Hardness (N)	20.27 \pm 0.058	20.67 \pm 0.058	20.83 \pm 0.058	21.27 \pm 0.116	21.5 \pm 0.1	22.07 \pm 0.058
Thickness(mm)	4.18 \pm 0.025	4.15 \pm 0.010	4.32 \pm 0.046	4.38 \pm 0.075	4.32 \pm 0.078	4.31 \pm 0.045

Sustained drug release was shown by all formulations in phosphate buffer (pH 7.4). Fig. 5 and Fig. 6 showed the swelling characteristics of guar gum and pectin respectively. The swelling index was calculated with respect to time. As time increases, the swelling index also increased, this is because weight gain by tablet was increased proportionally with rate of hydration up to certain limit. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium.

The direct relationship was observed between swelling index and polymer concentration, and as polymer concentration increases, swelling index was found to increase^{23, 24}. It has been observed that the cumulative percent drug release decreases with increasing concentration of polymer and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of natural polymer. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix²⁵⁻²⁹.

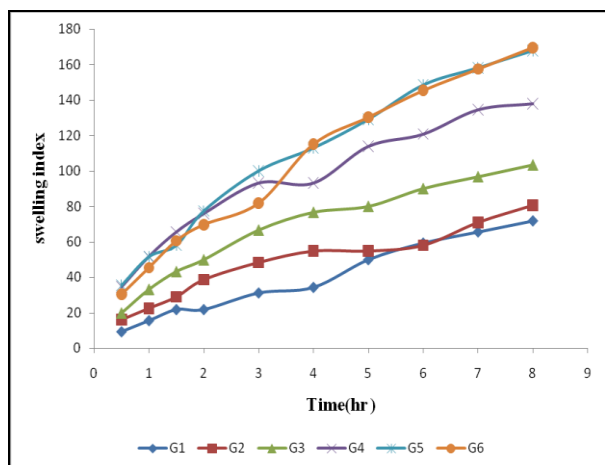


FIG. 4: SWELLING INDEX PROFILE FOR GUAR GUM BASED TABLETS

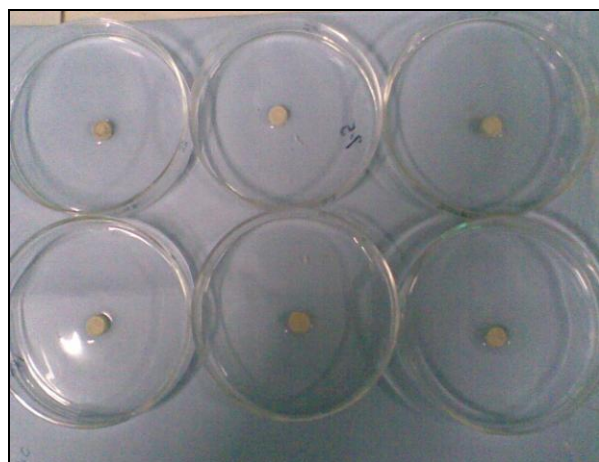


FIG. 5: SWELLING INDEX STUDY FOR DIFFERENT BATCHES OF TABLETS

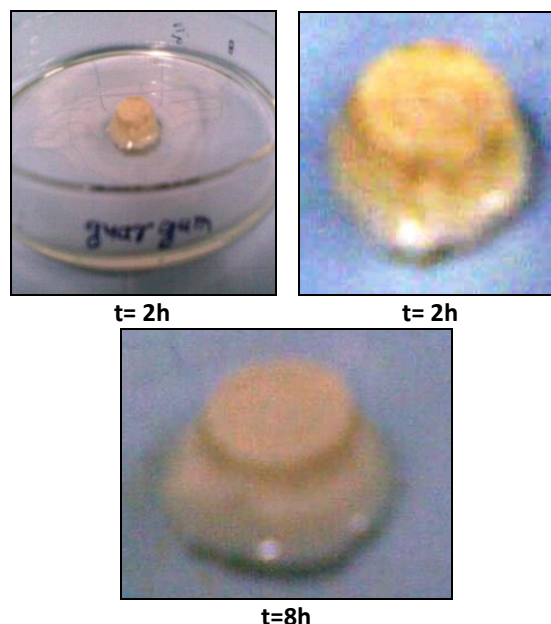


FIG. 6: DIFFERENT STAGES DURING SWELLING STUDY OF TABLETS

The in vitro release of Diclofenac sodium from Guar gum has been shown in Figure 7. From the findings, obtained so far it can be concluded that Batch F of guar gum in the concentration ratio of 1:2.5 (drug: polymer) was promising concentration for oral sustained release tablet of Diclofenac sodium.

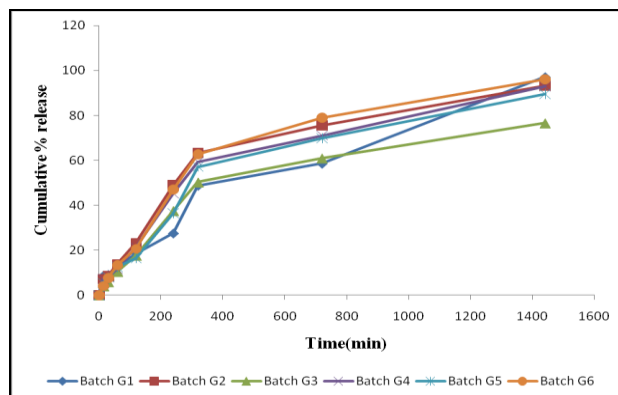


FIG. 7: RELEASE PROFILE FOR GUAR GUM MATRIX TABLET

CONCLUSIONS: Based on the results obtained, it is possible to design promising oral controlled release matrix tablet containing Diclofenac sodium.

REFERENCES:

1. Ansel HC and Loyd VA: Pharmaceutical dosage forms and Drug Delivery System. Lippincott's Williams and Wilking, Hong Kong 1999; 8:275-280.
2. Sujja AJ, Munday DL, and Khan KA: Development and evaluation of a multiple-unit oral sustained release dosage form for S (+)-ibuprofen: preparation and release kinetics. *Int. J. Pharm* 1999; 193(1):73-84.
3. Khullar P, Khar RK and Agarwal SP: Guar Gum as a hydrophilic matrix for preparation of Theophylline Controlled Release dosage form. *Ind. J. Pharm. Sc.* 1999; 61(6):342-345.
4. Alderman DA, A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int. J. Pharm. Tech. Prod. Manuf.* 1984; 3: 1-9.
5. Ranga R K, Padmalatha K D, Buri P: Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. *J. Controlled Release* 1990; 12:133-141.
6. Wassel GM, Omar SM, Ammar NM: Application of guar flour and prepared guaran in tablet manufacture. *J Drug Res* 1989; 18:1-8.
7. Duru C, Colombo P, Gaudy D, Massimo G, Barthelemy P: Comparative study of the disintegrating efficiency of polysaccharides in a directly tabletable formulation. *Pharmaceut Technol Int* 1992; 4:15-16, 20, 22-23.
8. Baweja JM, Misra AN: Modified guar gum as a tablet disintegrant. *Pharmazie* 1997; 52:856-859.
9. Khullar P, Khar RK, Agarwal SP. Guar gum as a hydrophilic matrix for preparation of theophylline controlled-release dosage form. *Indian J Pharm Sci* 1999; 61:342-345.
10. Misra AN, Baweja JM: Modified guar gum as hydrophilic matrix for controlled release tablets. *Indian Drugs* 1997; 34:216-223.
11. Bhosale AV, Hardikar SR, Patil N, Patel U, Sumbe Y, Jgtap R: Formulation and in-vitro evaluation of microbially triggered ibuprofen delivery for colon targeting. *International Journal of Pharmaceutical Technology and Research* 2009; 1: 328-333.
12. Linshu L, Marshall L and Fishman B: Pectin in controlled drug delivery – a review. *Journal of Control Release* 2007; 14:15-24.
13. Naggar VF, El-Khawas M, Ismail FA, Boraie NA: Pectin, a possible matrix for oral sustained release preparations of water-soluble drugs. *STP Pharma Sci* 1992; 2:227-234.
14. Ahrabi SF, Madsen G, Dyrstad K, Sande SA, Graffner C: Development of pectin matrix tablets for colonic delivery of model drug ropivacaine. *Eur J Pharm Sci* 2000; 10:43-52.
15. Sungthongjeen S, Pitaksuteepong T, Somsiri A, Sriamornsak P: Studies on pectins as potential hydrogel matrices for controlled-release drug delivery. *Drug Dev Ind Pharm* 1999; 25:1271-1276.
16. Bravo SA, Lamas MC, Salamon CJ: In-vitro studies of diclofenac sodium controlled- release from biopolymeric hydrophilic matrices. *J. Pharm. Pharmaceut. Sci.* 2002; 5: 213-219.
17. Reddy KR, Mutalik S, and Reddy S: Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. *AAPS PharmSciTech* 2003; 4:61.
18. Indian Pharmacopoeia. Ministry of health. The controller of publications, New Delhi. 1996; 4; 432.
19. Sujja-areevath J, Munday DL, Cox PJ, Khan KA: Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations. *Int J Pharm* 1996; 139:53-62.
20. Nokano M, Ogata A: In vitro release characteristics of matrix tablets: Study of Karaya gum and Guar gum as release modulators. *Ind J Pharm Sc* 2006; 68(6):824-826.
21. Gwen MJ, Joseph RR, Rhodes CT: *Modern Pharmaceutics*, Marcel Dekker, Inc, New York. 1996; 72(3):581.
22. USP30-NF25, The official compendium of standards. The United States Pharmacopoeial Convention, 2007.
23. Lantz RJ, Schwartz JB: Tablets. In: Lieberman HA, Lachman L, editors. *Pharmaceutical dosage forms. 2nd Ed.* New York, USA: Marcel Dekker, Inc, 2005; 15-20, 69.
24. Khullar P, Khar RK, Agarwal SP. Evaluation of guar gum in the preparation of sustained-release matrix tablets. *Drug Dev Ind Pharm*, 1998; 24: 1095-1109.
25. Krishnaiah YSR, Rama Rao T, Ushasree M, Satyanarayana S: A study on the in vitro evaluation of guar gum as a carrier for oral controlled drug delivery. *Saudi Pharm J* 2001; 9:91-98.
26. [26] Sujja-areevath J, Munday DL, Cox PJ and Khan KA: Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulations. *Eur J Pharm Sci* 1998; 6:207-217.
27. Abrahamsson B, Alpsten M, Bake B, Larsson A, Sjogren J: In vitro and in vivo erosion of two different hydrophilic gel matrix tablets. *Eur J Pharm Biopharm* 1998; 46:69-75.
28. Sujja-areevath J, Munday DL, Cox PJ, Khan KA: Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulation. *Int J Pharm* 1996; 139:53-62.
29. Ei-Arini SK, Leuenberger H: Modelling of drug release from polymer matrices: Effect of drug loading. *Int J Phar* 1995; 121:141-148.
30. Harland RS, Gazzaniga A, Sanagalli ME, Colombo P, Peppas NA. Drug/polymer matrix swelling and dissolution. *Pharm. Res.*, 1998; 5(8): 488-494.
31. Ritger PL, Peppas NA. A simple equation for description of solute release II Fickian and anomalous from swellable devices. *J Control Rel*, 1987; 5: 37-42.
32. Munday D L, Cox P J. Compressed xanthan and karya gum matrices: hydration, erosion and drug release mechanisms. *Int J Pharm*, 2000; 203: 179-182.