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Formulation and evaluation of sustained release gastroretentive dosage form of Metformin HCl

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ABSTRACT

Metformin HCL is an oral anti-diabetic drug and it comes under biguanide class. Plasma half–life of Metformin after intravenous administration, about 1.5 to4 h. Absorption of the metformin HCl is limited to upper part of the GI tract and therefore its bioavailability from both immediate and sustained release marketed dosage forms is 50-60%. So metformin is suitable for gastro retentive drug delivery system, which may improve bioavailability. Floating matrix tablets containing of Metformin HCL were prepared using wet granulation method using HPMC K100M, Eudragit RL 100 as polymer and Sodium Bicarbonate as gas generating agent. The prepared formulations wereevaluated for hardness, weight variation, friability and drug content,floating time and in vitro drug releasecharacteristics.Comparison between optimized and marketed formulation by similarity factor (f_2) divulged similarity in release profile between both. Release kinetic study showed that all batches followed Fickian diffusion.

Keywords: Metformin HCL, Gastro retentive drug delivery system, Extended-release dosage forms, HPMC K100M, Eudragit RL 100

INTRODUCTION

Oral route is considered to be convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process. However, this route has several physiological problems, including an unpredictable gastric emptying rate, a brief gastrointestinal transit time (8–12 h), and the existence of an absorption window in the upper small intestine for several drugs [1]. These difficulties have prompted researchers to design gastro retentive drug delivery systems [2,3].

Hydroxypropylmethylcellulose (HPMC) is hydrophilic cellulose ether widely used as a pH independent release retarding materials due to their non-toxicity, easy handling and predictable release behavior of the drug, HPMC is often used as [4,5]Methacrylic resins (Eudragit) appear particularly attractive due to their high chemical stability and high compatibility properties[6]. There are several studies reported in the literature that substantiate the use of Eudragit RL 100 polymers in the development of control release matrix tablet [7].

Metformin hydrochloride (HCL) an orally administered biguanide, which is widely used in the management of and the type -II diabetes, is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 -4.5 h [8].

An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occurs during the initially period of treatment. The compound has relatively short plasma half life of 1.5-4.5 hours and the low absolute bioavailability of 50%-60% [9].

MF is reported to be absorbed mainly in upper part of GIT. It is having narrow absorption window and high water solubility, and it would be more beneficial to retain the drug in stomach for prolonged duration so as to achieve maximum absorption and better bioavailability. (FDDS) would be retained for prolonged periods of time in stomach and release drug in a sustained manner, thus providing drug continuously to its absorption sites in a controlled manner and increases the magnitude of drug effect.

The present study was an attempt to develop floating tablets of Metformin HCL which on oral administration prolongs its gastric residence time thereby increasing bioavailability, diminishing side effects and enhanced patient compliance. Hence floating matrix tablets of metformin HCL were prepared with hydrophilic gelling polymer (HPMC), Eudragit RL 100 and an effervescent agent (potassium bicarbonate) to provide sustained release of metformin hydrochloride upto 12 hours in the gastric medium.

MATERIALS AND METHODS

Metformin HCl and Hydroxypropyl Methylcellulose (HPMC K 100M)were received as a generous gift from Vama Pharma (Nagpur, India). Microcrystalline cellulose (MCC, Avicel PH 101) and Eudragit RL100 were purchasedLoba Chemie Laboratory Chemicals Ltd (Mumbai, India). All other ingredients used were laboratory reagents and used as such without further testing.

Study of physical interaction between drug and polymer:
Fourier Transform Infrared Spectrometry (FTIR)
To investigate any possible interactions between the drug and the polymers utilized, the FTIR spectra of pure Metformin HCL and its physical mixtures (1:1) with polymer (Eudragit RL 100, HPMC K100M) were were obtained using Fourier Transform Infrared Spectrophotometer. The samples were prepared using KBr disks compressed under pressure of 10 Ton/nm^2. The samples were scanned from 4000 to 400cm-1.The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer.

Differential Scanning Calorimetry (DSC):
Thermal analysis was carried out using a differential scanning calorimeter (Mettler Toledo DSC 822). The samples were placed in an aluminium-sealed pan and preheated to 200° C. The sample was cooled to room temperature and then reheated from 40° to 450° C at a scanning rate of 10° C/min.

PREPARATION OF TABLETS BY WET GRANULATION TECHNIQUE
Floating matrix tablets containing of Metformin HCL were prepared using wet granulation method using HPMC K100M andEudragit RL 100 as polymer. All ingredients and drug were accurately weighed and individually passed through sieve no. 60, mixed and granulated with 10% solution of PVP K30 in isopropyl alcohol. The wet mass was passed through sieve no.16 and dried at 45ºC for 2hrs. Dried granules were passed through sieve no. 24, and were mixed with weighed quantity of sodium bicarbonate and lubricated with magnesium stearate. Compression force was kept constant throughout the study. Compression was carried out using 14 mm standard flat punches. Tablet weight was adjusted to 1000 mg.The composition of each formulated tablets are shown in Table 1.

TABLE 1.Composition of Various Trial Formulations for the SR tablet containing 500mg metformin HCL

F. code	Ingredients (mg.)							
	Metformin HCL	Eudragit RL100	HPMC K100M	Na.Bicarbonate	Citric Acid	PVP K30	Mg. Sterate	MCC
A1	500	-	100	40	20	100	10	230
A2	500	-	200	40	20	100	10	130
A3	500	-	300	40	20	100	10	30
B1	500	100	-	40	20	100	10	230
B2	500	200	-	40	20	100	10	130
B3	500	300	-	40	20	100	10	30
C1	500	75	225	40	20	100	10	30
C2	500	150	150	40	20	100	10	30
C3	500	225	75	40	20	100	10	30

EVALUATION OF TABLETS:
Pre Compression evaluation:
The granules were evaluated for angle of repose, loose bulk density; tapped bulk density, Compressibility index and Hausner's index [10-12].

Post Compression evaluation:
The prepared tablets were characterized immediately for hardness, weight variation, friability and drug content [13, 14]. The weight variation of the tablet was evaluated (n=20) tablets using an electronic balance. The tablet hardness was tested by using Monsanto hardness tester (Campbell Electronics, India). Tablet friability (n=10) was determined by using Roche friabilator (Campbell Electronics, India) for 4 minutes at a speed of 25 rpm. The thickness of the tablet determined using vernier caliper. Drug content was determined by using UV/Visible spectrophotometer (Shimadzu 1601, Kyoto, Japan) by measuring the absorbance of standard and sample at 233nm.

In- vitrodrug release studies:
Drug release studies were conducted using USP dissolution apparatus 2, Paddle type (Electro lab, Mumbai, India) at the speed of 50 rpm at 37±0.5ºC. The dissolution media used were 900 mL of 1.2 pH HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of prewarmed (37±0.5 ºC) fresh dissolution medium was replaced to maintain the volume constant. The amounts of Metformin HCL released in the dissolution medium were determined spectrophotometrically at 233 nm using (Mode No. UV 2300, Techcomp). Results are given as the mean values of three determinations.

Determination Of Release Mechanism and kinetics
The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), higuchi (cumulative percentage of release versus square root of time) [15] and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models [16].

In model-dependant approaches, release data were fitted to five kinetic models including the zero-order, first order, Higuchi matrix, Peppas–Korsmeyerand Hixson–Crowell release equations to find the equation with the best fit [17]. In case of Kosmeyer-Peppas model, the drug release from such devices having constant geometry will be observed till the polymer chains rearrange to equilibrium state. The Higuchi square root model also gives the drug release from planer surface of an insoluble heterogeneous matrix by diffusion through the itragranular openings created by porosity of the matrix tablet. Thus, to evaluate the mechanism of drug release from sustain release tablet, release data is plotted in Kosmeyer et al equation as log cumulative % of drug release vs log time, and exponent n was calculated through the slope of the straight line.

$$\mathbf{M_t/M_\infty = Kt}$$

Where,
M_t/M_∞ = fraction solute release
t = release time
K = kinetic constant characteristic of the drug/ polymer system
n = exponent that characterizes the mechanism of release of traces

Table 2.Release exponent (n) and drug transport mechanism.

Release Exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion
0.5 < n < 0.89	Non-Fickian diffusion
0.89	Case-II transport
n > 0.89	Super case II transport

In vitro buoyancy studies:
The in vitro buoyancy was determined by floating lag time and floating duration were evaluated in a dissolution vessel (dissolution apparatus, Lab India) filled with 900 ml of 0.1N HCL (Ph 1.2) previously set at 37±0.5^{O}C with paddle rotation at 100 rpm.

Similarity Factor:
To evaluate and compare dissolution data, the dissolution profile was statistically analyzed using dissolution similarity factor f_2[18].The equation for calculating f_2 is given below.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{t} Wt \left(R_t - T_t \right)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n = numbers of dissolution time point
W_t = Optional weight factor
R_t = Reference dissolution point at time t
T_t = Test dissolution point at time t

The f_2 value between 50 and 100 suggest that the dissolution is similar. The f_2 values of 100 suggest that the test and reference profile are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

RESULTS AND DISCUSSION

Study of physical interaction between drug polymers:
From the obtained FTIR spectrum of Metformin HCL, band was obtained at 3294.19 cm^{-1} due to N–H stretching (primary, secondary amines, amides), another band was at 1623.95 cm^{-1} due to N–H bending (primary amines) and another band was at 935.41due to N–H wagging (primary, secondary amines).From the obtained FTIR spectrum of HPMC K100M+Metformin, band was obtained at 3390.63due to N–H stretching(primary, secondary amines, amides), another band was at 2698.23due to H–C=O: C–H stretching(aldehydes)and another band was at 1623.95due to N–H bending(primary amines).

From the obtained FTIR spectrum of Eudragit RL100+ HPMC K100KM, band was obtained at 3473.56due O–H stretch, H–bonded(alcohols, phenols), another band was at 2950.89due to C–H stretching(alkenes)and another band was at 1728.10due to C=O stretching.

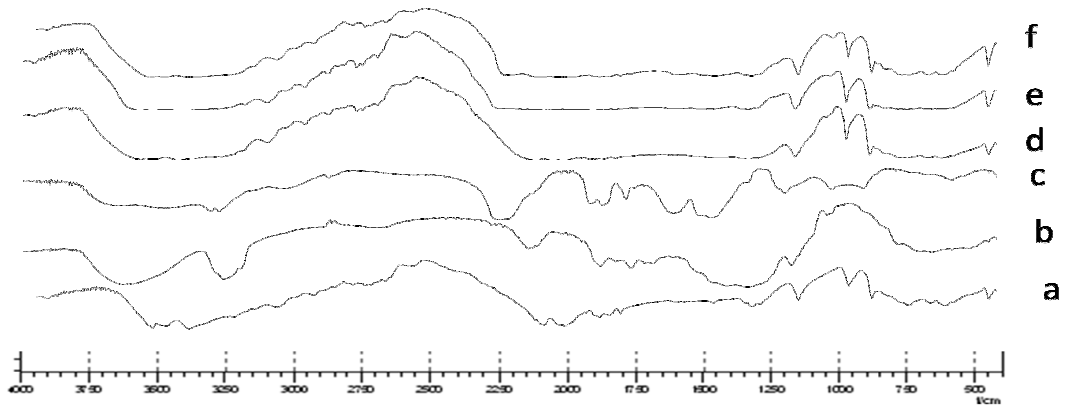

Figure 1:- (a) FT-IR of pure Metformin HCL,(b) HPMC K100M,(C) Eudragit RL 100, (d) Metformin HCL+HPMC K100M (e) Metformin HCL+Eudragit RL 100,(f)Metformin HCL + HPMC K100M+ Eudragit RL 100.

From the FT-IR studies, it was observed that the peaks of Metformin HCl was detected and identified in the spectrum of Metformin HCl loaded HPMC K100M, Metformin HCL loaded Eudragit RL 100, Metformin loaded HPMC K100M and Eudragit RL 100 confirming that there was no drug- polymer interaction between Metformin HCl and Polymer.

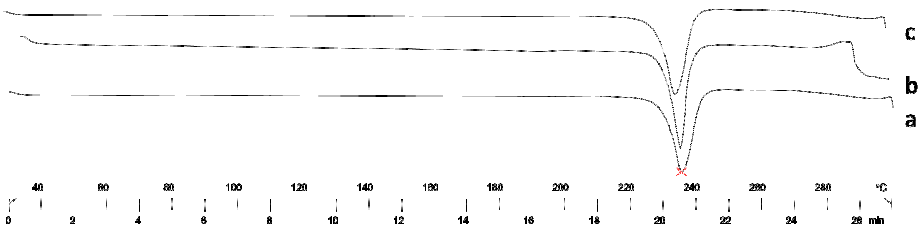

Figure 2.DSC Analysis of Metformin Hydrochloride (a), Metformin Hydrochloride and Eudragit RL100 (b),Metformin Hydrochloride and HPMC K100M

Differential Scanning Calorimetry (DSC):
Thermal analysis was carried out using a differential scanning calorimeter (Mettler Toledo DSC 822). The samples were placed in an aluminium-sealed pan and preheated to 200° C. The sample was cooled to room temperature and then reheated from 40° to 450° C at a scanning rate of 10° C/min.

Evaluation of granules:
The granules of proposed formulations were evaluated for LBD, TBD, Compressibility index, angle of repose and Hausner'sratio as shown in Table 3.

Table 3. Pre-compression Parameters:

Sr. No.	Batch	Carr's index	Hausners ratio	Angle of repose(º)
1	**A1**	11.904±0.022	1.135±0.028	26±1
2	**A2**	11.904±0.034	1.135±0.027	26±1
3	**A3**	12.341±0.121	1.189±0.013	28±1
4	**B1**	12.578±0.110	1.179±0.014	30±1
5	**B2**	14.876±0.134	1.201±0.017	32±1
6	**B3**	13.674±0.148	1.178±0.024	29±1
7	**C1**	15.234±0.123	1.187±0.019	28±1
8	**C2**	12.67±0.142	1.091±0.021	31±1
9	**C3**	13.891±0.111	1.182±0.009	32±1

Hausner's ratio and angle of repose. Carr's index was found to be in the range 11.904 to 16.034, hausner's ratio was found to be in the range 1.091 to 1.203 and angle of repose was found to be in the range 25 to 32. All formulations showed good flowability.

Tablet characteristics
The physical parameters such as hardness, thickness, friability and weight uniformity of all the formulated tablets were given in Table 4.

Table 4.Post Compression Parameters

F. Code	Hardness (kg/cm2)	Friability(%)	Weight Variation(%)	Drug Content(%)	Thickness (mm)
A1	7.36 ±0.06	0.470 ± 0.117	0.992 ±0.002	97.11±1..231	5.72 ±0.10
A2	6.20 ±0.04	0.337 ± 0.117	0.988 ±0.006	98.33±1.391	5.4 ±0.10
A3	7.43 ±0.06	0.405 ± 0.202	0.988 ±0.004	98.54±0.986	5.18 ±0.04
B1	7.55 ±0.05	0.302 ± 0.173	0.990 ±0.004	98.65±1.245	5.38 ±0.06
B2	7.23 ±0.08	0.235 ± 0.060	0.990 ±0.005	99.34±1.298	6.11 ±0.05
B3	6.93 ±0.11	0.336 ± 0.153	0.992 ±0.002	99.71±0.568	6.10 ±0.10
C1	7.58 ±0.04	0.268 ± 0.209	0.979 ±0.007	98.99±1.982	5.36 ±0.05
C2	7.87 ±0.07	0.372 ± 0.058	0.97 ±0.009	99.79±1.341	5.33 ±0.04
C3	7.24 ±0.07	0.432 ± 0.100	0.987 ±0.003	98.35±1.562	5.27 ±0.04

Hardness of all the tablets was in the range of 6.93 ±0.11 to 7.87 ±0.07kg/cm^2. The thickness and percentage friability ranged from 5.18 ±0.04 to 46.11 ±0.05mm ±.and 0.268 ± 0.209 to 0.470 ± 0.117 % respectively. All formulations showed less than 1% (w/w) friability which was within the prescribed limits. [12]

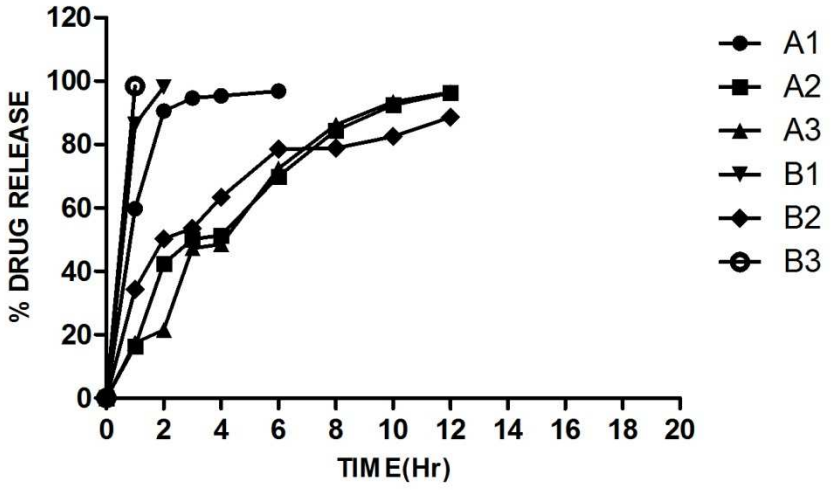

Figure 3: In vitro cumulative release of metformin HCL from batches A1 to B3

Drug release studies:
Drug release data of formulation containing different concentration of HPMC K100M and Eudragit RL100 as a polymer are given in Figure 3.

It was observed that as the concentration of polymer is increases upto 30% drug release was found to be more sustained. Batch A2, A3 was found to be having sustained drug release as compare to A1.Batch B2 was found to be sustained drug release as compare to B1 and B3.Drug release data of formulation containing different concentration of combination of Eudragit RL100 and HPMC K100M as a polymer are given as mean ± S.D, *(n=3)*. InFigure 4 .

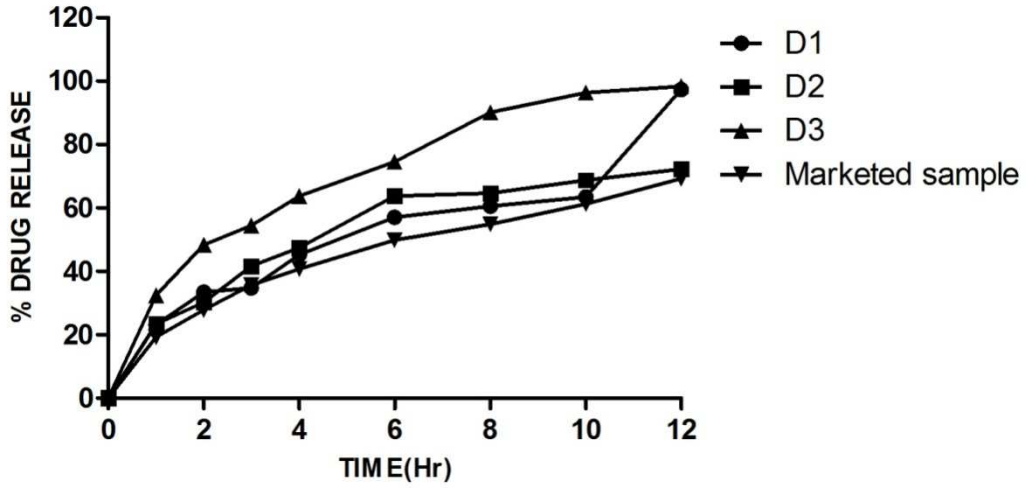

Figure4: In vitro cumulative release of metformin HCL from batches C1 to C3.

From figure i t was observed that Batch C 2 was found to be more sustained drug release as compare to C1 and C3.

Drug release kinetics:
To describe the kinetics of drug release from matrix tablets, release data was analysed according to different kinetic equations. The data was analysed by the regression coefficient method and regression coefficient value (r^2) of all batches as shown in Table 5.

TABLE 5: *in vitro* Release kinetics parameters of metformin HCL from the Matrix tablet.

F.Code	Zero order		1st order		Matrix		Hix.Crow		Korsmeyer-Peppas		
	R	K	R	K	R	K	R	k	R	N	k
A1	0.660	42.08	0.6854	-1.22	0.9203	65.7193	0.6848	-0.2673	0.6483	0.0138	82.5730
A2	0.872	7.24	0.8274	-0.14	0.9932	21.3402	0.8473	-0.0255	0.9645	0.3814	21.9231
A3	0.769	7.99	0.9284	-0.15	0.9812	23.3602	0.9433	-0.0395	0.9745	0.4816	24.9231
B1	0.745	40.332	0.7106	-1.17	0.8017	62.474	0.7270	-0.2322	-0.9277	-0.0066	91.4677
B2	0.759	39.7947	0.7749	-1.00	0.9777	66.7229	0.8680	-0.2532	0.6626	0.0143	93.1997
B3	0.836	3.8315	0.9017	-0.04	0.9929	11.2757	0.8822	-0.0145	0.9792	0.5426	10.4953
C1	0.869	7.9997	0.9284	-0.15	0.9812	23.3602	0.9433	-0.0395	0.9745	0.4816	23.9231
C2	0.541	7.730	0.8192	-0.12	0.9527	23.3204	0.7483	-0.0351	0.7483	0.3885	29.2718
C3	0.628	9.6893	0.9571	-0.20	0.9717	29.0643	0.8952	-0.0522	0.9883	0.3852	36.5203

The results shown in table 5 the release of maximum batches follows Korsmeyer-Peppas eq., which states that the release of drug might follow the mixed kinetics. It was found that all batches follow Fickian diffusion (n = 0.1 to 0.5).

The results shown in table 5 that the release of five batches follows Korsmeyer-Peppas eq.and remaining batches follows Matrix eq.which states that the release of drug might follow the mixed kinetics. However all batches follow Fickian diffusion (n = 0.1 to 0.5) as projected by Korsmeyer-Peppas eq.

Buoyancy test:
The floating lag time and floating duration for the formulated tablets are shown in table 6.

Table 6 : Buoyancy test of floating tablet

Sr.No.	**Batch**	FLT*	TFT (Hr)*
1	**A1**	5 min 12 sec	>12
2	**A2**	6 min 24 sec	>12
3	**A3**	15 min 5 sec	>12
4	**B1**	31 min 3sec	>12
5	**B2**	29 min 4 sec	>12
6	**B3**	24 min 17 sec	>12
10	**C1**	5 min 9 sec	>24
11	**C2**	7 min 6 sec	>24
12	**C3**	22 min 19 sec	>12

**n=3*

From table it was observed that the floating lag time ranges from 5 min 9 sec to 24 min 17 sec. Tablet of all batches remained buoyant for more than 12 hours expect tablet of batches C1,C2 remained buoyant for more than 24 hours and tablet of batch C3 remained buoyant for less than 6 hours.

Similarity Factor

Similarity factor between marketed and optimized formulation are shown in Table 7.

Table 7. Similarity factor between marketed and optimized formulation

Sr. No.	Compared Formulation	Similarity factor (f_2)*	Significant Difference
1	Glumet SR and C2	56.76	**No**

f_2< 50 – Statistical significant difference; f_2> 50 – No statistical significant difference

CONCLUSION

The findings of the present study demonstrate that the hydrophilic matrix of HPMC alone could not control the Metformin HCL release effectively for 12 h whereas when combined with Eudragit RL 100 and potassium bicarbonateshowed more sustained release of drug from their matrices, more total floating time and thus could be successfully employed for formulating sustained-release matrix tablets.Comparison between optimized and marketed formulation by similarity factor (f_2) divulged similarity in release profile between both. Release kinetic study showed that all batches followed Fickian diffusion. Diffusion coupled with erosion might be the mechanism for the drug release from hydrophilic and hydrophobic polymer based matrix tablets which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional metformin HCL tablets.

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