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Formulation and Optimization of Megaloporous Matrix Tablet Containing Losartan Potassium

Patel Amrit Lal*, Gautam Surya Prakash, Sudhakar C.K., Jain Sanjay

Smriti College of Pharmaceutical Education, 4/1 Pipaliya Kumar Kakad, Maya Kheri Road, Indore (M.P.)-452010, India

ABSTRACT

The purpose of this study is the formulation and optimization of Megaloporous matrix tablet containing Losartan potassium to give an initial immediate effect followed by sustained release for 12 h from the matrix embedded tablets at a constant rate. These Megaloporous matrix tablets were prepared with two kinds of granules, insoluble restraining-phase matrix granule (RMG) which controls the release rate of the drug and soluble housing-phase matrix granule (HMG) which controls liquid penetration into the system and leaching out of drug immediately. Eudragit RS 100 as release retardant and Sodium Starch Glycolate (SSG) as superdisintegrant were used to constitute the RMG and HMG, respectively. The RMG and HMG granules were prepared by wet and dry granulation respectively and mixture of both granules compressed as a tablet. The Megaloporous matrix tablets were characterized by friability, hardness, Swelling index Drug content uniformity and *in vitro* drug release study. *In vitro* drug release were performed by USP apparatus type II. The optimization of the tablets were done on the basis of the concentration of Eudragit RS 100 in the RMG, SSG and Carbopol in the HMG and it was found that the drug release rate decreased with increasing of the concentration of the Eudragit RS 100 and drug release rate increased with increasing of the concentration of the SSG in RMG and HMG phases, respectively. The release kinetic of the formulations was evaluated by using different release kinetic models and it was seen that the target profile was nearly achieved. This study suggests using Megaloporous tablets in therapy, which could be prepared with a simple and cheap way similarly to conventional tablets to obtain an immediate and constant drug release which mimic Bilayer tablet.

Keywords: Megaloporous matrix tablet, Losartan potassium, Eudragit RS 100, Sodium Starch Glycolate, Carbopol 934p.

INTRODUCTION

Losartan potassium is a potent, highly specific Angiotensin II type 1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hours. Because of its relatively short plasma half-life patients are routinely asked to take Losartan potassium in divided daily doses, once every 6 to 8 h. Such frequent drug administration may reduce patient compliance and therapeutic efficacy. Biphasic delivery system where an initial rapidly releasing loading dose is followed by a more gradual sustained dose is increasing in popularity due to therapeutic advantages for certain type of antihypertensive therapy. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules. [1-5]

The Megaloporous inert matrix system can be viewed principally as a single-unit device that comprises two structures, which operate together to transfer the drug from the dosage form with a constant rate to the dissolution liquids over an extended period of time. One of the structures is called the restraining-phase matrix granule (RMG) which comprises the drug and insoluble release rate-controlling material (Eudragit RL100, Eudragit RS100, carnauba wax); it controls the release rate of the drug. The other structure is the housing-phase matrix granule (HMG); it contains drug and soluble penetration rate-controlling material Eudragit L100, Eudragit S100, Carbopol 934 used to controls liquid penetration into the system. Liquid penetration into the inner parts of the device discloses an increasing part of the restraining phase surface area, available for drug delivery to the liquids in the pores. The rate at which the drug releasing surface of the restraining phase is exposed to the extraction liquids in the large pores, decreases with respect to time, but simultaneously, the total pore surface area exposed to the liquids and contributing to the release process, increases. [6-9]

The present study aims at formulating Megaloporous matrix tablets of Losartan potassium with a fast release HMG phase using sodium starch Glycolate and a sustaining layer using hydrophobic polymers Eudragit RS 100.

***Corresponding author: Patel Amrit Lal,** Smriti College of Pharmaceutical Education, 4/1 Pipaliya Kumar Kakad, Maya Kheri Road, Indore (M.P.)-452010, India; **E-mail:** amritlal_p@yahoo.com

MATERIALS AND METHODS

Materials

Losartan potassium was obtained from IPCA Ratlam, Eudragit RS 100 was obtained from Ranbaxy Laboratories Ltd Dewas, Carbopol 934p, Sodium starch Glycolate, Lactose monohydrates and Magnesium Stearate was obtained from Loba Chemie Pvt. Ltd. Mumbai, and PVP K30 was obtained from Himedia Pvt. Ltd. All materials and solvents used were of analytical grade.

Preparation of matrix granules

HMG were prepared by dry granulation method. Initially, the Losartan potassium was mixed with Carbopol 934P, Lactose, Sodium starch Glycolate materials by geometric mixing for 10 min., then after it was precompressed on a rotatory 16 station punching machine (Rimek minipress), and granules were formulated by passing these precompressed tablets through Sieve #22 and then #44. Then Granules were dried in petri dish.

RMG were prepared by wet granulation method. The Losartan potassium was mixed with Lactose, E RS-100, by geometric mixing for 10 min., binders solution 10% W/v prepared by dissolving PVP K30 in granulating fluid ethyl alcohol and dry mixing of Losartan potassium was blended with binders. The prepared blend was dried in hot air oven at 40^{o}C. At semi-dried condition the granules were screened through Sieve #22 and #44. Then granules were dried in petri dish.

Table 1: Formulation of the HMG phase

Ingredients	MG P1	MG P2	MG P3	MG P4	MG P5	MG P6	MG P7	MG P8
Losartan potassium (mg)	9	9	9	9	9	9	9	9
Carbopol 934P (mg)	25	25	37.5	37.5	25	25	37.5	37.5
Sodium starch glycolate (mg)	12.5	20	12.5	20	12.5	20	12.5	20
Lactose (mg)	63	59	57	53	57	53	50.5	47

Table 2: Formulation of the RMG phase

Ingredients	MGP1	MGP2	MGP3	MGP4	MGP5	MGP6	MGP7	MGP8
Losartan potassium (mg)	46	46	46	46	46	46	46	46
E RS-100 (mg)	25	25	25	25	37.5	37.5	37.5	37.5
Lactose (mg)	63	59	57	53	57	53	50.5	47
PVP k30 (w/v)	10%	10%	10%	10%	10%	10%	10%	10%
Magnesium Stearate (mg)	5	5	5	5	5	5	5	5

Characterization of granules

Prior to compression, granules were evaluated for their characteristic parameters, such as tapped density, Carr's index and angle of repose. Carr's compressibility index and Hausner's ratio was calculated from the bulk and tapped densities. [10]

Compatibility testing of drug with polymer

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Losartan potassium was determined on Fourier transform infrared spectrophotometer.

Compression of Megaloporous matrix tablet

Required portions of HMG and RMG were mixed, lubricated with magnesium stearate and compressed on a rotatory 16 station punching machine (Rimek minipress) using 8.73 mm flat punches.

Physical tests for the Megaloporous matrix tablet

Diameter and thickness were determined by Venire caliper. Weight variation was determined for weighing 20 tablets. Hardness was determined by taking 3 tablets from each formulation using a Monsanto hardness tester. Friability was determined by first weighing 10 tablets by placing in a friability tester (Roche type), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. [11]

Tablet % swelling ratio

The swelling behavior of formulation is to understand the influence of swelling and erosion behavior on drug release and also to determine the effect of polymer viscosity on the swelling and erosion. The degree of swelling was observed by placing the tablet from each formulation in a 150 ml beaker containing 90 ml of 0.1N HCl for initial two hours followed by addition of 30 ml of 0.2 M Tribasic sodium phosphate in order to obtain a final pH of 6.8 in the medium. The temperature was maintained at 37±0.2ºC throughout the studies. At the end of 12 h, the tablet was withdrawn, kept on tissue paper and weighed. The % weight gain by the tablet was calculated by formula. [12]

Drug content uniformity

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar, an accurately weighed quantity of powder equivalent to 55 mg of drug was transferred to a 100 ml volumetric flask. Few ml of water was added and shaken for 15 min. Volume was made up to 100 ml with distilled water. The solution was filtered through Whatmann filter paper (No. 41). 5 ml of the filtrate was diluted to 100 ml with 0.1N HCl. Absorbance of the resulting 10 mg/ml solution was recorded at 205.5 nm. [13]

***In-vitro* release study**

Release of Losartan potassium was determined using USP type II six stage dissolution test apparatus (VEEGO, VDA-6DR) at 50 rpm. The dissolution was studied in two steps:

Acid stage: The in vitro release of Losartan potassium from the formulated tablets was carried out by using 750 ml of 0.1 N HCl, maintained at 37.0±0.5°C and a stirring rate of 50 rpm for the first 2 h. Samples was withdrawn after regular interval of time 2 ,4, 6, 8, 10, 15, 20, 25, 30, 40, 60, 120 minutes and analysis was done in UV spectrophotometer (UV 1700 by Shimadzu Corporation) after proper dilution.

Buffer stage: Addition of 250 ml 0.2 M Tribasic sodium phosphate in the basket that has been equilibrated to 37±0.5°C, pH 6.8. An operation of apparatus is continuing for 10 h and withdraws aliquot of fluid at every 1 h interval and analyze. [14]

RESULT AND DISCUSSION

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, Friability, drug content, *in vitro* drug dissolution studies and stability studies. All the studies were performed in triplicate, and results are expressed as mean ±SD.

Fig. 1: The photograph of the Megaloporous tablets before and after dissolution procedures

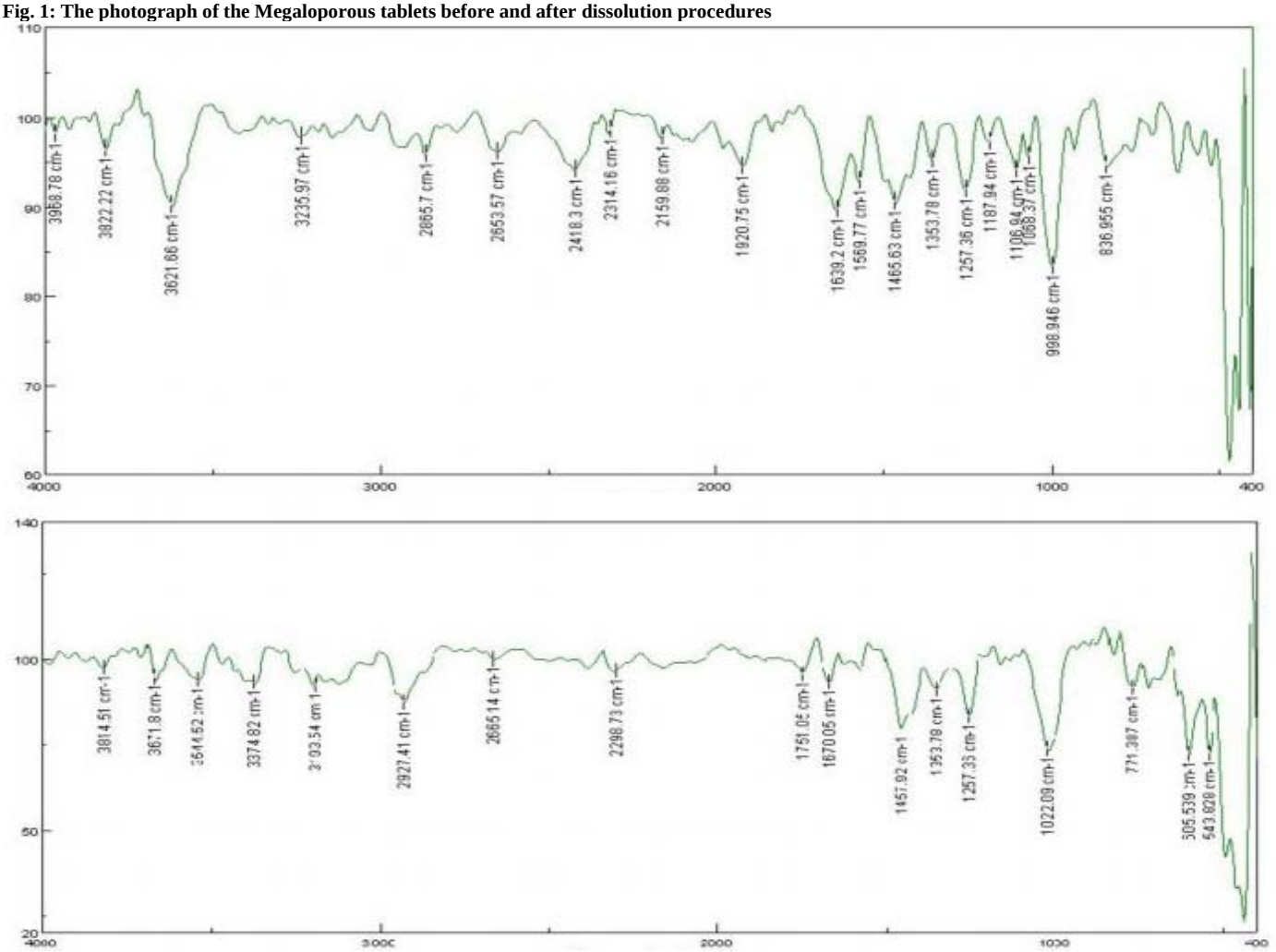

Fig. 2: FTIR spectra of (A) drug and (B) drug with polymer

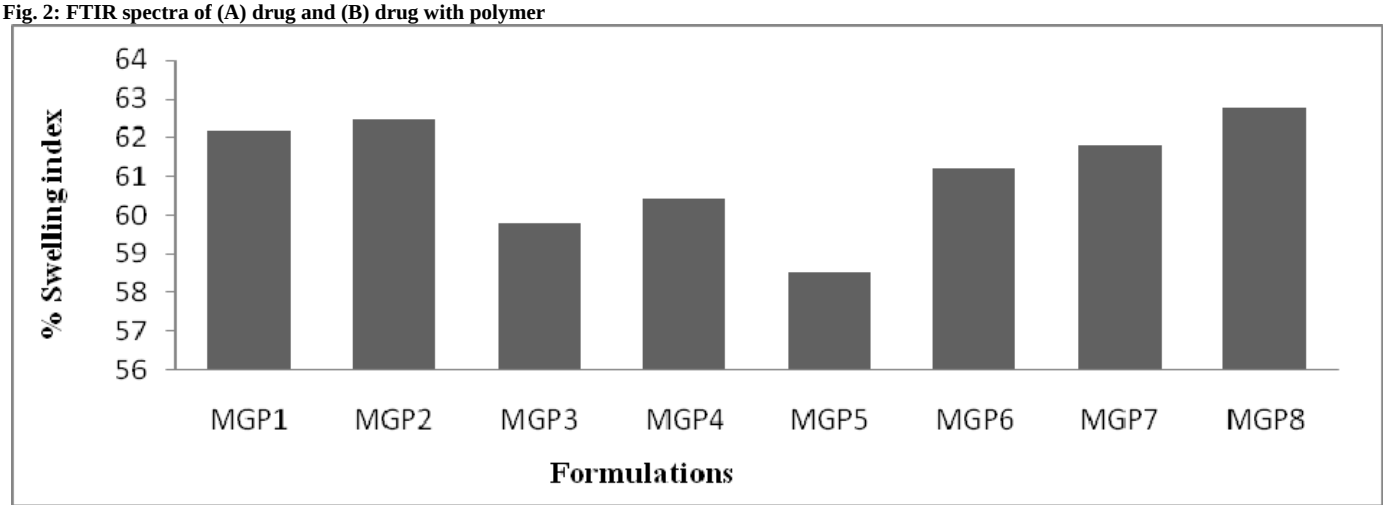

Fig. 3: Percentage swelling index of different formulations

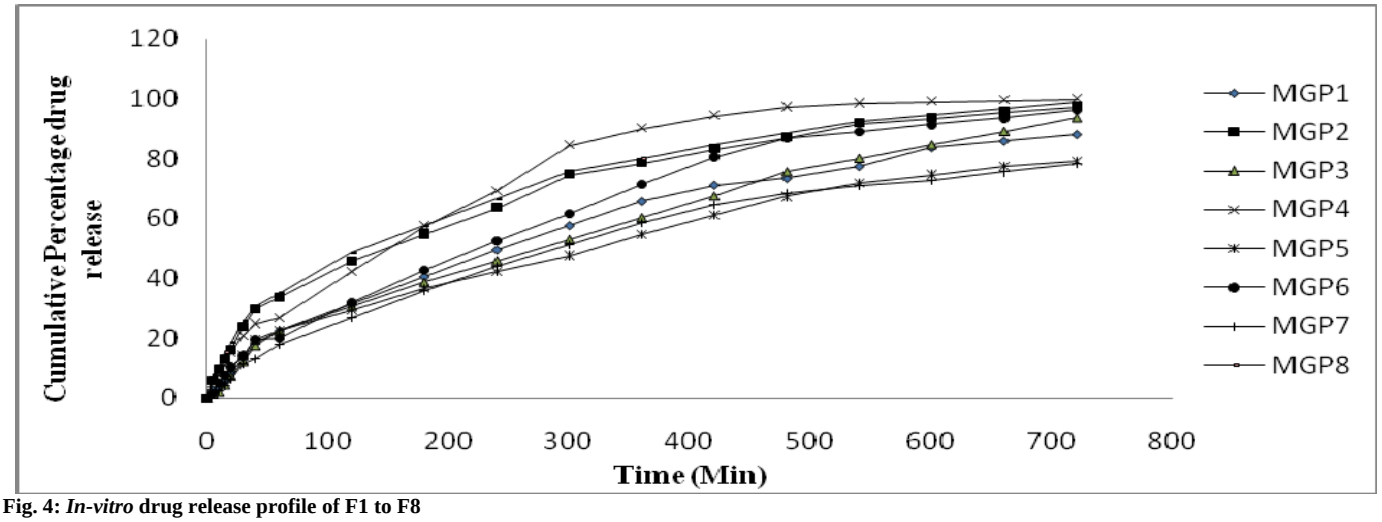

Fig. 4: *In-vitro* drug release profile of F1 to F8

Table 3: Different kinetic models for Megaloporous matrix tablets

Formulation	Drug release kinetics, correlation coefficient 'r^2'			
	Zero order	First order	Higuchi	Korsmeyer Peppas
MGP1	0.978	0.996	0.995	0.725
MGP2	0.976	0.990	0.988	0.699
MGP3	0.986	0.967	0.993	0.638
MGP4	0.916	0.964	0.973	0.607
MGP5	0.987	0.994	0.995	0.750
MGP6	0.911	0.985	0.990	0.656
MGP7	0.970	0.993	0.992	0.767
MGP8	0.965	0.971	0.987	0.665

Characterization of granules blend

The granules prepared for compression of sustained release tablets were evaluated for their flow properties. Angle of repose was in the range of 21 ±0.09 to 26 ± 0.23^0 which indicates excellent flow of the granules for all formulations. The bulk density of the granules was in the range of 0.460 ± 0.12 to 0.515 ± 0.03 g/ml and the tapped density was in the range of 0.544 ±0.05 to 0.590 ±0.04 g/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 13.72 ± 0.03 to 19.56 ± 0.04 %, the Hausner's ratio was found to be in the range of 1.139±0.08 to 1.196±0.04, indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Compatibility testing of drug with polymer

Major functional groups present in Losartan potassium show characteristic peaks in IR spectrum. Fig. 2 shows peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different polymer. The major peaks are identical to functional group of Losartan potassium. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

Evaluation of Losartan potassium Megaloporous matrix tablets

The Losartan potassium sustained release tablets were off-white, smooth, and flat shaped in appearance. The Diameter and thickness of sustained release tablets was measured by Venire caliper and was ranged between 7.9mm to 8.5mm and 5.6±0.07and 6.3±0.31mm respectively. The weight variation for different formulations (F1 to F8) was found to be 300.4±1.3% to 301.3±1.4%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the tablets was measured by Monsanto hardness tester was controlled between 7±1.15 and 7±1.58 kg/cm ^{2}. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug assay for F1 to F8 was found to be in between 92.80 to 106.93 of Losartan potassium, it complies with official specifications.

Swelling studies

The swelling index was calculated with respect to time. As time increase, the swelling index was increased, because weight gain by hydration. It was found to be 58.52 to 62.77 %.

Drug content uniformity

The percentage of drug content for F1 to F8 was found to be in between 98.54±1.7 to 100.86±1.2 of Losartan potassium, it complies with official specifications.

***In-vitro* dissolution studies**

From the dissolution study of batch MGP-1 to MGP-8, it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 12 hrs. When cumulative % drug release plotted versus time it was observed that, for the superdisintegrant used, an increase in superdisintegrant concentration induce an increase in the release rate. And an increase in polymer concentration induces a decrease in the release rate. The percentage drug release from batch MGP-1 to MGP-8 varies from 78.3 to 99.9 %.

RELEASE KINETICS

The data obtained from in vitro dissolution studies were fitted in different models viz. zero order, first order, Higuchi and Korsmeyer-Peppas equation, the results were shown in Table 3. It was also observed that highest correlation for formulations was found for Zero order profile (R^2 > 0.99), which indicates the drug release via diffusion mechanism from hydrophilic matrices. To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsmeyer-Peppas equation. A value of n for all matrices studied here was ranged 1.241 to 1.916, indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism. [15-23]

CONCLUSION

The aim of the study was to study the effect of concentration of superdisintegrant, hydrophilic and hydrophobic polymers on in vitro release rate and to study release kinetic from Megaloporous matrix tablets of Losartan potassium. From the graph (Fig. 4) it shows an initial burst release over 25% of Losartan potassium was released within first half an hour of dissolution study. This initial high amount of Losartan

potassium release can be attributed to release of drug from the HMG phase of the formulation. The initial release of Losartan potassium was due to SSG. This high percent release can be described to release of drug from the HMG phase and also release of drug from the surface of the tablet. The release rate was found to be decreasing as the concentration of Eudragit RS100 increase due to swelling is less because of higher concentrations of insoluble polymer. In MGP8 cumulative percent drug release was about 98.7% in 12 hr. A value of n for all matrices studied was ranged 1.241 to 1.916 indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism.

REFERENCES

1. Angelo Appiotti MD., Luca Gualdi MD, Marco Alberti MD., Massimo Gualdi, MD., 1998. Comparative Study of the Analgesic Efficacy of Flurbiprofen and Diclofenac in Patients Following Excimer Laser Photorefractive Keratectomy. Clinical Therapeutics. 20, 5.
2. Dennis J., et al., 1991. Bioavailability of Flurbiprofen Following Buccal Administration Pharmaceutical Research. 8, 5.
3. Varshney Himanshu M., Tanwar Y.S., 2010. Effect of different surfactants on the release pattern of cocoa butter suppositories containing Flurbiprofen sodium. Acta Pharmaceutica Sciencia. 52, 129-136.
4. Foye's. Principle of Medicinal chemistry. 5, Lippincott Williams & Wilkins. 2002; 752-753.
5. Tripathi KD. Essentials of medical pharmacology. Published by Jaypee brothers medical publisher 2008; 185: 189-195.
6. De Haan P, Lerk C. Father Megaloporous system: a novel principle for zero order drug delivery. II. A model for the mechanism of drug delivery. Int. J. Pharm 1986; 34: 57-66.
7. Thanikachalam Sivakumara, Prabal Kumar Mannaa. Design and Evaluation of Diclofenac Sodium Megaloporous Matrix System Aimed for Colonic Drug Delivery. Iranian Journal of Pharmaceutical Sciences 2007; 3:1-12.
8. Is Ik Ozguney. Dissolution characteristics of Megaloporous tablets prepared with two kinds of matrix granules. IL FARMACO 2004; 59: 549–555.
9. Van Der Veen C, Menger NR, Lerk CF. Factors affecting the release rate of a highly soluble drug from a programmed release Megaloporous system. Eur. J. Pharm.Biopharm 1994; 40: 77–80.
10. Raghuram Reddy K, Srinivas Mutalik, Srinivas Reddy. Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation. AAPS PharmSciTech 2003; 4: 61.
11. Lieberman A Herbert, Lachman Lion,Schwartz B Joseph. Pharmaceutical dosage forms: Tablets. 3, 3, CBS Publisher and Distributers, New Delhi, 2005; 200-714.
12. Hindustan Abdul Ahad, Chitta Suresh Kumar, Kishore Kumar Reddy B. Fabrication and in vitro Evaluation of Gliclazide Abelmoschus esculentus Fruit Mucilage Prolonged Release Matrix Tablets. Journal of Pharmacy Research 2011; 4: 118-120.
13. British Pharmacopoeia. London UK: Her Majesty's stationary office. 2009; 2846.
14. The United States Pharmacopoeia and National Formulary USP 32/NF 21. Rockville: The United States Pharmaceutical Convention Inc. MD, 2003; 25-29.
15. Peppas LB, Peppas NA. Solute and penetrant diffusion in swelling polymers, IX. The mechanism of drug release from pH-sensitive swelling controlled systems. J. Control Release. 1989; 8: 267–274.
16. Harrish Shoeb M, Jaweria Tazeen, Hamid A, Merchant Rabia, Ismail Yousuf. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak. J. Pharm. Sci. 2006; 19(2): 119-124.
17. Hendeles L, Iafrate RP, Beinberger M. A clinical and pharmacokinetic basis for the selection and use of s1ow release theophylline products. Clinical Pharmacokinetics. 1984; 9: 95-135.
18. Pranitha Yeluri, Ashok Kumar P, Someshwara Rao B, Kulkarni SV, Ranjit kumar P. Formulation and in vitro evaluation of controlled release matrix tablet of lamivudine. Journal of Global Pharma Technology. 2009.
19. Higuchi T. Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm. Sci. 1963; 52: 1145-1149.
20. Harland RS, Gazzaniga A, Sangalli ME, Colombo P, Peppas NA. Drug-polymer matrix swelling and dissolution. Pharm Res. 1988; 5: 488-494.
21. Patra Chinam Niranjan et al. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Acta Pharm. 2007; 57: 479–489.
22. Divya Tewari, Richard K, Lewis et al. Development of single layer Acetaminophen extended release tablet with biphasic release. Pharmaceutical Technology Report. 2007.
23. Raghuram Reddy K, Srinivas Mutalik, Srinivas Reddy. Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation. AAPS PharmSciTech. 2003; 4 (4): 61.