



University of HUDDERSFIELD

University of Huddersfield Repository

Shoaib, M Harris, Tazeen, Jaweria, Merchant, Hamid A. and Yousuf, Rabia Ismail

Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC.

Original Citation

Shoaib, M Harris, Tazeen, Jaweria, Merchant, Hamid A. and Yousuf, Rabia Ismail (2006) Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pakistan Journal of Pharmaceutical Sciences*, 19 (2). pp. 119-124. ISSN 1011-601X

This version is available at <http://eprints.hud.ac.uk/id/eprint/19640/>

The University Repository is a digital collection of the research output of the University, available on Open Access. Copyright and Moral Rights for the items on this site are retained by the individual author and/or other copyright owners. Users may access full items free of charge; copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational or not-for-profit purposes without prior permission or charge, provided:

- The authors, title and full bibliographic details is credited in any copy;
- A hyperlink and/or URL is included for the original metadata page; and
- The content is not changed in any way.

For more information, including our policy and submission procedure, please contact the Repository Team at: E.mailbox@hud.ac.uk.

<http://eprints.hud.ac.uk/>

**EVALUATION OF DRUG RELEASE KINETICS
FROM IBUPROFEN MATRIX TABLETS USING HPMC**

**M. HARRIS SHOAIB*, JAWERIA TAZEEN, HAMID A. MERCHANT
AND RABIA ISMAIL YOUSUF**

*Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi,
Karachi-75270, Pakistan*

ABSTRACT

The aim of this study is to develop a once-daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model was based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

Keywords: Ibuprofen; sustained release; hydrophilic matrix; HPMC; direct compression.

INTRODUCTION

In chronic inflammatory diseases like rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other non-rheumatoid arthropathies treatment is usually prolonged and large doses are required (Dollery, 1999). Ibuprofen a phenylpropionic acid derivative is established as first-line NSAID for rheumatoid arthritis and chronic arthropathies. The mechanism of action of ibuprofen involves not only inhibition of prostaglandin synthesis but also decreased production of pro-inflammatory cytokines such as interleukin 1β and tumour necrosis factor α ; inhibition of leucocyte leucotriene B₄ and nitric oxide; and possibly a positive effect on the production of oxyradicals and signaling transduction via the NF κ B pathway. In therapeutic use, ibuprofen proved to have a favourable risk: benefit ratio and predictable adverse effects (Rainsford, 2002). Thus for patient compliance, improve bioavailability, minimize total drug quantity, minimize accumulation on chronic use and reduce fluctuation in drug level sustained release of ibuprofen is desirable.

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance (Lordi, 1986). Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. Hydroxypropyl methylcellulose (HPMC) is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible

release profiles, cost effectiveness and utilization of existing conventional equipment and methods (Colorcon, 2005). Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses (Sung *et al.*, 1996).

Direct compression was used to compress the tablets, as keeping in mind that HPMC is a hydrophilic polymer that swells to a significant extent upon contact with water. Various studies of drug release mechanism, effect of formulation variables on HPMC matrices are based on direct compression (Somade and Singh, 2002; Sung *et al.*, 1996).

Several mathematical models have been published, to elucidate the water and drug transport processes and to predict the resulting drug release kinetics (Korsmeyer *et al.*, 1986a,b; Cohen and Erneux, 1988a,b; Gao *et al.*, 1995; Ju *et al.*, 1995; Siepmann *et al.*, 1999a,b). The mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into consideration. These include the diffusion of water into the HPMC matrix, HPMC swelling, drug diffusion out of the device, polymer dissolution, axial and radial transport in a 3-dimensional system, concentration dependent diffusivities of the species, moving boundaries, and changing matrix dimensions, porosity and composition. Each model makes certain assumptions and due to these assumptions, the applicability of the respective models is restricted to certain drug-polymer systems (Siepmann *et al.*, 2000).

*Corresponding author: Tel.: +9221-4816410; fax: +9221-4987344 - E-mail: harrishoaib2000@yahoo.com

The aim of this work was to prepare uncoated hydrophilic matrix tablets containing ibuprofen as a model drug, and HPMC as hydrophilic matrix to retard drug release. Ibuprofen used as 800mg per tablet and 2 tablets will be indicated as a single dose which will maintain the required plasma level of ibuprofen for 24 hrs. (Data sheet, 2005). Ibuprofen was directly compressed with HPMC along with release modifier (microcrystalline cellulose) and lubricant (magnesium stearate) into caplet. The manufacturing process was validated against pre-defined acceptance criteria on three experimental batches. *In vitro* dissolution studies were performed on formulation along with various other usual testing. Another objective of this work is to evaluate drug release data using various kinetic models and to determine the mechanism of drug release.

MATERIALS AND METHODS

Materials

The following materials were used: Ibuprofen (Himont Chemicals, Lahore, Pakistan) a gift from Efroze Chemical Industries, HPMC 4000cps (USP Type-2208) (Dow Chemicals, USA), Avicel PH-101 (FMC Corporation, USA), magnesium stearate (Merck KGaA, Darmstadt, Germany) were obtained and used as received. All other chemicals used were of analytical grade.

Preparation of tablets

Experimental batches of 1.2Kg each were prepared by direct compression having ibuprofen (66.67%), HPMC (20.00%), Avicel PH-101 (12.33%) and magnesium stearate (1.0%). Mixing of powders was performed by geometric dilution method in polythene bag. Then this blend was compressed with manually operated single-punch tablet machine (KORSCH Erweka, Frankfurt, Germany), using 19.0mm length, 8.8mm breadth caplet shaped concave punches with a target compression weight of 1.2g/tab containing 800mg active so as to achieve two tablets once daily as a single dose.

Evaluation of tablets

Tablets were subjected to various physical tests which include weight variation (Mettler Toledo B204-S, Switzerland), thickness, length & breadth, hardness (OSK Fujiwara Hardness Tester, Tokyo, Japan), friability (Friabilator, H.Jurgens GmbH & Co., Bremen, Germany) as per BP official methods. *In vitro* release study was performed using USP <711> apparatus type II at 50 rpm (Erweka DT700, Husenstamm, Germany). The dissolution medium used was 900 ml phosphate buffer pH 7.2 for 12 hrs; maintained at $37 \pm 0.5^\circ\text{C}$. The drug release was evaluated by taking sample of 10 ml (which were replaced with fresh medium) at predetermined time intervals and absorbance was measured ($\lambda = 221\text{nm}$) after filtration and suitable dilution (UV Spectrophotometer 150-02, Shimadzu Corporation, Kyoto, Japan). Drug content was analyzed

using HPLC (LC-5A, SPD-2A, Shimadzu Corporation, Kyoto, Japan) as per official method of ibuprofen (BP, 2004).

Process validation

Experimental batches were validated to confirm the accuracy and reproducibility of physical and chemical characteristics. Mixing time was validated by performing content uniformity tests for ibuprofen in the blend at three stages of the mixing time of one hour i.e., 75%, 85% and 100% of the mixing time. While compression; hardness, thickness and weight variation was evaluated and data was compared for all three batches. *In vitro* release profile and assay results were also evaluated and compared with pre-defined criteria.

Data analysis

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjioannou *et al.*, 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = k_0 t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log} C = \text{Log} C_0 - kt / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

Where, Q_t is the amount of drug released in time t , Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made: *cumulative % drug release vs. time* (zero order kinetic model); *log cumulative of % drug remaining vs. time* (first order kinetic model); *cumulative % drug release vs. square root of time* (Higuchi model) *log cumulative % drug release vs. log time* (Korsmeyer model) and *cube root of drug % remaining in matrix vs. time* (Hixson-Crowell cube root law).

Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t / M_\infty = Kt^n \quad (5)$$

Where M_t / M_∞ is fraction of drug released at time t , k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices.

Table 1: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS AND DISCUSSION**Preparation and evaluation of matrix tablets**

Tablets were compressed without any problem and do not require any change in ratio of excipient in formulation. Tablets prepared were smooth, shiny and do not require coating as for experimental purpose (for patient compliance and palatability aqueous polymer coating can be performed). Weight variation was within limit of $\pm 5\%$ and hardness was also set at 16.00 kg ± 5 kg. Actual values are given in table 2. Length and breadth was found fixed as per punch size and thickness was controlled as well to an average of 9.18mm and S.D. was found as little as 0.0131.

Table 2: Physical and chemical parameters of formulated ibuprofen tablets

Weight Variation (%) n = 20	Thickness (mm) n = 20	Friability (%) n = 10	Hardness (Kg) n = 20	Drug content (%) n = 2
Mean = 1.2209mg + 2.71%, - 3.84% S.D = 0.0040	Mean = 91.8 + 4 mm, - 2 mm S.D = 0.0131	0.0664	Mean = 16.87 + 4.7 kg, - 5.57 kg S.D = 2.9420	Mean = 98.40 S.D = 2.3193

S.D = Standard Deviation, + = Maximum, - = Minimum.

Table 3: Release parameters of Ibuprofen sustained release tablets

Zero Order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
r^2	$k_o (h^{-1})$	r^2	$k_1 (h^{-1})$	r^2	$k_H (h^{-1/2})$	r^2	n value	$K_{KP} (h^{-n})$	r^2	$k_{HC} (h^{-1/3})$
0.9672	4.0042	0.9933	0.1414	0.9994	17.569	0.9942	0.2465	0.4265	0.9967	0.1415

By holding the tablet weight and thickness constant, the surface area and volume were essentially fixed. All tablets contained 800mg $\pm 5\%$ (66.67% w/w) of Ibuprofen as confirmed by assay procedure. Mean drug content value obtained was 98.40% (S.D. of 2.3193) which was found satisfactorily within limits.

In-vitro dissolution studies and duration of release

For the controlled release under investigation, which is a matrix-tablet comprising drug, and hydrophilic polymer, the release should follow three steps. First step is the penetration of the dissolution medium in the tablet matrix (hydration). Second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet, to the surrounding dissolution medium (Kiortsis *et al.*, 2005). The ibuprofen released at first hour was 45.30%, 43.1% and 47.2%; at 6h 70.92%, 69.10% and 73.02%; and at 12h drug release was 89.23%, 88.10% and 89.15% respectively for three experimental batches. For predictive completion of release the drug release data of ibuprofen obtained from dissolution is plotted as concentration (mg/L) vs. time (h). The straight line indicates zero order in accordance with Eq. 1. Linear regression analysis of the data yields the equation of best line as $c = 35.59t + 390.32$ and $R^2 = 0.9672$. According to Eq. 1, the slope of line corresponds to the zero order rate constant. Therefore rate of dissolution is $k_0 = 35.59 \text{ mgL}^{-1} \text{ h}^{-1}$. The rate of release in terms of amount of ibuprofen dissolved or released per unit time can be obtained as:

$$k_0 \times V \quad (6)$$

where V is volume of dissolution medium (L).

The rate of release calculated from Eq. 6 as 32.03 mg/h. Assuming that this rate of release remains constant throughout the release process, the duration of release was calculated as 24.97 h (similarly 23.86 h and 24.2 h for other two batches) by using 800mg, which was comparable to the required duration of release i.e., 24h. Hence the formulation allows a gradual release of the active substances from the gel matrix. Ibuprofen diffuses through an outer gel layer which erodes allowing the aqueous medium to penetrate further into the core.

The sustained absorption phase that results provides prolonged plasma levels of ibuprofen in the systemic circulation, reducing the dosage frequency normally required for a drug with a plasma half life of about two hours. The mean plasma profile of two sustained release 800mg tablets if compared to one conventional release 400mg tablet taken four times daily showed that the sustained release formulation reduced the peaks and troughs characteristics of the conventional release tablets. The area under the plasma concentration /time curve for two sustained release tablets was almost identical to that of four conventional release 400mg tablets (Data Sheet, 2005).

Process validation

Content uniformity for all the three batches was found within acceptable limits (95-105%). Drug content was measured as 96%, 99% and 102%, where it was noted that no significant difference was found in drug content at 85% and 100% for all three batches indicating that adequate mixing was achieved at 54min (85%) and further mixing may be omitted. Weight variation was found comparable for three batches; average weight was measured as 1.2209g, 1.2198g and 1.2301g. The RSD for variation among different batches was only 0.46%.

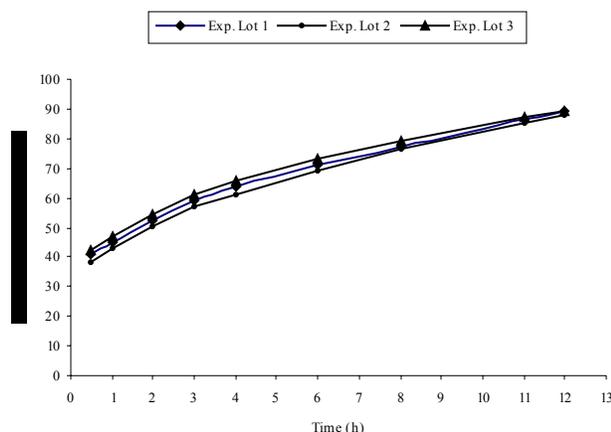


Fig. 1: Drug release profile of Ibuprofen sustained release formulation.

Reproducibility was also confirmed by comparing drug release profile for all three batches. Refer fig.1 for comparative release profile for three experimental batches. Duration of release was further verified and confirmed the accuracy and reproducibility of drug release for 24 hours.

Drug release kinetics

As shown in Fig. 2, 3, 4 and 5 plots drawn, according to various kinetic models, were giving linear relationship. In Zero order plot (fig. 2) the r^2 value obtained is 0.9672 and first order (fig. 3) gave 0.9933 describing the drug release rate relationship with concentration of drug. The best linearity was found in Higuchi's equation plot (fig. 4) ($r^2 = 0.9994$) indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion.

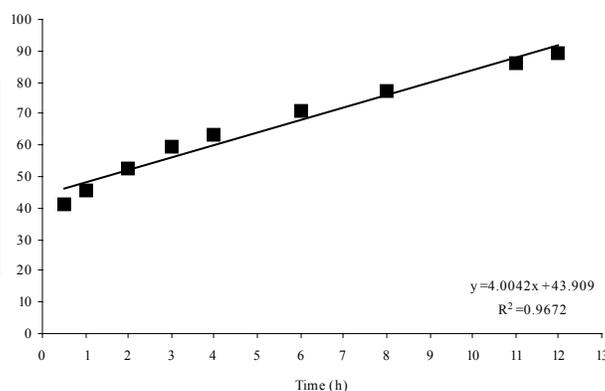


Fig. 2: Zero order release model of Ibuprofen sustained release formulation.

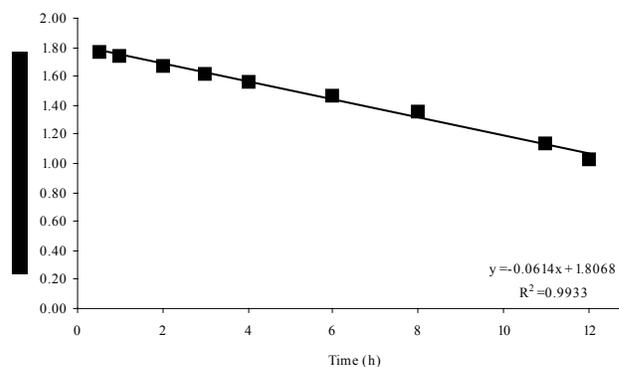


Fig. 3: First order release model of Ibuprofen sustained release formulation.

The dissolution data was also plotted in accordance with Hixson Crowell cube root law (fig. 5). Applicability of data ($r^2 = 0.9967$) indicates a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time.

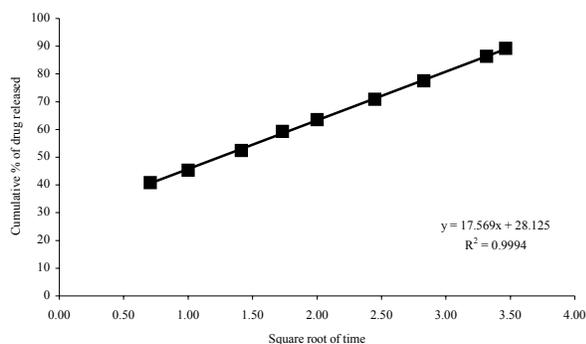


Fig. 4: Higuchi release model of Ibuprofen sustained release formulation.

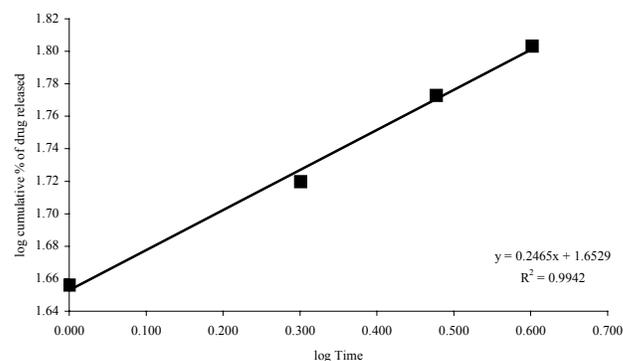


Fig. 6: Korsmeyer – Peppas Model for mechanism of drug release (first 60% drug release)

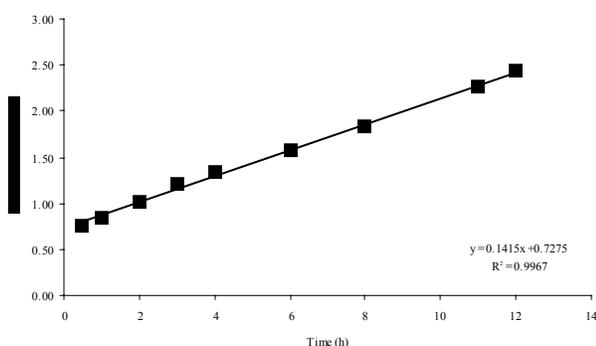


Fig. 5: Hixson-Crowell cube root plots of Ibuprofen sustained release formulation.

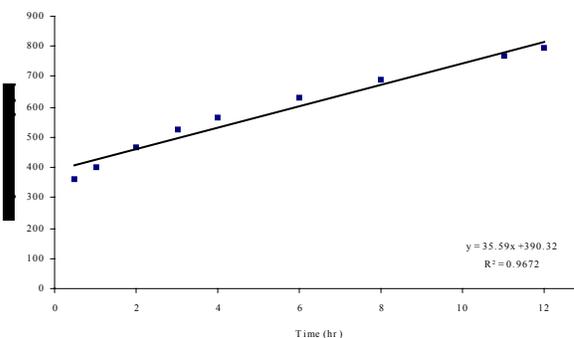


Fig. 7: Prediction of drug release using concentration (mg/L) vs. time (hr)

Mechanism of drug release

By incorporating the first 60% of release data mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release, are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion (Cox *et al.*, 1999). Table 1 describes the limits of this analysis for cylindrical shape, e.g. a tablet. The value of the release exponent in ibuprofen sustained release obtained as 0.2465 which as per table 1 is beyond the limits of Korsmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion controlled drug release mechanism, this is not automatically valid for HPMC (Siepmann and Peppas, 2001).

CONCLUSION

Ibuprofen sustained release matrix tablet was prepared successfully using HPMC as polymer to retard release and achieve required dissolution profile. Drug release kinetics of this formulation correspond best to Higuchi's model and drug release mechanism as per n value of Korsmeyer & Peppas (Power law) can not be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion.

ACKNOWLEDGEMENT

Jaweria Tazeen expresses gratitude to Efroze Chemical Industries(Pvt.) Ltd. Karachi in providing active material (Ibuprofen) and use of Dissolution apparatus (Erweka DT700).

REFERENCES

Bourne DWA (2002). Pharmacokinetics. *In*: Banker GS, Rhodes CT, Modern Pharmaceutics, 4th ed., Marcel Dekker Inc., New York, pp.67-92.

- British Pharmacopoeia, (2004). The Stationary Office London, UK, Ibuprofen Tablets.
- Cohen DS and Erneux T (1988a). Free boundary problems in controlled release pharmaceuticals. I: diffusion in glassy polymers. *SIAM. J. Appl. Math.*, **48**: 1451-1465.
- Cohen DS and Erneux T (1988b). Free boundary problems in controlled release pharmaceuticals. II: swelling-controlled release. *SIAM. J. Appl. Math.*, **48**: 1466-1474.
- Colorcon (2005). Methocel Literature, Oral Modified Release System, http://www.colorcon.com/pharma/mod_rel/methocel/index.html
- Cox PJ, Khan KA, Munday DL and Sujja-areevath J (1999). Development and evaluation of a multiple-unit oral sustained release dosage form for S(+)-ibuprofen: preparation and release kinetics. *Int.J.Pharm.*, **193**: 73-84.
- Data Sheet (Sustained Release Ibuprofen 800mg) (2005). <http://www.medsafe.govt.nz/Profs/Data/sheet/b/brufenretardtab.htm>
- Dollery C (1999). Therapeutic Drugs, 2nd ed., Churchill Livingstone, Edinburgh London, pp.11-13.
- Gao P, Nixon PR and Skoug JW (1995). Diffusion in HPMC gels. II. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. *Pharm. Res.*, **12**: 965-971.
- Hadjioannou TP, Christian GD, Koupparis MA and Macheras PE (1993). Quantitative Calculations in Pharmaceutical Practice and Research, VCH Publishers Inc., New York, pp.345-348.
- Higuchi T (1963). Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J.Pharm. Sci.*, **52**: 1145-1149.
- Hixson AW and Crowell JH (1931). Dependence of reaction velocity upon surface and agitation (I) theoretical consideration. *Ind. Eng. Chem.*, **23**: 923-931.
- Ju RTC, Nixon PR, Patel MV and Tong DM (1995). Drug release from hydrophilic matrices. 2. A mathematical model based on the polymer disentanglement concentration and the diffusion layer. *J.Pharm.Sci.* **84**: 1464-1477.
- Kiortsis S, Kachrimanis K, Broussali Th and Malamataris S (2005). Drug release from tableted wet granulations comprising cellulosic (HPMC or HPC) and hydrophobic component. *Eur. J. Pharm. Biopharm.*, **59**: 73-83.
- Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA (1983). Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, **15**: 25-35.
- Korsmeyer RW, Lustig SR and Peppas NA (1986a). Solute and penetrant diffusion in swellable polymers. I. Mathematical modeling. *J. Polym. Sci. Polym. Phys. Ed.*, **24**: 395-408.
- Korsmeyer RW, von Meerwall E and Peppas NA (1986b). Solute and penetrant diffusion in swellable polymers. II. Verification of theoretical models. *J. Polym. Sci. Polym. Phys. Ed.*, **24**: 409-434.
- Lordi NG (1986). Sustained release dosage form. In: The Theory and Practice of Industrial Pharmacy, 3rd Ed., Lea & Febiger, Philadelphia, USA, pp. 430-456.
- Rainsford K (2002). Discovery, mechanisms of action and safety of ibuprofen, Highlights of International Ibuprofen Foundation conference held at the Royal College of Physician, London 15-16th April 2002, pp.4-5.
- Siepmann J, Kranz H, Peppas NA and Bodmeier R (2000). Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. *Int. J. Pharm.*, **201**: 151-164.
- Siepmann J, Kranz H, Bodmeier R and Peppas NA (1999b). HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics. *Pharm. Res.*, **16**: 1748-1756.
- Siepmann J and Peppas NA (2001). Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv.Drug Deliv.Rev.*, **48**: 139-157.
- Siepmann J, Podual K, Sriwongjanya M, Peppas NA and Bodmeier R (1999a). A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. *J. Pharm. Sci.*, **88**: 65-72.
- Sinclair GW and Peppas NA (1984). Analysis of non-Fickian transport in polymers using simplified exponential expressions. *J. Memb. Sci.*, **17**: 329-331.
- Somade S and Singh KK (2002). Comparative Evaluation of Wet Granulation and Direct Compression Methods for Preparation of Controlled Release Ranitidine HCL Tablets, May-June: IJPS. <http://www.indianpharma.org/journal/index.php/2002/3may%20-%20june/comevaluation.html>
- Sung KC, Nixon PR, Skoug JW, Roburt Ju T, Gao P, Topp EM and Patel MV (1996). Effects of formulation variables on drug and polymer release from HPMC based matrix tablets. *Int. J. Pharm.*, **142**: 53-60.

Received: 11-02-06 – Accepted: 15-4-2006