Invest Clin 54(4): 347 - 359, 2013

Design and evaluation of a gastroretentive drug delivery system for metformin HCl using synthetic and semi-synthetic polymers.

Venkata Srikanth Meka[1,2], Adinarayana Gorajana[1], Senthil Rajan Dharmanlingam[1], Venkata Ramana Murthy Kolapalli[2]

[1]School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia-57000.
[2]A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, India

Keywords: gastroretentive, floating, carboxymethyl ethyl cellulose, *in vitro* dissolution, polyethylene oxide, metformin HCl.

Abstract. The aim of the present research was to prepare and evaluate a gastroretentive drug delivery system for metformin HCl, using synthetic and semi-synthetic polymers. The floating approach was applied for preparing gastroretentive tablets (GRT) and these tablets were manufactured by the direct compression method. The drug delivery system comprises of synthetic and semi-synthetic polymers such as polyethylene oxide and Carboxymethyl ethyl cellulose (CMEC) as release-retarding polymers. GRT were evaluated for physico-chemical properties like weight variation, hardness, assay friability, *in vitro* floating behaviour, swelling studies, *in vitro* dissolution studies and rate order kinetics. Based upon the drug release and floating properties, two formulations (MP04 & MC03) were selected as optimized formulations. The optimized formulations MP04 and MC03 followed zero order rate kinetics, with non-Fickian diffusion and first order rate kinetics with erosion mechanism, respectively. The optimized formulation was characterised with FTIR studies and it was observed that there was no interaction between the drug and polymers.

Corresponding author: Venkata Srikanth Meka, School of Pharmacy International Medical University (IMU), Bukit Jalil, Kuala Lumpur 57000, Malaysia. (E-mail address: venkatasrikanth@imu.edu.my).Tel:+60327317276.

Diseño y evaluación de un sistema gastro-retentivo de administración de metformina HCl, utilizando polímeros sintéticos y semisintéticos.

Invest Clin 2013; 54 (4): 347 - 359

Palabras clave: gastro-retentivo, flotación, carboximetil etil celulosa, *in vitro* disolucion, óxido de polietileno, metformina HCl.

Resumen. El objetivo del presente trabajo consistió en preparar y evaluar un sistema de administración gastro-retentivo de metformina HCl, utilizando polímeros sintéticos y semisintéticos. Se aplicó el método de flotación para la elaboración de los comprimidos de retención gástrica (CRG) y éstos se prepararon mediante el método de compresión directa. El sistema de suministro del fármaco estaba constituido por polímeros sintéticos y semisintéticos, tales como el óxido de polietileno y la carboximetil etil celulosa, como agentes retardadores de la liberación del fármaco. Se evaluaron las propiedades físico-químicas de los CRG, tales como: variación de peso, dureza, friabilidad, comportamiento flotante *in vitro*, capacidad de inflación, estudios de disolución *in vitro* y su tasa de orden cinético. Se seleccionaron dos fórmulas (MP04 y MC03), sobre la base de la liberación del fármaco y las propiedades de flotabilidad, como fórmulas óptimas. Estas fórmulas MP04 y MC03 optimizadas siguieron cinéticas de velocidad de orden cero, con difusión no-Fickian y tasa cinética de primer orden con mecanismo de erosión, respectivamente. Las fórmulas óptimas se caracterizaron con estudios FTIR y se observó que no hubo interacción entre el fármaco y los polímeros.

Recibido: 06-05-2013 Aceptado: 10-10-2013

INTRODUCTION

Oral dosage forms have been developed for the past four decades due to their significant therapeutic advantages, such as ease of administration, patient compliance and flexibility in formulation (1). Nowadays, the trend is going towards the preparation of novel controlled drug delivery systems, in which the release of the active drug can be controlled for a longer period of time. However in controlled drug delivery, the drug absorption is inadequate and highly variable in individuals due to physiological variabilities, such as gastrointestinal transit, as well as gastric residence time of the dosage forms (1). Gastroretentive technology is an alternative to overcome this problem. Through this gastroretentive technology, the dosage form is able to remain in the gastric region for several hours and hence, significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves the bioavailability, reduces drug waste and improves the solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines (2).

The gastric retention of the dosage forms can be achieved by several methods such as floatation, mucoadhesion, swellable system, hydrodynamically balanced system, sedimentation, expansion modified shape

systems, etc (3). Out of these techniques, floatation is the most convenient and effective method for gastric retention. Gastroretentive floating drug delivery systems can be buoyant in the gastric medium for prolonged periods of time due to its lower bulk density, compared to the gastric medium. While the system is floating on the gastric contents, the drug will be released constantly at a desired rate from the dosage form and the gastric residence time will be enhanced. Due to the increase in the residence time of the dosage form, a greater amount of the drug can be released in the gastric region, improving its bioavailability and also providing a better control of fluctuations of the drug in the plasma (4).

In the present investigation metformin HCl was selected as a model drug for the development of gastroretentive drug delivery systems. Metformin HCl is a biguanide antihyperglycemic agent used in the management of non-insulin dependent diabetes mellitus (type II diabetes) (5). Metformin, in pharmacological doses, does not reduce basal blood glucose concentrations below the physiological range, in either diabetic or non-diabetic animals or humans. Hence, it is considered as an antihyperglycemic agent rather than a hypoglycemic agent. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin is slowly and incompletely absorbed from the GIT after oral administration. The absolute bioavailability of a 500 mg tablet given under fasting conditions is approximately 50-60%. Due to its incomplete absorption in GIT, it has been selected as a drug candidate for developing a gastro retentive dosage form (6).

There has been little research exposure on carboxymethyl ethyl cellulose (CMEC), which is a novel semi-synthetic polymer, used in the present investigation. In the industry, it can be used as an enteric coating polymer. Polyethylene oxide (PEO) is a hydrophilic synthetic polymer, available in different grades. In the present research, PEO WSR Coagulant and CMEC were used as retarding polymers. Calcium carbonate was used in the delivery system as an effervescent agent.

MATERIALS AND METHODS

Materials

MetforminHCl was provided by Unichem Laboratories Ltd (Goa, India). PEO, Carboxymethyl ethyl cellulose, calcium bicarbonate and magnesium stearate were obtained as gift samples from Hetero drugs Ltd (Hyderabad, India). All other reagents and chemicals were of analytical grade.

Preparation of GRT of metformin HCl

Gastroretentive tablets were prepared by the direct compression method. All the ingredients were weighed accurately as mentioned in Table I, sifted through a 40# mesh screen. Metformin HCl was geometrically mixed with release retarding polymers followed by the addition of an effervescent agent. Dry mixing was done for 5 min in a polybag. The blend was lubricated with presifted magnesium stearate (sieve # 60) for 3 min. Pre-formulation parameters were evaluated for the blends and then compression was carried out by a 16-station rotary tablet punching machine (M/s. Cadmach Machinery Co. Pvt., Ltd., India), using 19 × 11.1 mm caplet shaped plain punches at the hardness of 4-6 Kg/cm^2. The formulated tablets were stored in an air tight container at room temperature for further evaluation of the tablet parameters. Calcium carbonate was fixed to 10% w/w to the total tablet weight in all the formulations.

TABLE I
FORMULA OF METFORMIN HCL GASTRORETENTIVE FLOATING TABLETS

Ingredients	MP 01	MP 02	MP 03	MP 04	MP 05	MC 01	MC 02	MC 03	MC 04	MC 05
Metformin HCl	500	500	500	500	500	500	500	500	500	500
PEO	125	250	375	500	625	-	-	-	-	-
CMEC	-	-	-	-	-	125	250	375	500	625
Calcium bicarbonate	73	87	100	115	128	73	87	100	115	128
Magnesium stearate	7	8	10	10	12	7	8	10	10	12
Tablet weight (mg)	705	845	985	1125	1265	705	845	985	1125	1265

Determination of flow properties of the lubricated blend

Angle of repose method. The angle of repose was determined by the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The gum powder was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius of the base (r) of the pile was determined and the tangent angle of the repose (θ) was calculated by the following equation (7).

$$\tan \theta = h/r$$

Determination of the compressibility index and the Hausner ratio

The compressibility index (C.I) and the Hausner's ratio of the lubricated blend was determined by measuring the Bulk density (BD) and Tapped density (TD) of a powder.

The BD was determined by the three tap method. An amount of powder equivalent to 10 g was accurately weighed, placed in a 100 mL measuring cylinder without compaction and the volume occupied was measured and the initial bulk density was calculated by the following equation (8).

$$\text{Bulk density} = \frac{\text{mass of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density (TD) of a powder is the ratio of the mass of the powder to the volume occupied by the powder after a fixed number of taps. The tapped density of the powder represents its random dense packing (8).

An amount of powder equivalent to 10 g was accurately weighed, transferred into a 100 mL measuring cylinder and placed on to the tapped density tester (model C-TDA2, Campbell Electronics, Mumbai, India) and subjected to USP-II method i.e., 250 drops per minute with a drop height of 3 mm ± 10%. The volume of the powder blend was measured after each increment of 250 drops until the difference between succeeding measurements is less than 2%. The final volume was recorded and the tapped density was calculated by the following equation.

$$\text{Tapped density} = \frac{\text{mass of the powder}}{\text{Tapped volume of the powder}}$$

Hausner's ratio was determined by dividing the tapped density (TD) with bulk density (BD), and the Carr's compressibility index (CI) was determined using following equation (8):

$$\text{CI}(\%) = \left(\frac{\text{TD} - \text{BD}}{\text{TD}}\right) \times 100$$

Evaluation of the tablets

The floating tablets were evaluated for physicochemical parameters like weight

variation, hardness, friability assay, buoyancy characteristics, swelling studies, *in vitro* dissolution studies and release mechanism studies.

Weight variation

Twenty tablets were selected at random and weighed individually for the determination of weight variation of tablets. The mean and standard deviation were determined (9).

Hardness test

Five tablets were selected at random and the hardness of each tablet was measured on a Monsanto hardness tester.

Friability test

The friability test was carried out in a Roche Friabilator (8). Twenty tablets were weighed (X_o) initially and put in a rotating drum. They were subjected to 100 falls from a 6-inches height (25 rpm for four minutes). After complete rotations the tablets were dedusted by using a camel hairbrush and weighed (X). The percent loss in weight or friability (f) was calculated by the formula given in the following equation:

$$f = \left(1 - \frac{X}{X_0}\right) \times 100$$

Assay

From each batch, 10 tablets were randomly collected and powdered in a glass mortar. 50 mg of the accurately weighed powder were transferred into a 100 mL volumetric flask. The drug was extracted with 25 mL of 0.1 N HCl with vigorous shaking on a mechanical shaker for 1hr and filtered into a 50 mL volumetric flask through 0.45 μm Millipore nylon filter disc and the filtrate was made up to the mark with 0.1N HCl. Further appropriate dilutions were made and the absorbance was measured at 232 nm against blank (0.1 N HCl).

Floating characteristics

All the formulated GRT were subjected to *in vitro* floating studies and for each batch, 5 tablets were used. The floating lag time (FLT) was determined in 1 liter glass beaker containing 900 mL of 0.1N HCl maintained at 37 ± 0.5°C. The time required by the dosage form to emerge on to the surface of the dissolution medium after placing it into the dissolution medium was determined as FLT. The duration of time for which the dosage form constantly remained floating on the surface of medium was determined as the total floating time (TFT) (10).

Swelling studies

The swelling ability of the GRT was determined in 900 mL of acidic medium (0.1N HCl) at room temperature. A weighed tablet was immersed in the medium and it was removed periodically from the medium. After draining the free water, the tablets were measured for weight gain. The swelling index (% SI) was expressed by the equation shown below (11).

***In vitro* dissolution studies**

The release profile of metformin HCl from floating tablets was determined by using a Dissolution Tester USP XXIII (LABINDIA, Disso 200). The dissolution test was performed using 900 mL 0.1N HCl solution at 37 ± 0.5°C and the paddles were rotated at 50 rpm. At appropriate time intervals, a 5 mL aliquot was with-

$$\%SI = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

drawn from the dissolution medium and it was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to suitable concentrations with 0.1 N HCl. The absorbances of the solutions were measured at 232 nm for the estimation of metformin HCl content with a UV-Visible double beam spectrophotometer (Elico SL210, India). Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The dissolution experiments were done in triplicate.

Release kinetics

Mathematical models such as zero-order, first-order, Higuchi, Hixon-Crowell (erosion) and Korsemeyer-Peppas were applied to observe the release profile data, to analyze the rate mechanism and the pattern of the drug release (12-16). The order of drug release from the matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi's or erosion equations.

The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations.

Zero order model:
$Q_t = Q_0 + K_0 t$

First order model:
$\log C = \log C_0 - K_1 t / 2.303$

Higuchi model:
$Q_t = k_2 t^{1/2}$

Hixson-Crowell cube root model:
$(W_0^{1/2} - W_t^{1/2}) = Kt$

Korsemeyer-Peppas model:
$Q_t / Q_\infty = k_p . t^{n}$

where, Q_t is the amount of drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$), C_0 is the initial concentration of drug, W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t, Q_∞ is the amount of drug dissolved in time ∞. K_0, K_1, K_2, K_h and K_p refer to the kinetic constants obtained from the linear curves of zero-order, first order, Higuchi model, Hixson-Crowell cube root law and Korsemeyer–Peppas, respectively.

Optimization

Formulations were optimized based on the 12 h drug retarding property, minimal polymer quantity and good floating properties. Optimized formulation was further characterized with Fourier transformation-infrared spectroscopy (FTIR) for drug-polymer interaction studies.

Statistical analysis

All data obtained were subjected to the Student's t-test ($p < 0.05$) for significance of difference.

Fourier transform-infrared spectroscopy (FTIR)

FTIR was used to identify the drug excipient interaction. FTIR studies were performed on drug, polymer and optimized formulation. Samples were analyzed by the potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500 cm^{-1}.

RESULTS AND DISCUSSION

Pre-compression studies

Flow characteristics of the material being compressed are important parameters and hence, studies were undertaken for the evaluation of flow characteristics of the lubricated blend. The results of flow properties of the prepared lubricated blends are shown in Table II. The angle of repose values were within the range of 25-30° and

TABLE II
FLOW PROPERTIES OF LUBRICATED BLEND

Formulation	Angle of repose (°)	Compressibility Index (%)	Hausner ratio
MP01	29.45	8.4	1.17
MP02	29.28	10.1	1.14
MP03	28.94	11.01	1.13
MP04	26.72	12.89	1.12
MP05	25.54	13.25	1.12
MC01	29.97	13.9	1.18
MC02	29.65	13.7	1.17
MC03	28.65	11.5	1.17
MC04	27.84	10.2	1.45
MC05	26.45	9.5	1.13

26-30° for PEO and CMEC based formulations respectively, which indicated excellent flow properties as per the U.S Pharmacopeia (USP) powder flow properties. (As per USP, If Angle of repose values 25-30: Excellent, 31-35: Good and 36-40: Fair) (17). The compressibility index and Hausner's ratio of all the formulations were in the range of 8-14 and 1.12 to 1.18 respectively, indicating that flow properties of the blends were good as per USP. CMEC and PEO were free flowing materials, which made the tablet mixture an excellent flow. Hence, the author compressed the tablets by the direct compression method instead of granulation methods.

Srikanth *et al.* had formulated the floating drug delivery system of ofloxacin with gum karaya. The floating tablets were evaluated for buoyancy studies in 0.1 N HCl. The floating lag times of all the formulations were within the range of 2-4 min (18).

Tableting properties

The results of the weight uniformity, hardness, friability, as well as drug content, are presented in Table III. All the formulations of metformin HCl prepared by using the selected polymers such as PEO and CMEC complied with compendia standard for uniformity of weight. As a measure of mechanical strength, these formulations exhibited satisfactory hardness of 4 to 6 kg/cm^2 and the same fact was further supported by friability of less than 1%. The assay of the drug in all the formulations was found to be>99%. Thus, all the formulations were found to be of good quality, fulfilling all the official requirements.

***In vitro* floating studies**

All the formulations were evaluated for *in vitro* buoyancy properties and results are mentioned in Table III. Floating lag time of PEO and CMEC based formulations were found to be in the range of 3-7 min and 7-12 min respectively. From the results, it was observed that PEO based formulations exhibited faster buoyancy properties than CMEC formulations, because of its hydrophilic nature. CMEC is a hydrophobic enteric coated polymer and it did not allow opening the pores/channels so easily on the surface of the tablet. So that it took some time for the penetration of gastric medium

TABLE III
TABLETING CHARACTERISTICS OF METFORMIN HCL TABLETS

Formulation	Weight[x] (mg)	Assay[y] (%)	Hardness* (Kg/cm²)	Friability** (%)	FLT* (min)	TFT* (h)
			PEO			
MP01	703±1. 21	99.12±1.5	4-6	0.21	6±0.5	6±0.6
MP02	846±1.45	98.99±1.4	4-6	0.34	5±0.9	8±0.4
MP03	985±1.38	99.92±1.7	4-6	0.36	4±0.1	10±0.4
MP04	1124±1.14	99.02±0.84	4-6	0.41	4±0.4	12±0.8
MP05	1265±1.49	100.55±1.44	4-6	0.42	3±0.3	14±0.6
			CMEC			
MC01	704±1.65	99.78±1.73	4-6	0.15	7±0.8	7±0.8
MC02	845±1.38	99.45±1.41	4-6	0.19	8±0.1	9±0.7
MC03	986±1.91	99.12±1.34	4-6	0.20	9±0.4	10±0.2
MC04	1125±1.43	99.45±1.24	4-6	0.24	10±0.4	12±0.1
MC05	1266±1.67	100.01±1.11	4-6	0.29	11±0.1	13±0.1

x: mean ± s.d. (n=20); y: mean ± s.d. (n=10); * n=5; ** n= 20 FLT: floating lag time; TFT: total floating time

into the tablet. Hence, the floating lag time was delayed in CMEC formulations. By comparing the PEO and CMEC based formulation buoyancy properties, it was observed the floating lag time decreased with increased concentrations of PEO and vice versa, in the case of CMEC formulations. Total floating times of same based formulations were in the range of 6-14 h and 8-16 h respectively. All the formulations exhibited excellent floating properties. From the buoyancy properties, it was observed that calcium bicarbonate is essential for the floating, which liberates carbon dioxide in the form of effervescence, when it contact with the acidic medium. When the gas is expelled out from the dosage form, the density of the tablet will fall below 1 g/mL, and the tablet becomes buoyant (19).

Swelling studies

The swelling studies of the GRT were conducted for 14 h. Swelling index of the PEO and CMEC based formulations exhibited a range of 75-99% and 25-35%, respectively. From the results, it was observed that CMEC had a less swelling property when compared to PEO. As the concentration of the polymer increases, the swelling index was increased and the results are shown in Fig. 1.

***In vitro* dissolution studies**

In-vitro dissolution data showed that, the increment of the polymer concentration of PEO or CMEC progressively retarded the drug (Figs. 2 and 3). The lowest PEO concentration (MP01) showed 100% drug release in 6 hrs, whereas the highest polymer concentration (MP05) in 14 h. When the concentration of the hydrophilic synthetic polymer, i.e PEO, was increased, the time taken for its swelling in the media was increased due to high viscous gel strength. The pore distribution became less on the effective surface area of the tablet which is exposed to the dissolution media. Therefore, the diffusion of the drug from the

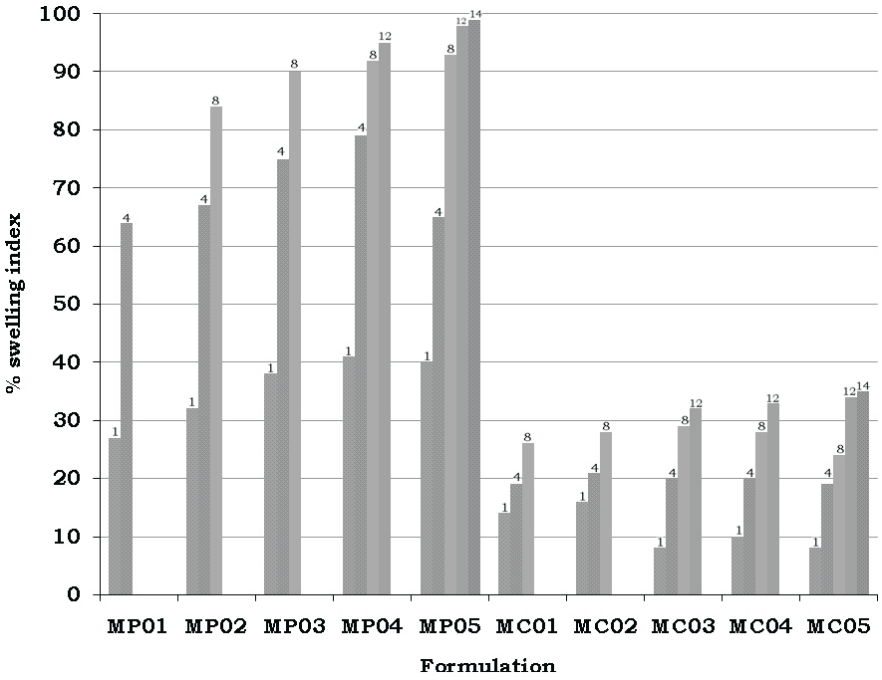

Fig. 1. Swelling index of metformin HCl GRT at different time intervals. Numbers above the bars represent time (in hours) of swelling.

matrix was retarded to its maximum and the drug release was slowed down (20, 21). Another semi-synthetic polymer, CMEC was used for the gastric retention of the active drug. As the concentration of CMEC increased, the drug retardation was also increased. The formulations MC01, 02, 03, 04 and 05 showed maximum drug release at 8, 10, 12, 13 and 14 h respectively. The formulation MC03 showed more excellent buoyancy and drug retarding properties than all other formulations. Even though CMEC had less swelling behavior, it had good retardation properties. The order of the drug retarding capacity of the polymer and their drug-polymer ratio among the two polymers was as follows: CMEC (1:0.75) > PEO (1:1).

From the results of the dissolution profiles between the different formulations, it is clear that the dissolution profiles of batch MP01 to MC05 were quite different from those of the other batches. A statistical analysis by two-way ANOVA was conducted for batches MP01 to MC05 (% drug release was the dependent variable and time was the repeated factor). Results showed that, there is a significant difference between the batches.

Ashok A *et al.* (22).had prepared the metformin HCl floating drug delivery system by incorporating natural polymers guar gum and k-carrageen and a synthetic polymer HPMC K100 (HPMC), either alone or in combination. Sodium bicarbonate and citric acid was used as a gas generating agent. Formulation prepared with combination of 6% w/w k-carrageen and 11%w/w guar gum showed good gel strength, stable and persistent buoyancy for 12 h, least floating lag time of 58 sec, with good matrix integrity throughout dissolution period. At the drug: polymer ratio of 1:0.2 retarded the drug for 12 h.

Based upon the buoyancy and dissolution properties of the prepared floating tablets, it was confirmed that the present metformin floating drug delivery systems can be buoyant in the gastric medium for

prolonged periods of time. The metformin can be released constantly at a desired rate from the dosage form, while the system is floating on the gastric contents. Due to increase in the residence time of the dosage form in GIT, more amount of the drug can be released in the gastric region, so that it may improve the bioavailability of the drug and also allows for a better control of fluctuations in the plasma drug concentrations.

Release kinetics

The dissolution profiles of metformin HCl floating tablets were fitted to various kinetic models, their rate order kinetics and correlation coefficient values are mentioned in Table IV. From the results, it was observed that, all the formulations made with PEO followed zero order kinetics with higher regression values (r) and exhibited non-Fickian mechanism. Whereas CMEC based formulations followed first order kinetics with higher regression values and exhibited erosion mechanism (Table IV). From the results, it can be concluded that, the PEO polymer will retard the drug by diffusion mechanism, whereas CMEC controlled the drug release by erosion mechanism.

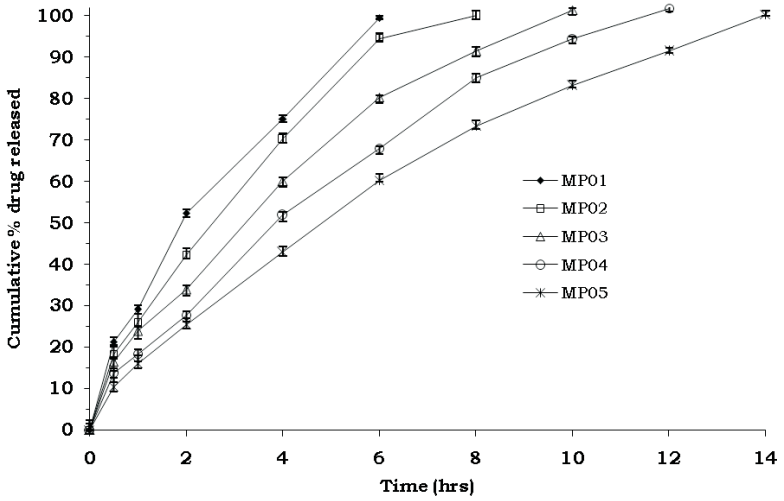

Fig. 2. Dissolution profile of metformin HCl GRT prepared by PEO.

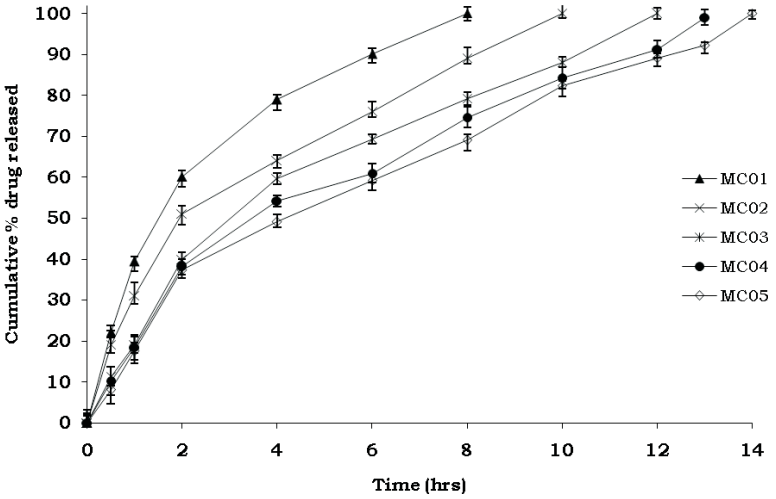

Fig. 3. Dissolution profile of metformin HCl GRT prepared by CMEC.

TABLE IV
RATE ORDER KINETICS AND RELEASE MECHANISM

Formulation	Zero order		First order		Higuchi	Hixson-Crowell	Peppas	
	K_0	r	K_1	r	r	r	n	r
MP01	24.285	0.9987	1.0690	0.9453	0.9920	0.9751	0.8798	0.9997
MP02	12.522	0.9765	0.4468	0.9669	0.9945	0.9932	0.6756	0.9962
MP03	9.8999	0.9899	0.2948	0.9897	0.9983	0.9980	0.6578	0.9959
MP04	8.48	0.9839	0.2667	0.9766	0.9972	0.9953	0.7198	0.9969
MP05	7.0701	0.9857	0.1911	0.9848	0.9997	0.9988	0.7059	0.9987
MC01	21.655	0.9456	0.4762	0.9987	0.9825	0.9921	0.4891	0.9987
MC02	11.358	0.9322	0.3761	0.9977	0.9865	0.9927	0.4387	0.9916
MC03	8.9839	0.9546	0.2536	0.9903	0.9876	0.9965	0.4798	0.9917
MC04	7.6518	0.9587	0.2001	0.9947	0.9535	0.9939	0.5267	0.9896
MC05	6.6999	0.9742	0.1713	0.9892	0.9934	0.9948	0.5835	0.9906

Optimization

Based on the low polymer concentration, good buoyancy properties and drug retardation property up to 12 h, the formulations MP04 and MC03 were selected as optimized formulations.

Fourier transformation-infrared spectroscopy (FTIR)

The FTIR spectrum of metformin HCl, PEO, CMEC, MP04 and MC03 was shown in the Fig. 4**.** The drug metformin HCl showed characteristic primary amine group stretch at 3370 cm^{-1} and 3294 cm^{-1}, secondary amine group stretch at 3173 cm^{-1} and C-N stretch at 1625 cm^{-1} and 1567 cm^{-1}(Fig 4)**.** The FTIR spectrum of PEO showed the characteristic alcoholic–OH stretch at 3436 cm^{-1}, -C-O-C asymmetric stretch at 1257 cm^{-1} and -C-O-C symmetric stretch at 1042 cm^{-1}. The FTIR spectrum of CMEC showed the characteristic alcoholic-OH stretch at 3476 cm^{-1}, C-H stretch at 2976 cm^{-1}, -C=O stretch at 1761 cm^{-1} and -C-O-C asymmetric stretch at 1378 cm^{-1}.

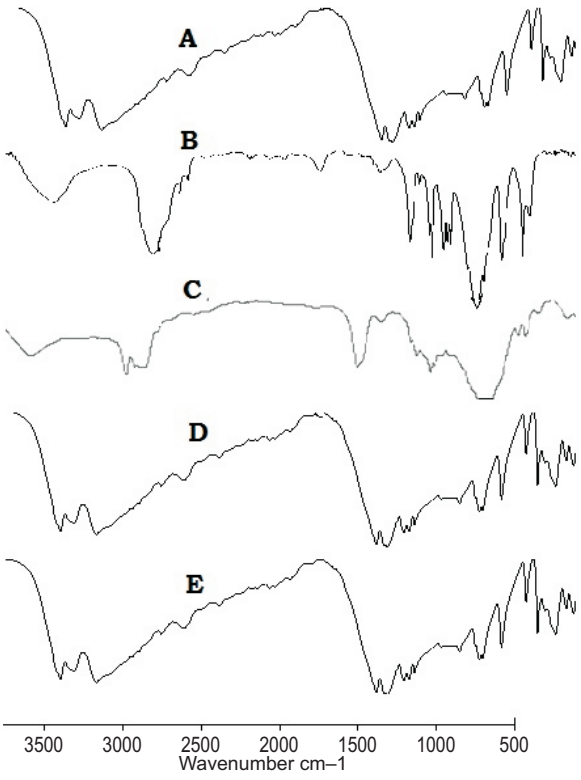

Fig. 4. FTIR spectra of (A) metformin HCl (B) PEO (C) CMEC D) MP04 (E) MC03.

Optimized formulations MP04 and MC03 showed all the characteristic peaks of metformin HCl with minor shifts in its FTIR spectrum indicated that there was no interaction between the polymer and drug.

As a conclusion, metformin HCl, available as conventional and controlled release tablets in the market, can be successfully formulated as gastroretentive floating tablets which has the advantage to retain the dosage form in the effective site of absorption for long period of time and release the drug in a sustained manner, ultimately achieving the desired steady state concentration level and increased bioavailability of the drug. The present investigation successfully proves that metformin HCl can be designed as gastroretentive dosage form with desired qualities, using a synthetic polymer (PEO), semi-synthetic polymer (CMEC) and calcium carbonate as an effervescent agent.

ACKNOWLEDGEMENT

The author M.V.Srikanth is thankful to Unichem Laboratories, Goa for providing the gift samples and to M Chaitanya Krishna and Sudhakar for providing valuable information to carry out the research work.

REFERENCES

1. **Srikanth M V, Janaki Ram B, Sunil SA, Sreenivasa Rao N, Ramanamurthy KV.** Gastroretentive drug delivery systems: Novel approaches and its evaluation- A review. Int J Pharm Rev Res 2011; 10(1): 203-216.
2. **Aleksovskia A.** Floating gastro-retentive dosage forms – a novel approach for targeted and controlled drug delivery. Human 2012; 2(1): 23-30.
3. **Bardronnet P, Faivre V, Pugh WJ, Piffaretti JC, Falson F.** Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*. J Cont Rel 2006; 111: 1-18.
4. **Pooja M, Kamal S, Navneet S, Surender V,Vipin K.** Floating drug delivery system: an innovative acceptable approach in gastro retentive drug delivery. Arch Appl Sci Res 2010; 2:257-270.
5. **Takeda Pharmaceuticals America.** Actoplus Met (pioglitazone hydrochloride and metformin hydrochloride) tablets prescribing information. Lincolnshire, IL; 2011 Jul.
6. **Raju DB, Sreenivas R, Varma MM.** Formulation and evaluation of floating drug delivery system of metformin hydrochloride. J Chem Pharm Res 2010; 2(2): 274-278.
7. **Srikanth MV, Uhumwangho MU, Sunil SA, Sreenivasa Rao N, Ravi Kiran CH, Ramanamurthy KV.** Design and evaluation of taste masked drotaverine HCl orodispersible tablets using polymethacrylate polymers. Der Pharmacia Lettre 2010; 2(6): 223-231.
8. **Carr RL.** Evaluation of flow properties of solid. Chem Eng 1965; 72: 163-168.
9. **Indian Pharmacopoeia**. Govt. Of India, Ministry of Health and Family Welfare, the Indian Pharmacopoeia Commission, Ghaziabad, India, Vol. I, 2007; 183.
10. **Srikanth MV, Uhumwangho MU, Rao NS, Sunil SA, Ram BJ, Ramanamurthy KV.** Formulation and evaluation of gastro retentive floating drug delivery system for propranolol HCl. J Pharm Allied Sci 2011; 8(2):1339-1348.
11. **Debajyoti R, Prusty AK.** Designing and in vitro studies of gastric floating tablets of tramadol hydrochloride. Int J Appl Pharm 2010; (4): 12-16.
12. **Srikanth MV, Sunil SA, Rao NS, Ram BJ, Kukati L, Ramanamurthy KV.** Thermal sintering: a novel technique in the design of gastroretentive floating tablets of propranolol HCl and its evaluation. Invest Clin 2012; 53(3): 223-236.
13. **Anjali Devi N, Venkateswarlu V.** Design and characterization of floating controlled release tablets of imatinibmesylate for site specific drug delivery. Int Res J Pharm 2012; 3(9): 185-193.
14. **Higuchi T.** Mechanism of sustained action medication: Theoretical analysis of rate re-

lease of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52:1145- 1149.
15. **Korsmeyer R, Gurny R, Peppas N.** Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15:25-35.
16. **Wamorkar V, Manjunath S, Yallagatti M**. Gastro-retentive formulation of metoclopramide: design and optimization using d-optimal design technique. J App Pharm 2012; 1(04): 465-479.
17. **US Pharmacopeia** (USP 29). United States pharmacopoeial convention. Philadelphia, PA: Inc. National Publishing; Chapter. Powder flow. 1174, 2005.
18. **Srikanth MV, Rao NS, Sunil SA, Sharma GS, Uhumwangho MU, Ramanamurthy KV.** Formulation and evaluation of gastro retentive floating drug delivery system of ofloxacin. Drug Invention Today 2011; 3(3):7-9.
19. **Srikanth MV, Rao NS, Sunil S A, Janaki Ram B, Ramanamurthy KV. A** statistical experimental approach for the development of propranolol HCl gastric floating tablets and its evaluation. Acta Pharm Sinica B 2012; 2(1): 60-69.
20. **Swarna Kamala CH, Srinivas Reddy K, Hadassah M, Hepsibha EM, Sridevi S**. Formulation and evaluation of gastroretentive floating tablets of gabapentin using effervescent technology. Int J Pharm Biomed Res 2012; 3(4): 202-208.
21. **Srikanth MV, Sunil S A, Janaki Ram B, Ramanamurthy KV.** Design and in vitro evaluation of effervescent gastric floating drug delivery systems of propranolol HCl. Invest Clin 2012; 53(1):60-70.
22. **Hajare AA, Patil VA.** Formulation and characterization of metformin hydrochloride floating tablets. Asian J Pharm Res 2012, 2(3): 111-117.