International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE **V-1, I-4, 2012**

Sustained Release Hydrophilic Matrix Tablet of Ibuprofen: Influence of Polymers on In-Vitro Release and Bioavailability

Kumar V*, Soni GC, Prajapati SK

[*]*Institute of Pharmacy, Bundelkhand University, Jhansi - 284128. U.P. India*
Manuscript No: IJPRS/V1/I4/00195, Received On: 25/10/2012, Accepted On: 29/10/2012

ABSTRACT

In the present study, an attempt has been made to evaluate the effect of hydrophilic polymers on the release profile of drug from matrix system. Ibuprofen, a non-steroidal anti-inflammatory drugs (NSAIDs) was used as a model drug to evaluate its release characteristics from different matrices. Matrix tablets of Ibuprofen were prepared by direct compression process using different hydrophilic excipients (Methocel K4M, Methocel K100M, PolyoxWSR 1105 & Metolose 90 SH 100 SR).Before compression the formulations were evaluated for angle of repose, % compressibility and Hausner's ratio. Tablets were evaluated for hardness, friability, weight variation, uniformity of thickness & diameter, and drug content and results were found in acceptable limits. In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II at 50 rpm with 900 ml 0.1N HCl & phosphate buffer solutions (PBS) of pH 7.4, maintained at 37±0.50C. The release kinetics was analyzed using the zero-order, first-order model equation, Higuchi's square-root equation, and the Korsmeyer-peppas model. In vitro release studies revealed that the release rate decreased with increases in polymer proportion. The matrix tablet containing 20% Methocel K100M & Polyox WSR 1105 (in ratio 1:1) (Formulation F6) were found to show good initial release (34.52% in initial hour) and allowed sustained release up to 12 hours. Bioavailability parameters including Cmax, Tmax, AUC(0-t), for both tablet were compared. The sustained release tablet produce optimized Cmax and extended Tmax. Relative bioavailability of the test tablet was calculated as 124.14% for 12 hr. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on polymer concentration and it was found to be diffusion coupled with erosion. Bioavailability parameters including Cmax, Tmax, AUC(0-t), for both tablet were compared. The sustained release tablet produce optimized Cmax and extended Tmax. Relative bioavailability of the test tablet was calculated as 124.14% for 12 hr. The developed controlled release matrix tablets of Ibuprofen, with sustained release characteristics might be able to minimise the demerits of conventional therapy having Ibuprofen.

KEYWORDS

Ibuprofen, sustained release, in-vitro, Bioavailability.

INTRODUCTION

Ibuprofen, (RS)–2–(4–(2–methyl–propyl)phenyl)propanoic acid, is a non-steroidal anti-inflammatory drug (NSAID)used for inflammatory and painful diseases of rheumatic and non-rheumatic origin.

***Address for Correspondence:**
Vinay Kumar
Department of Pharmaceutics,
Institute of Pharmacy, Bundelkhand University,
Jhansi - 284128. U.P. India
E-Mail Id: Vinaykumar070786@gmail.com

The anti-inflammatory activity of NSAID's and most of its other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostagladins, which are mediators of the inflammatory process.1,2Ibuprofen is a potent inhibitor cyclo-oxygenase(Cox)*in-vitro and in-vivo,* thereby decreasing the synthesis of prostaglandins, prostacyclin, and thromboxane products[1].

Ibuprofen is one of the safest and most potent non-steroidal anti-inflammatory drug in market. It may be tolerated better than other NSAIDs. Due to rapid excreation of ibuprofen in urine, large amount of drug is required for conventional dosage form. However it is suffers from limited aqueous solubility, gastrointestinal side effects and hardening of the tablets on aging[2,3]. Due to short half-life of ibuprofen (about 2 hours) and rapid excretion from urine for prevention of drug fluctuation in blood, ibuprofen must be administered frequently[4].

Hydrophilic polymer matrix systems are widely used in oral sustained release drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[5]. 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[6].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[7].

Water-soluble polymer polyethylene oxide (PEO) has been extensively used as a sustained release excipient to modify drug release and dissolution from solid hydrophilic matrix preparations. This is mainly attributed to the desirable hydration and modified release properties by PEO of variable grades and molecular weights[8-11]. Once in contact with a liquid, PEO will start to hydrate and swell, forming a hydrogel layer that regulates further penetration of the liquid into the matrix and the diffusion of the drug molecules from the dosage form[12]. As a result of hydrogel formation, the rate of water intake slows down while that of drug releases declines and prolongs. The formation of a hydrogel layer on the surface of a modified release matrix tablet is generally categorized into three stages, i.e., initial hydrogel increase due to polymer swelling; maintenance of constant gel layer thickness between swelling and dissolution front; reduction in gel layer thickness due to depletion of the glassy core[13-14].

METOLOSE is nonionic water-soluble cellulose ether which is derived from pulp. To produce METOLOSE, the pulp is first treated with caustic soda to obtain alkali-cellulose, and this is etherified with chloromethane or with the combination of chloromethane and propylene oxide at high temperature. Cellulose is not soluble in water due to its crystalline structure with strong intermolecular hydrogen bonding between OH groups. When the hydrogen atoms of some of the OH groups are substituted with methyl or hydroxypropyl groups, the resulting methoxy and hydroxypropoxy groups interfere with the intermolecular hydrogen bonding, so that the polymer chains are less strongly bound to each other. This allows water to penetrate into the intermolecular spaces of cellulose, and the polymer becomes water-soluble[15-16].

The objective of present investigation is design and evaluates sustained release tablets of ibuprofen using Methocel K4M, Methocel K100M, Polyox WSR 1105 & Metolose 90 SH 100 SR as release retardant. Drug release from hydrophilic matrices is known to be a complex interaction between swelling, diffusion and erosion mechanisms. Previous work has demonstrated that Methocel K100M and Polyox has useful hydrogels for producing a constant in-vitro drug release. This work was an attempt to determine the relative contribution of the drug release mechanisms from Ibuprofen matrix tablets produced with Methocel K100M and the highly hydrophilic Poyox. Different concentrations of hydrophilic polymers, in physical mixture Methocel K100M, Methocel K100M, Metolose 90SH 100 SR and Polyox WSR 1105 in 1:1 ratio were tested to evaluate their performance as release-controlling agents[17].

MATERIALS AND METHODS

Ibuprofen gift sample obtained from S.S. Pharmaceuticals Pvt. India, Methocel K4M, Methocel K100M, Polyox WSR1105 from Colorcon Asia Pvt. Limied & Metolose 90 SH 100 SR gift sample obtained from Signet Chem. Microcrystalline Cellulose and magnesium stearate were analytical reagent grade and used without further putification.

Preparation of Sustained release Matrix tablet (Direct compression method)

Matrix tablets, each containing 400 mg Ibuprofen and weighing 600 mg were prepared by direct compression techniques using in combination with Methocel K4M and Polyox, Methocel K100M and Polyox, and Metolose with Polyoxas matrices **(Table 1).** Methocel K4M and Polyox, Methocel K100M and Polyox, and Metolose with Polyox were in percent (10%, 15% and 20%) and in ratio 1:1.Drug, other preparation excipients (except the lubricant) of tablets were mixed thoroughly with a pestle and mortar. All the powders were passed through mesh # 80.

Microcrystalline cellulose and magnesium stearate were finally added as glidant and lubricants. The drug and powdered gum were compressed (13 mm diameter, biconvex punches) using a single punch tablet compression machine (Cadmach, Ahmedabad, india) prior to the compression, the formulation powder (blend) was evaluated for several tests.[4,5,8,9,10,11]

Evaluation of Sustained Release Hydrophilic Matrix Tablet

Evaluation of Pre Compression Parameters of Tablet

Angle of Repose (θ)[9]

The frictional forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. Angle of repose was determined by using funnel method. Powder was poured from funnel, which can be raised vertically until a maximum cone height

$$\theta = \tan^{-1}(h/r)$$

Whereas; θ is angle of repose, h is height of pile and r is the radius of the base pile.

Table 1: Formulation chart

	K4M + POLYOX			K100M + POLYOX			METOLOSE +POLYOX		
INGRIDIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug(Ibuprofen)	400	400	400	400	400	400	400	400	400
HPMC K4M	**30**	**45**	**60**	----	-----	----	----	----	---
HPMC K100	----	----	---	**30**	**45**	**60**	----	----	----
Polyox WSR 1105 LEO	**30**	**45**	**60**	**30**	**45**	**60**	**30**	**45**	**60**
Metolose 90SH 100SR	----	----	----	----	---	----	**30**	**45**	**60**
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Micro-crystalline cellulose	135	105	75	135	105	75	135	105	75
TOTAL	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**	**600**

Weight in “mg”

Bulk Density (Db)[6]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) into a measuring cylinder and the initial volume was noted. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder.

Tapped Density (Dt)[8]

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 100 times. Tapping was continued until the difference between successive volumes is less than 2% (ina bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M/Vt$$

Where, M is the mass of powder, Vt is the tapped volume of the powder**.**

Compressibility Index (Carr's Consolidation Index)[6]

One of the ways of measurement of free flowing powder is compressibility as computed from density of a powder. It was calculated by using the formula:

$$\% \text{ Compressibility} = \left(\frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}\right) \times 100$$

Hausner Ratio[6]

Hausner ratio is an indirect index of ease of powder flow. If the Hausner ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the formula:

$$\text{Hausner Ratio} = Dt/Db$$

Where, Db = Bulk density of the powder,

Dt = Tapped density of the powder.

Each value was an average of five determinations

Evaluation of Post Compression Parameters of Tablet

Appearance

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light.

Dimension

Thickness and diameter were measured using a calibrated barmier caliper. Five tablets of each formulation were picked randomly and dimensions determined.

Hardness Test[7]

The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm^2. Five tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated.

Friability Test [6,20]

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. It was rotated at arate of 25 rpm. After 100 rotations (4 min), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0 % and the percent friability was determined using the following formula;

$$\text{Friability} = [(W1-W2)/W1] \times 100$$

Where,

W1 = weight of the tablet before test,

W2 =weight of the tablets after test

Weight Variation Test [10,20]

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the

permissible limits (± 5%). The percent deviation was calculated using the following formula.

Percentage Deviation = (Individual Weight–Average Weight/Average Weight) × 100

Drug Content Estimation [11,21]

Twenty tablets were weighed and powdered, 400 mg of equivalent of Ibuprofen was weighed and dissolved in 100 ml of phosphate buffer pH 7.4, filtered, diluted suitably and analyzed for drug content at 221 nm using UV spectrophotometer(UV 1700 Shimadzu, Japan).

Swelling Behavior of Sustained Release Matrix Tablets[23]

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behaviour of all formulation was studied. One tablet from each formulation was kept in a Petridis containing pH 7.4 phosphate buffer. At the end of 0.5 hr., the tablet was withdrawn, dried with tissue paper, and weighed. Then forevery1,2,3 and 4 hr., weights of the tablet were noted, and the process was continued till the end of 4 hr. Percentage weight gain by the tablet was calculated by formula[6];

S.I. = {(Mt-Mo) / Mo} X 100,

Where, S.I. = swelling index, Mt = weight of tablet at time t(h) and Mo = weight of tablet at zero time.

In-Vitro Release Studies Tablets[5,9,13,17]

The in vitro dissolution studies were carried out using USP apparatus type II at 50 rpm. The dissolution medium consisted phosphate buffer pH 7.4 for 12 hours (900 ml), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (UV spectrophotometer, Shimadzu 1700, Japan) at 221 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay.

Kinetic Analysis of Release Data Of Tablets[5,9,13]

Drug release kinetics The Korsmeyer and Peppas equation was used to analyze the data obtained from the in-vitro release studies to evaluate the kinetic models and release mechanism of Ibuprofen from the matrices. The software PCP Disso V2.08 and DD Solver was used.

Korsmeyer and Peppas equation (Korsmeyer and Peppas, 1981) is:

$$\mathbf{Mt/\ M\infty = kt^n}$$

Where Mt/M∞ is the fraction of drug release at time **t**, **k** is a constant incorporating the properties of the macromolecular polymeric system and the drug. The **n** is an exponent used to characterize the transport mechanism. For example, n = 0.45 for Case I or Fickian diffusion, 0.45 < n < 0.89 for anomalous behaviour or non-Fickian transport, n = 0.89 for Case II transport, and n > 0.89 for Super Case II transport. 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. Case II generally refers to erosion of polymeric chain and anomalous transport (non-fickian) refers to a combination of both diffusion and erosion controlled drug release.[1,3]

In-Vivo Studies (In Vivo Bioavailability Studies In Rabbits)[16, 17]

The in-vivo study was performed as per the guidelines approved by the committee for the purpose of control and supervision of experiments on animals (CPCSEA), ministry of social justice empowerment, and government of India. The central animal facilities of institute of pharmacy, Bundelkhand University provided six young and healthy male albino rabbits with mean weight of 2.5 ± 0.5 kg. The study was conducted with the approval of (protocol approval number: BU/Pharm/IAEC/11/020) and as per guidelines prescribed by institutional animal Ethecs committee, Bundelkhand University, under the supervision of registered veterinarian.

Preparation of Calibration Curves in Blood Plasma

The calibration curve of Ibuprofen was prepared in blood plasma by preparing 1 to 10 µg/ml dilutions. The aliquots of 1, 2, 3, 4…….10 ml of stock solution (10µg/ml) were transferred quantitatively into a series of 10 ml volumetric flasks and volume was made up to10 ml with blood plasma to produce solutions of concentration ranging 1to10 µg/ml. the absorbance of these solution was determined at λmax (221 nm) against blank(blood plasma).

Experimental Design

Rabbits, weighing 2.00-2.50 kg were divided into two groups, each consisting of three animals. Rabbits were kept on fasting 12 hrs before drug administration and until 24 hrs post dosing. Water ad-libitum was given throughout the study. The dose selected of Ibuprofen was 51.40 mg. The first group received oral administration (marketed preparation) of 400 mg tablet in blood plasma. The second group received oral SR hydrophilic matrix tablet in blood plasma.

Collection of Blood Sample

For the collection of blood samples use 1 ml syringe fitted with a 25 gauge needle. Blood samples of 1.5 ml were collected in the specific time intervals. The blood samples were collected in clean 2 ml centrifuges tubes without anticoagulants. The blood was separated by placing the tubes in a centrifuge 15 min at 2000rpm. Separated serum samples were taken by micro pipette and diluted up to suitable requires dilution with phosphate buffer pH 7.4. The plasma drug concentration of Ibuprofen was analyzed by UV spectrophotometer at 221.0 nm.

Pharmacokinetic Analysis[24]

The peak plasma concentration (Cmax) and time of its occurrence (Tmax) were read directly from Ibuprofen concentration-time data. For other parameters the concentration –time data were analysed using a computer based pk solver (pharmacokinetic software). Non-compartmental apporach could describe successfully the Ibuprofen plasma concentration. The AUC and AUMC were calculated by trapenzoidal method. The ratio of AUC and AUMC was used to estimate the mean residual time (MRT) of drug.

Relative Bioavailability[24]

The percent relative bioavailability of the test tablet was calculated with the following formula:

$$\text{Percent relative bioavailability} = \frac{\text{AUC } 0-t\,(\text{Test})}{\text{AUC } 0-t\,(\text{Reference})} \times 100$$

RESULT AND DISCUSSION

The sustained release tablets were prepared by direct compression technique. The sustained release matrix tablet subjected to various evaluation studies done as pre-compression parameters like angle of repose, bulk density, compressibility index, hausner ration and post-compression parameters like Weigh uniformity test, Hardness, Thickness, Friability (%F),Thickness, Content uniformity, *In vitro* drug release, Swelling Index, *In vivo* bioavailability study) and storage condition studies.

Evaluation of tablets

Angle of Repose, Bulk Density, Compressibility Index, Hausner Ratio

In the present study, Ibuprofen Sustained release hydrophilic matrix tablets were prepared by using hydrophilic polymers namely Methocel K4M, Methocel K100M, Polyox WSR 1105 & Metolose 90 SH 100 SR in percent 10%, 15% & 20% in ratio 1:1 concentrations. All the formulations showed good blend properties for direct compression and hence tablets were prepared by direct compression technology. All parameters of powder blend show in table 2.

Weight Variation, Thickness, Hardness and Friability

The results showed that weight variation, thickness were lying within limits. Because of variation in the compressional forces there is a slight variation in hardness of tablets. As the

Table 2: Pre compression parameters of matrix tablet

F. Code	Angle of Repose (θ)*	Bulk density (gm/cm^3)*	Tapped Density (gm/cm^3)*	Compressibility Index*	Hausner Ratio*
F1	28.21±0.93	0.54±0.03	0.69±0.02	21.78±3.28	1.28±0.06
F2	28.64±0.57	0.54±0.03	0.70±0.02	22.67±3.82	1.30±0.06
F3	28.14±1.80	0.55±0.01	0.71±0.02	22.92±2.61	1.30±0.05
F4	28.93±0.62	0.53±0.02	0.69±0.04	23.06±2.58	1.30±0.04
F5	28.63±0.49	0.54±0.01	0.70±0.03	23.46±4.41	1.31±0.08
F6	**28.07±1.00**	**0.54±0.02**	**0.70±0.02**	**22.47±2.52**	**1.29±0.04**
F7	28.59±1.16	0.55±0.03	0.72±0.04	23.09±6.12	1.31±0.10
F8	28.48±1.39	0.55±0.01	0.71±0.05	21.26±6.69	1.28±0.10
F9	28.84±0.92	0.56±0.01	0.70±0.04	20.62±4.62	1.26±0.08

Table 3: post compression parameters of matrix tablet

	Uniformity of weight#	%Drug content	% Friability	Hardness (Kg/cm^2)	Thickness (mm)	Diameter
F1	599.75±2.40	99.44±1.25	0.67±0.08	8.10±0.29	6.00±0.06	13.00 ±00
F2	599.75±1.97	101.06±1.44	0.57±0.05	8.13±0.05	6.02±0.07	13.00 ±00
F3	600.50±2.42	101.21±1.21	0.64±0.08	8.23±0.12	6.00±0.06	13.00 ±00
F4	599.75±2.53	102.31±1.05	0.61±0.07	8.07±0.12	6.12±0.04	13.00 ±00
F5	599.75±2.53	100.13±1.39	0.57±0.07	8.17±0.09	6.13±0.07	13.00 ±00
F6	**600.50±2.59**	**100.56±1.02**	**0.58±0.08**	**8.37±0.09**	**6.02±0.07**	**13.00 ±00**
F7	600.00±2.49	100.88±1.01	0.61±0.09	8.17±0.17	6.00±0.06	13.00 ±00
F8	600.50±2.74	101.49±0.86	0.74±0.07	8.17±0.17	6.10±0.09	13.00 ±00
F9	600.00±2.29	100.60±1.35	0.59±0.10	8.27±0.17	6.00±0.13	13.00 ±00

*Each value was an average of five determinations
Results of one batch, n = 20 tablets

proportion of polymers increases the hardness of the tablets was found to increase. The friability loss was found to be within the limits in all the friability tablet was found to mechanically strong. All results shown in table 3.

In-Vitro Drug Release

The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the peripheral towards the center, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium. The hydrated gel layer thickness determines the diffusional path length of drug.

The in-vitro drug release profiles of Ibuprofen from tablets containing Methocel K4M, Methocel K100M, Polyox WSR 1105 & Metolose 90 SH 100 SR in different percentage and in ratio 1:1 are shown in Table 4 respectively. After 2h, the initial pH 1.2 was changed to pH7.4 continue the dissolution up to 12 h. It was shown that as the amount of excipients in the matrix increased, there would be a greater degree of excipient hydration with simultaneous swelling. This resulted in corresponding lengthening of the drug diffusion pathway and drug release rate.

Drug release was generally linear for most of the formulations, especially Methocel K100M with Polyox matrices (Formulation F6). Such linear release was from hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer. Methocel K100M with Polyox is nonionic hydrophilic excipients their hydration process is independent of pH. During the test, all the formulation swelled and the outer layer of most of tablets appeared to be hydrated after being placed in dissolution medium.

The profiles of the formulation of F1 to F9, and the erosion and drug release at different Polymer percent (10%, 15% and 20%) in ratios of 1:1 are shown in figure-1. In each case of hydrophilic excipients there was an initial burst of hydrophilic excipients erosion from the matrices during the acidic pH thereafter, the erosion hydrophilic excipients slowed considerably. It follows, therefore, that the hydrated Methocel K100M with Polyox matrices network maintains its tight integrity with drug release by erosion and dissolution of the drug accounting for most of the weight loss during the remainder of the experimental period. Furthermore, there is a greater burst of Methocel K100M with Polyox matrices erosion in the formulation containing the lower proportion of Methocel K100M with Polyox matrices in 10% (ratio 1:1) and 15% (ratio1:1) drugs: excipients ratios.

In all the formulations, it has been observed that by increase the concentration of hydrophilic polymers in the formulations there by respectively retard the drug release form the matrices.

There are the effects of excipients on drug release:-

Effect of Methocel K4M + Polyox on drug release (Ratio 1:1)

In the formulation F1, F2 and F3 the polymer percentage was 10%, 15% and 20% in the ratio 1:1. The formulation F1 show the release of drug 97.983% at 8 hrs. Formulation F2 show the drug release 97.687 at 10 hrs and Formulation F3 show the drug release 97.392% at 11 hrs. It showed that when increasing the amount of excipients the release of drug was decreasing with the time.

Effect of of Methocel K100M + Polyox on drug release (Ratio 1:1)

In the formulation F4, F5 and F6 the polymer percentage was 10%, 15% and 20% in the ratio 1:1. The formulation F4 show the release of drug 98.574% at 8 hrs. Formulation F5 show the drug release 98.870% at 10 hrs and Formulation F6 show the drug release 98.870% at 12 hrs. It showed that when increasing the amount of excipients the release of drug was decreasing with the time.

Table 4: In-vitro % drug release studies of formulation

Time(hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	11.945	10.762	10.171	20.519	12.24	9.284	24.07	11.058	9.284
2	28.502	24.363	19.041	35.007	24.363	18.15	38.55	22.293	19.928
3	41.511	34.415	30.572	45.059	34.415	24.07	50.97	34.12	33.528
4	50.677	43.876	37.668	59.842	43.581	37.08	59.25	46.242	40.033
5	66.051	57.477	45.355	76.104	55.999	46.54	72.85	58.068	45.65
6	84.382	71.373	58.068	86.748	68.121	59.84	82.313	68.121	55.407
7	92.661	84.678	71.669	93.252	85.565	67.54	90.000	78.469	65.164
8	97.983	88.226	84.087	98.574	90.887	76.58	97.096	87.635	74.921
9	---	95.322	90.591	---	93.548	84.55	---	92.957	84.974
10	---	97.687	94.435	---	98.87	89.34	---	97.983	90.591
11	---	---	97.392	---	---	96.505	---	---	97.100
12	---	---	---	---	---	98.87	---	---	---

Effect of Metolose + Polyox on drug release (Ratio 1:1)

In the formulation F7, F8 and F9 the polymer percentage was 10%, 15% and 20% in the ratio 1:1. The formulation F7 show the release of drug 97.096% at 8 hrs. . Formulation F8 show the drug release 97.983% at 10 hrs and Formulation F9 show the drug release 97.100% at 11 hrs. It showed that when increasing the amount of excipients the release of drug was decreasing with the time.

Swelling behavior studies[23]

The swelling behavior studies were carried out with hydrophilic excipients formulation of drug:excipient ratio of 1:1(20%), which resulted in the better dissolution profile. The results of swelling and erosion tests were shown in fig.2.

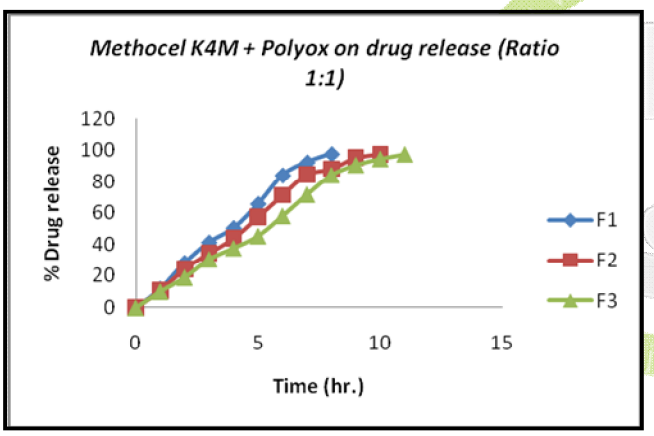
The swelling behavior indicates the rate at which this formulation absorbs water from dissolution media and swells. The change in weight is characteristic of water uptake and swelling, started from the beginning and continued until 4 h of experiment (figure-2)[3,10]

Determination of the Release Kinetics[21]

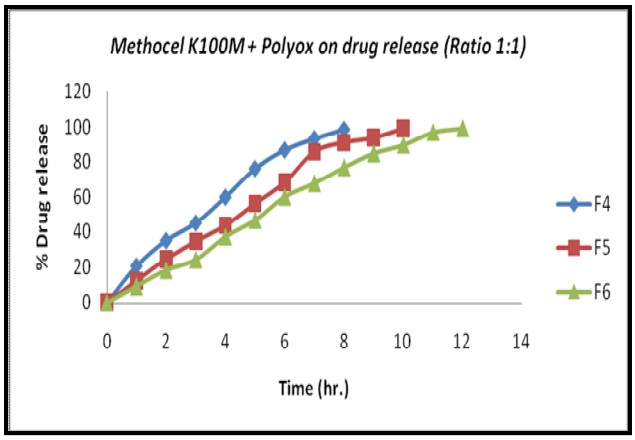
To evaluate the drug release kinetics, formulations showing a significant slow release were chosen. In general, the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a “front” defined at an exact speed; simultaneously, the thickness of the area increased with time in the opposite direction. The mechanism of drug release can be described by a second phenomenon that involves the

disentanglement and erosion of the polymer. The release process involves the penetration of water into dry matrix followed by hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

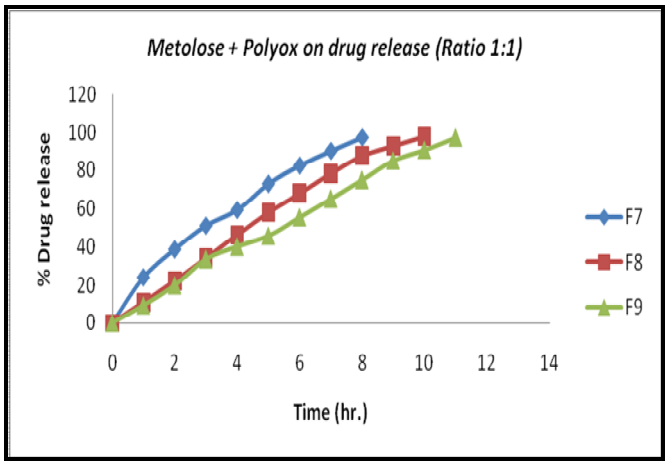
By using Korsmeyer and Peppas (Korsmeyer and Peppas, 1981) Equation, the n values were obtained between 0.67 and 0.946 (table 3) for all formulations. These values are characteristic of anomalous kinetics (non Fickian) and super case –II transport, suggesting that more than one mechanism may be involved in release kinetics. The release pattern of Ibuprofen from different formulation was obtained by plotting log Mt/M∞ versus log time was shown in Figure-3. In case of Methocel K4M, Methocel K100M, Polyox WSR 1105 & Metolose 90 SH 100 SR of all formulations shows super case II transport kinetics.



Effect of Methocel K4M + Polyox on drug release (Ratio 1:1)



Effect of Methocel K100M + Polyox on drug release (Ratio 1:1)



Effect of Metolose + Polyox on drug release (Ratio 1:1)

Figure 1: effect of excipients on drug release

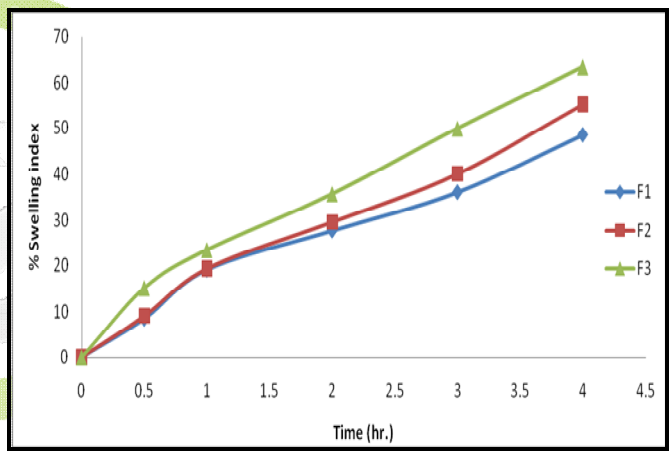


Figure 2: % swelling Index of F1-F3

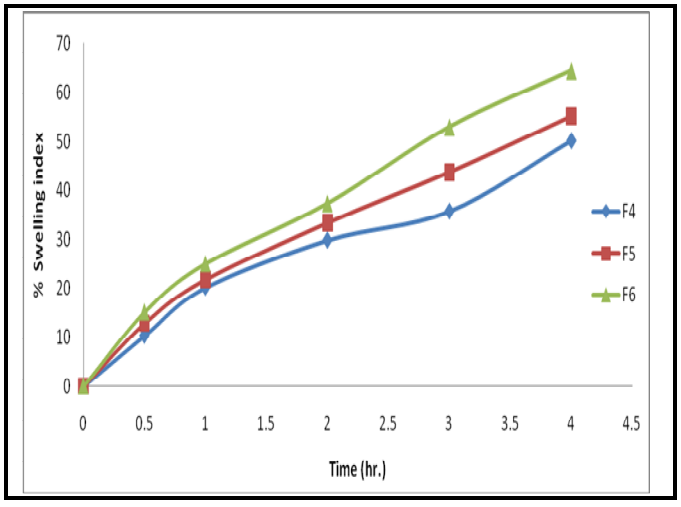


Figure 3: % swelling Index of F4-F6

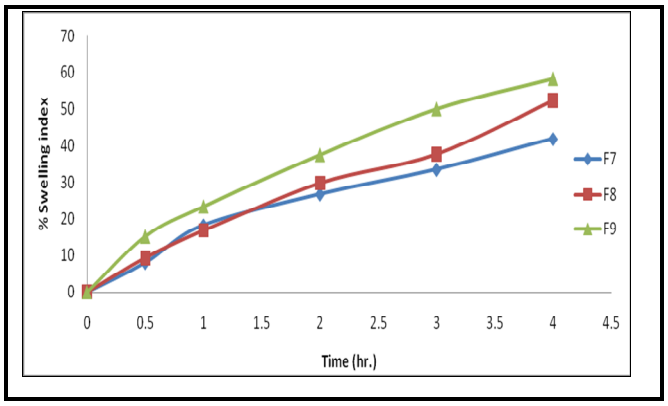


Figure 4: % swelling Index of F7-F9

FTIR Studies

The FTIR spectra of pure drug and formulation containing Methocel K4M, Methocel K100M, Polyox WSR 1105 &Metolose 90 SH 100 SR are shown in **figure-4.** From the figure it is clear that the characteristic peaks present in the standard FTIR spectra of Ibuprofen show peaks at 945.94 due to O-H bending, 1268.72 due to C-O stretching, 1378.69 due to CH_2 and CH_3, 1417.65 due to Ar C-C stretching, 1720.98 due to C=O stretching, 2921.51 due to $–CH_2$ stretching. The principle peaks of the drug was identified and matched with the standard FTIR of the drug, confirming that there is no interaction between the drug and excipients.

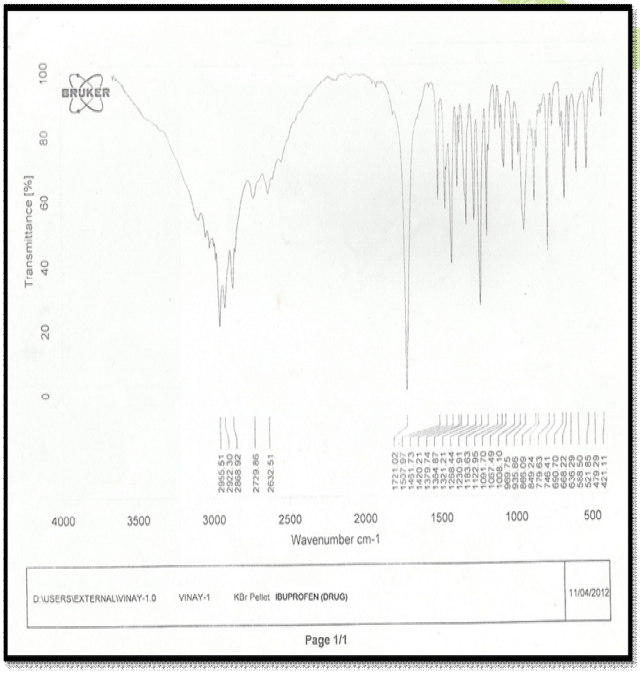


Figure 5: FTIR Spectra of Drug (Ibuprofen)

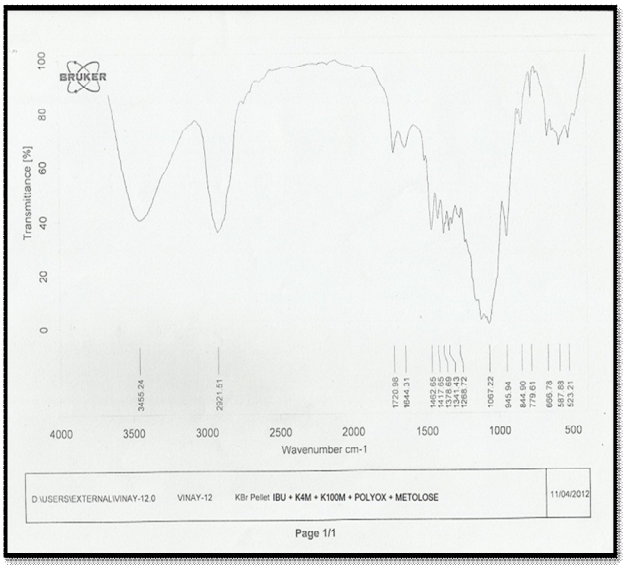


Figure 6: FTIR Spectra of Drug with all Excipients

In-vivo Studies (In vivo bioavailability studies in rabbits)[16,17,21]

Pharmacokinetic of Ibuprofen

Significance of higher value of peak plasma concentration (C_{max}) and peak time (T_{max})were found for market vs formulation (F6) 33.57±0.76 at 1.5 hr. for market and 22.87±1.63 at 2 hr. for optimized formulation F6. The half-life $t_{1/2}$found for market tablet 2.03 hr. but in optimized tablet found 4.98 hr. the MRT_{0-12} found 3.99 for market and 8.09 for formulation. The AUC_{0-6} for market and formulation found 98.43 & 87.42 and AUC_{0-12} for market and formulation found 116.98 & 114.37. The AUC_{0-inf} for market and formulation found 119.69 & 179.60.

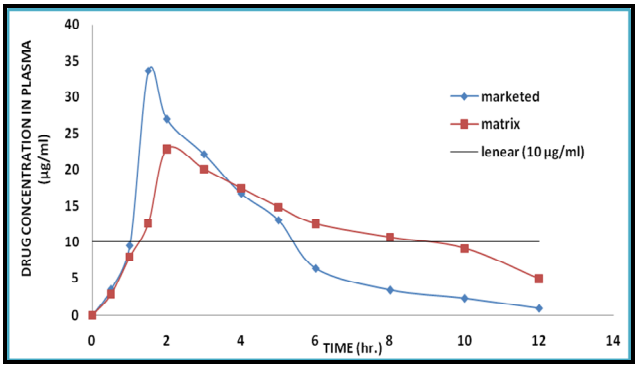


Figure 7: Plasma concentration time profile curve of Marketed tabletand formulation (F6)

Table 5: % Swelling of all Formulations

% Swelling Index			
Time (hr.)	**F1**	**F2**	**F3**
0	0	0	0
0.5	8.44±0.08	9.06±0.08	15.11±0.08
1	19.06±0.08	19.28±0.08	23.39±0.08
2	27.61±0.08	29.56±0.08	35.72±0.08
3	36.06±0.08	40.06±0.08	49.94±0.08
4	48.44±0.08	55.11±0.08	63.39±0.08
% Swelling Index			
Time (hr.)	**F4**	**F5**	**F6**
0	0	0	0
0.5	10.28±0.08	12.78±0.08	15.78±0.21
1	20.11±0.08	21.78±0.08	25.22±0.21
2	29.89±0.08	33.44±0.08	37.39±0.08
3	35.78±0.08	43.78±0.08	52.94±0.08
4	50.11±0.08	55.22±0.08	64.39±0.28
% Swelling Index			
Time (hr.)	**F7**	**F8**	**F9**
0	0	0	0
0.5	7.94±0.08	9.28±0.08	15.06±0.08
1	18.17±0.08	16.72±0.08	23.39±0.08
2	26.78±0.08	29.78±0.08	37.39±0.08
3	33.44±0.08	37.61±0.08	50.06±0.08
4	41.78±0.08	52.39±0.08	58.22±0.08

Table 6: Kinetic Data Treatment

F. Code	**Zero order**		**First order**	**Higuchi**		**Korsmeyer's**			**Best fit model**
	r^2	**K_0**	**r^2**	**r^2**	**kH**	**r^2**	**n**	**kKP**	
F1	0.991	13.065	0.861	0.923	44.062	0.992	0.936	14.669	Korsmeyer's
F2	0.981	10.876	0.908	0.936	43.157	0.992	0.871	14.091	Korsmeyer's
F3	0.982	9.904	0.920	0.945	42.182	0.992	0.946	10.786	Korsmeyer's
F4	0.978	13.762	0.877	0.960	47.413	0.994	0.765	20.980	Korsmeyer's
F5	0.983	10.867	0.857	0.933	43.099	0.994	0.881	13.799	Korsmeyer's
F6	0.998	9.280	0.846	0.935	41.700	0.993	0.910	10.937	Zero order
F7	0.971	13.510	0.898	0.982	47.114	0.999	0.675	24.120	Korsmeyer's
F8	0.989	10.672	0.879	0.942	42.352	0.996	0.873	13.787	Korsmeyer's
F9	0.995	9.219	0.853	0.936	39.007	0.993	0.913	11.073	Zero order

Table 7: Plasma drug concentration studies of F6 formulation and Marketed Tablet

S. No.	Time (hr.)	Plasma concentration (µm/ml)	
		Ibuprofen(Marketed Tablet)	Optimized formulation(F6) S.R. matrix tablet
1	**0**	0	0
2	**0.5**	3.46±0.30	2.85±0.10
3	**1**	9.48±0.56	7.91±0.29
4	**1.5**	33.57±0.76	12.60±0.25
5	**2**	26.90±1.69	22.87±1.63
6	**3**	22.14±0.87	20.08±0.57
7	**4**	16.70±1.21	17.43±0.98
8	**5**	13.00±0.27	14.82±1.06
9	**6**	6.32±0.59	12.51±0.70
10	**8**	3.37±0.28	10.65±0.46
11	**10**	2.28±0.27	9.12±0.88
12	**12**	0.92±0.12	4.91±1.39

Table 8: Pharmacokinetic Parameter of F6 With Market Preparation

Parameters	Marketed Tablet	S.R. Hydrophilic Matrix Tablet (F18)
C_{max} (µg/ml)	33.57	22.87
T_{max} (hr.)	1.5	2.0
$t_{1/2}$	2.03	4.98
$AUC_{(0-6)}$	98.43	87.42
$AUC_{(0-12)}$	116.98	144.37
$AUC_{(0-inf)}$	119.69	179.60
$AUMC_{(0-inf)}$	477.30	1452.40
$MRT_{(0-inf)}$	3.99	8.09
$Fr_{(0-6)}$	---	88.39 %
$Fr_{(0-12)}$	---	124.14 %

Stability Studies [21]

The stability of this optimized formulation F6 was known by performing stability studies for

60 days at short term stability study of 25^0C±75% RH and 45^0C±75% RH on optimized formulation (climate zone IV condition for accelerated testing). The formulation was found to be stable, within significant change in the hardness, disintegration time, and in vitro drug release pattern.

Stability study at 25 °C

- At room temperature 25 °C the stability of Sustained release hydrophilic matrix tablet formulation (F6) evaluated for hardness of tablet was 8.33±0.29 at 0 day but end of the month it was 7.90±0.16 and 7.53±0.12was at the end of 2nd month.
- The friability of formulation (F6) was evaluated 0.48±0.08 at 0 day and it was recorded 0.68±0.11 at the end of month while the friability of formulation was 0.77±0.17 at the end of 2nd month.
- The % drug content of the formulation was noted 100.37±1.05 at 0 day and it was 99.37±1.53 at the end of month while the % drug content of formulation was 98.75±1.00 at the end of 2nd month.
- The % drug release of the formulation was 98.87% at 0 day and it was 97.09% at the end of month while it was 96.80% at the end of 2nd month.
- The % drug content of the formulation was noted 100.37±1.05 at 0 day and it was 99.45±1.70 at the end of month while the % drug content of formulation was 99.14±1.47 at the end of 2nd month.
- The % drug release of the formulation was 98.87% at 0 day and it was 97.68% at the end of month while it was 97.10% at the end of 2nd month.

Stability study at 45°C

- At 45oC the stability of Sustained release hydrophilic matrix tablet formulation (F6) evaluated for hardness of tablet was 8.33±0.29 at 0 day but end of the month it was 7.40±0.16 and 7.07±0.29was at the end of 2nd month.
- The friability of formulation (F6) was evaluated 0.48±0.08 at 0 day and it was recorded 0.72±0.07 at the end of month while the friability of formulation was 0.82±0.07 at the end of 2nd month.

Table 9: stability studies of formulation F6 at 25°C

Properties	Time (days)			
	0	**15**	**30**	**60**
Hardness (kg/cm^2)	8.33±0.29	7.93±0.31	7.90±0.16	7.53±0.12
% friability	0.48±0.08	0.59±0.10	0.68±0.11	0.77±0.17
% Drug content	100.37±1.05	99.98±1.79	99.45±1.70	99.14±1.47
% In-vitro drug release (after 12hr)	98.87	97.98	97.68	97.10

Table 10: stability studies of formulation F6 at 45oC

Properties	Time (days)			
	0	**15**	**30**	**60**
Hardness (kg/cm^2)	8.33±0.29	7.970.12	7.40±0.16	7.07±0.29
% friability	0.48±0.08	0.57±0.03	0.72±0.07	0.82±0.07
Drug content	100.37±1.05	99.68±1.00	99.37±1.53	98.75±1.00
% In-vitro drug release (after 12 hrs.)	98.87	97.68	97.09	96.80

CONCLUSION

The tablets with Methocel K100M with Polyox resulted in more uniform sustained drug release matrices than Methocel K4M with Polyox and Metolose with Polyox control the drug release process and the smallest average size of the particles. Methocel K100M with Polyox matrices had marked sustained effect on the release of Ibuprofen than Methocel K4M with Polyox and Metolose with Polyox control matrices. The Methocel K100M with Polyox formulation was found to provide the required release rate, with zero-order release kinetics, it cost effective and more similar to reference standard. There was no chemical interaction between drug and polymer has been confirmed by FTIR studies. The predominant release mechanism varied with matrices composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in Methocel K100M with Polyox tablets.

ACKNOWLEDGEMENT

The authors acknowledge the financial support received from my parents. S.S. Pharmaceuticals Pvt. India, Colorcon Asia Pvt. Ltd India.Mr. Girish C. Soni (Guide), Dr. S.K. Prajapati (Co-Guide), and institute of Pharmacy Bundelkhand University Jhansi for their support and encouragement to carry out this work.

REFERENCES

1. Bogdan TIȚA, Adriana FULIAȘ, Geza BANDUR, Gerlinde RUSU and Dumitru TIȚA, Thermal Stability Of Ibuprofen. Kinetic Study Under Non-Isothermal Conditions Academia Romana Rev. Roum. Chim., 2010, 55(9), 553-558.

2. Reynolds JEF, Martindale; The Extra Pharmacopoeia; Thirty–First edition; Royal Pharmaceutical Society, London, 1996: 50.

3. Jacob LS, The National Medical Series for Independent Study Pharmacology. 4th edition; chapter 9, Lippincott Williems & Willins, 1996: 203-204.

4. Ritschel WA, Kearns GL, Handbook of basic pharmacokinetics, 5th edition. 1999: 491.

5. Lordi NG, Sustained release dosage form. In: The Theory and Practice of Industrial Pharmacy, 3rd Ed., Lea & Febiger, Philadelphia, USA, 1986, pp. 430-456.

6. Colorcon Methocel Literature, Oral Modified Release System, http://www.colorcon.com/pharma/mod_rel/methocel/index.html, 2005.

7. Sung KC, Nixon PR, Skoug JW, RoburtJu T, Gao P, Topp EM, Patel MV, Effects of formulation variables on drug and polymer release from HPMC based matrix tablets. Int. J. Pharm., 1996, 142: 53-60.

8. Apicella A, Cappello B, Del Nobile MA, La Rotonda MI, Mensitieri G, Nicolais L, Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials, 1993, 14:83–90.

9. Zhang F, McGinity JW, Properties of sustained-release tablets prepared by hot-melt extrusion. Pharm. Dev. Technol., 1999, 4, 241–250.

10. Razaghi AM, Schwartz JB, Investigation of cyclobenzaprinehydrochloride release from oral osmotic delivery systems containing a water-swellable polymer. Drug Dev. Ind. Pharm., 2002, 28, 631–639.

11. Choi SU, Lee J, Choi YW, Development of a directly compressible poly (ethylene oxide) matrix for the sustained release of dihydrocodeinebitartrate. Drug Dev. Ind. Pharm., 2003, 29, 1045–1052.

12. Colombo P, Bettini R, Santi P, Peppas NA, Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharm. Sci. Technol. Today, 2000, 3, 198–204.

13. Colombo P, Bettini R, Massimo G, Catellani PL, Santi P, Peppas NA, Drug diffusion front movement is important in drug release control

from swellable matrix tablets. J. Pharm. Sci., 1995, 84, 993–997.

14. Bussemer T, Peppas NA, Bodmeier R, Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system. Eur. J. Pharm. Biopharm., 2006, 56, 261–270.
15. http://www.signetchem.com/Signet-The-Complete-Excipients-Company-Product-METOLOSE.
16. Allen LV, Luner PE. In: Raymond CR, Paul JS, Paul JW, ed. Handbook of pharmaceutical excipients. The pharmaceutical press and the american pharmaceutical association. 2003, 354-357.
17. Jain S, Yadav SK, Patil UK, Preparation and evaluation of sustained release matrix tablet of furosemide using natural gum .Research J Pharm. and tech., 2008, 1(4), 374-376.
18. Malviya R, Srivastava P, Bansal M, Sharma PK, Preparation and Evaluation of Disintegrating Properties of Cucurbita Maxima Pulp Powder. International journal of pharmaceutical sciences. (accepted manuscript IJPS-09-119) 2010.
19. Raghvendra Rao NG, Gandhi Sager, Patel Tarun, Formulation and Evaluation of Sustained Release Matrix Tablets of Tramadol hydrochloride. International Journal of Pharmacy and Pharmacutical Sciences, 2009, 1(1), 60-70.
20. Indian pharmacopoeia (IP). Published by the controller of publications, delhi. 2007, 2, 599-600.
21. Singh M, Prajapati SK, Kumar V, Ali AM, Formulation Design and Evaluation of Mouth Dissolving Tablets Omeprazole Magnesium by Using Superdisintegrants International Journal for Pharmaceutical Research Scholars (IJPRS) 1(3), 2012.
22. Selvadurai Muralidharan, Subramania Nainar Meyyanathan, Kaliaperumal Krishnaraj, Sekar Rajan, Development of oral Sustained release dosage form for low melting chiral compound Dexibuprofen and it's in vitro-in vivo evaluation, International Journal of Drug Delivery, 2011, 3, 492-502.
23. Prajapati SK, Richhaiya R, Singh VK Singh AK, Kumar S, ChaudharyRKformulation and evaluation of once daily sustained release matrix tablet of aceclofenac using natural gums, Journal of drug delivery & therapeutics; 2012,
24. Amir Badshah, Fazalsubhan and khalidrouf "Controlled release matrix tablet of olanzapine: influence of polymers on the invitro release and Bioavailability." AASP PharmSciTEch, II (3), Sep 2010.

