International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.3, pp 1850-1859 , July-Sept 2011

Effect of Hydroxypropyl Methylcellulose and Ethyl Cellulose polymer on Release Profile and Kinetics of Metformin HCl from Matrix Tablets

Kamlesh J. Wadher[1]*, Rajendra B. Kakde[2], Milind J. Umekar[1]

[1]Department of Pharmaceutical Technology, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, India-441002

[2]University Department of Pharmaceutical sciences, R.T.M. Nagpur University, Amravati Road, Nagpur, 440033, India

Corres author: kamleshwadher@gmail.com
Phone. [M]. 09960099619, [O] 07109288650.

Abstract: Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. t has relatively short plasma half life, low absolute bioavailability. The need for the administration two to three times a day when larger doses are required can decrease patient compliance. The overall objective of the present work was to develop an oral sustained release metformin tablet prepared by direct compression method, using hydrophilic hydroxyl propyl methylcellulose and hydrophobic ethyl cellulose polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and *in vitro* drug release. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Hydrophilic matrix of HPMC alone could not control the Metformin release effectively for 12 h whereas when combined with Ethyl cellulose could slow down the release of drug and can be successfully employed for formulating sustained-release matrix tablets. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled to anomalous type. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.Similarity factor, *f*2 values suggest that the test and reference profile are identical.

Key words: HPMC, Ethyl cellulose, Matrix tablets, Release kinetics.

Introduction:

Type 2 diabetes mellitus (T2DM) is a worldwide public health challenge. The morbidity, mortality and economic consequences of T2DM are still a great burden to patients, society, health care systems and the economy. The existing treatments for glycaemic control have limitations either because of their side effects (particularly weight gain and hypoglycaemia) or contraindications that limit their use[1, 2]

Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with T2DM, acts by decreasing hepatic glucose output and

peripheral insulin resistance[3] The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality[4].

It 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[5,6].

An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea, that especially occur during the initial weeks of treatment[7]. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin.. SR products are needed for metformin to prolong its duration of action and to improve patient compliance.

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable ,increased convenience and patient compliance[8,9]. Among the different approaches , Incorporation of drug in the matrix of hydrophilic polymers[10-12] such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, alginates , scleroglucan and hydrophobic polymers [13]such as Eudragit and ethylcellulose have been successfully employed in the development of sustained release delivery systems because of their flexibility in terms of the range of release profiles attainable, cost effectiveness, low influence of the physiological variables on its release behavior, limited risk of dose dumping and broad regulatory acceptance[14].

Most commonly used polymers for such operations are cellulose ether derivatives, including hydroxypropyl methylcellulose [15](HPMC). Due to non-toxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is often used as release retarding materials[16]. The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly[17]. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution, the dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC[18].

However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system, which provides several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe application[19]. Ethylcellulose (EC) is an inert, hydrophobic polymer that has been widely used as a matrix- forming material for sustained release dosage forms[20].

Hence, in the present work, an attempt has been made to formulate the extended-release matrix tablets of metformin Hydrochloride using hydrophilic matrix material (HPMC) in combination with hydrophobic polymer ethylcellulose.

Materials:

Metformin hydrochoride was obtained from Universal Medicament (Nagpur, India). Microcrystalline cellulose (MCC, Avicel pH 101) was purchased from S. D. Fine Chem. Labs, (Mumbai, India). Hydroxypropyl methylcellulose (HPMC K4M, K15M and K100M) were obtained as a gift sample from colorcon, Mumbai, Ethyl cellulose was obtained as gift samples from Glenmark pharma, Nashik. All other ingredients used were of laboratory reagents and used as such without further testing.

Methods:

Study of physical interaction between drug and polymer:

Fourier Transform Infrared Spectrometry (FTIR) : Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 cm cm^{-1} using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). 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)
DSC study of untreated and spray-dried metformin hydrochloride samples were carried out on a differential scanning calorimeter (model DSC7, Perkin Elmer, UK). Samples, of 2 mg each, of untreated drug and spray-dried powder of the optimized batch were held for 1 minute at 50 °C and then heated gradually at 10 °C min–1 in crimped aluminum pans under a nitrogen atmosphere from 50 to 270 °C. The onsets of melting points and enthalpies of fusion of samples were automatically calculated by the instrtment.

Scanning electron microscopy (SEM):
Electron micrographs metformin hydrochloride matrix tablets before and after dissolution was obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Japan). The specimens were coated under vacuum with gold in an argon atmosphere prior to observation. The scanning electron microscope was operated at an acceleration voltage of 30kV.

Preparation of metformin hydrochloride matrix tablets:

Matrix tablets, each containing 500 mg metformin hydrochloride were prepared by a direct compression method. The composition of various formulations of the tablets with their codes is listed in Table 1. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, polymer (HPMC, Ethyl cellulose) and filler (MCC) was mixed thoroughly. Granulation was done manually with a solution of isopropyl alcohol. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an eight station rotary press (Rimek Minipress I Ahmadabad, India) at a constant compression force equipped with a 14-mm flat-faced punches at a compression force required to produce tablets of about 7–8 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Evaluation of tablets:

The prepared matrix tablets were characterized immediately after preparation for hardness, weight variation, thickness, friability and drug content[21, 22]. The weight variation of the tablets was evaluated (n=20) tablets using an electronic balance. The hardness of the tablets (n=6) was tested using a Monsanto hardness tester (Campbell Electronics, India). Friability (n=10) was determined in a Roche friabilator (Campbell Electronics, India) for 4 minutes at a speed of 25 rpm. (Campbell Electronics, India). The thickness of the tablets was measured by vernier caliper. Drug content was analyzed by measuring the absorbance of standard and samples at λ = 233 nm using UV/Visible spectrophotometer (Shimadzu 1601, Kyoto, Japan).

***in- vitro* drug release studies:**

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at 37±0.5 ºC. The dissolution media used were 900 mL of 0.1 mol/L HCl for first 2 h followed by pH 6.8 phosphate buffer solution 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 samples withdrawn were filtered through a 0.45 µ membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

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

Formulation code	Ingredients (mg.)							
	Metformin HCL	HPMC K 100M	HPMC K 4M	HPMC K 15M	Ethyl cellulose	MCC	Mg.stea-rate	Total
F1	500	100				390	10	1000
F2	500	150				340	10	1000
F3	500	200				290	10	1000
F4	500		200			290	10	1000
F5	500			200		290	10	1000
F6	500	150			50	290	10	1000
F7	500	100			100	290	10	1000
F8	500	50			150	290	10	1000

TABLE 2. Physical properties of the matrix tablets containing 500 mg metformin HCl as a SR formulation

Formulation Code	Hardness† (kg/cm2)	Friability† (%)	Weight Variation* (%)	Drug Content*(%)	Thickness† (mm)
F1	7.39±0.36	0.12±0.14	1001.68±2.13	99.54	4.42±0.06
F2	7.10±0.58	0.28±0.11	1001.28±4.13	99.84	4.53±0.04
F3	7.55±0.63	0.29±0.12	1001.48±3.13	97.23	4.29±0.07
F4	7.83±0.12	0.25±0.29	1003.58±4.13	99.24	4.33±0.04
F5	7.94±0.32	0.15±0.27	1004.58±5.13	98.54	4.39±0.06
F6	7.82±0.54	0.27±0.31	1004.26±2.46	97.34	4.22±0.08
F7	7.20±0.83	0.24±0.15	1001.38±6.13	99.94	4.52±0.05
F8	7.52±0.28	0.23±0.18	1 001.08±4.44	98.44	4.32±0.02

TABLE 3:*in vitro* Release Kinetics Parameters of Metformin HCl from the Matrix tablet.

Formulation code	zero order		First order		Higuchi		Hixon-crowell		Korsmeyer-peppas		
	r2	k	r2	k	r2	k	r2	k	N	r2	K
F1	0.757	12.56	0.957	-0.42	0.984	34.06	0.980	-0.082	0.437	0.981	38.103
F2	0.876	11.90	0.953	-0.34	0.994	31.76	0.988	-0.073	0.545	0.993	29.375
F3	0.945	10.88	0.941	-0.27	0.986	28.60	0.987	-0.062	0.629	0.993	22.589
F4	0.852	12.35	0.945	-0.44	0.994	33.10	0.989	-0.082	0.518	0.993	32.112
F5	0.901	11.96	0.943	-0.41	0.994	31.79	0.991	-0.078	0.571	0.996	28.005
F6	0.948	8.89	0.960	-0.20	0.986	25.61	0.991	-0.048	0.666	0.9966	18.458
F7	0.815	10.22	0.974	-0.29	0.990	30.17	0.982	-0.063	0.493	0.987	30.626
F8	0.800	9.66	0.960	-0.23	0.992	28.57	0.968	-0.055	0.485	0.991	29.643
Glycomet SR	0.922	8.98	0.928	-0.21	0.990	26.03	0.976	-0.050	0.59	0.991	21.466

Release kinetics[23,24]:

The release data obtained were treated according to zero-order, first-order, Higuchi and Korsmeyer-Peppas equation models. In model-dependant approaches, release data were fitted to five kinetic models including the zero-order (Eq. 1), first order (Eq. 2), Higuchi matrix (Eq. 3), Peppas–Korsmeyer (Eq. 4), and Hixson–Crowell (Eq. 5) release equations to find the equation with the best fit.

$R = k_1 t$ ----------Eq. 1

$\log UR = k_2 t / 2{:}303$----------Eq. 2

$R = k_3 \sqrt{t}$ ----------Eq. 3

$\log R = \log k_4 + n \log t$ ----------Eq. 4

$(UR)^{1/3} = K_5 t$ ----------Eq. 5

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4, and k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, and Hixon–Crowell model, respectively.

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to Kosmeyer et al's equation as

$M_t/M_\infty = K.t^n$

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

Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (i.e. Fickian diffusion, case II transport, or anomalous transport). In the present study, the limits considered were n = 0.45 (indicates a classical Fickian diffusion-controlled drug release) and n=0.85 (indicates a case II relaxational release transport; non-Fickian, zero-order release). Values of n between 0.45 and 0.85 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport[25].

In order to compare the release profile of different formulas with possible difference in release mechanisms (n values), a mean dissolution time (MDT) [26]was calculated using the following equation.

$$MDT = (n/n+1).\ K^{-1/n}$$

Where n = release exponent and k = release rate constant

To evaluate and compare dissolution data, the dissolution profile was statistically analyzed using dissolution similarity factor f_2. 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 release profile increases.

TABLE4: Dissolution Parameter of Sustained Metformin HCl Matrix tablets

Formulation code	t 25 %(h)	t 50 %(h)	t 75 %(h)	MDT(h)
F1	0.5	2.2	4.8	2.11
F2	0.6	2.5	5.6	3.14
F3	1.2	3.5	6.7	3.91
F4	0.6	2.3	5.7	2.93
F5	0.5	2.4	5.8	2.98
F6	1.6	4.5	8.2	4.46
F7	0.7	2.7	6.2	3.37
F8	0.8	3.1	6.9	3.80
GLYCOMET SR	1.3	4.1	8.1	4.69

Scanning electron microscopy (SEM):

Electron micrographs metformin hydrochloride matrix tablets before and after dissolution was obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Japan). The specimens were coated under vacuum with gold in an argon atmosphere prior to observation. The scanning electron microscope was operated at an acceleration voltage of 30kV.

Statistical Analysis:

The data was subjected to two ways ANOVA followed by Bonferroni post test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA) and in all the cases $p < 0.001$ was considered as significant.

Results and Discussion:

Study of physical interaction between drug and polymer:

FTIR studies revealed that metformin hydrochloride showed two typical bands at 3369 and 3296 cm^{-1} due to N-H primary stretching vibration and a band at 3170 cm^{-1} due to N-H secondary stretching, and characteristics bands at 1626 and 1567 cm^{-1} assigned to C=N stretching. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed as shown in figure 1.

DSC analyses were performed in order to evaluate possible solid-state interactions between the components and, consequently, to assess the actual drug-excipient compatibility in all the examined formulations. The thermal curves of pure components and those of some representative ternary systems are shown in Fig 2.

The DSC curve of pure Metfrmin exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237 ºC (Tonset = 231.2, Tpeak = 233.33 and ΔHfusion = -313.51 J/g). The thermal curves of both binary and ternary mixtures, obtained by simple blending corresponded to the superimposition of those of the single components, indicating the absence of solid-state interactions and allowing assessment of drug–polymers compatibility in all the examined formulations. As a further confirmation of the absence of any incompatibility problem, no variations in the thermal behavior of samples of binary and ternary combinations were observed after their tabletting and subsequent powdering. Thus no definite solid-solid interaction could be concluded Examination of all the DSC thermograms as shown in figure 2.

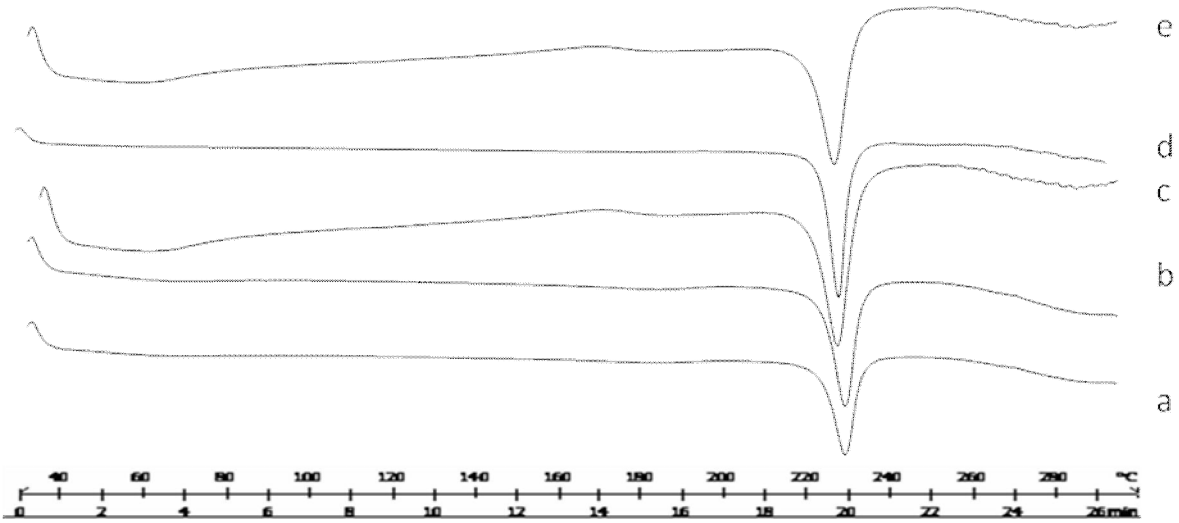

Figure1. : FT-IR spectra of pure metformin hydrochloride (a), and Physical mixtures of metformin hydrochloride with HPMC K4 M (b), HPMC K15 M (c), HPMC K100 M (d), and with HPMC K100 M and ethyl cellulose (e).

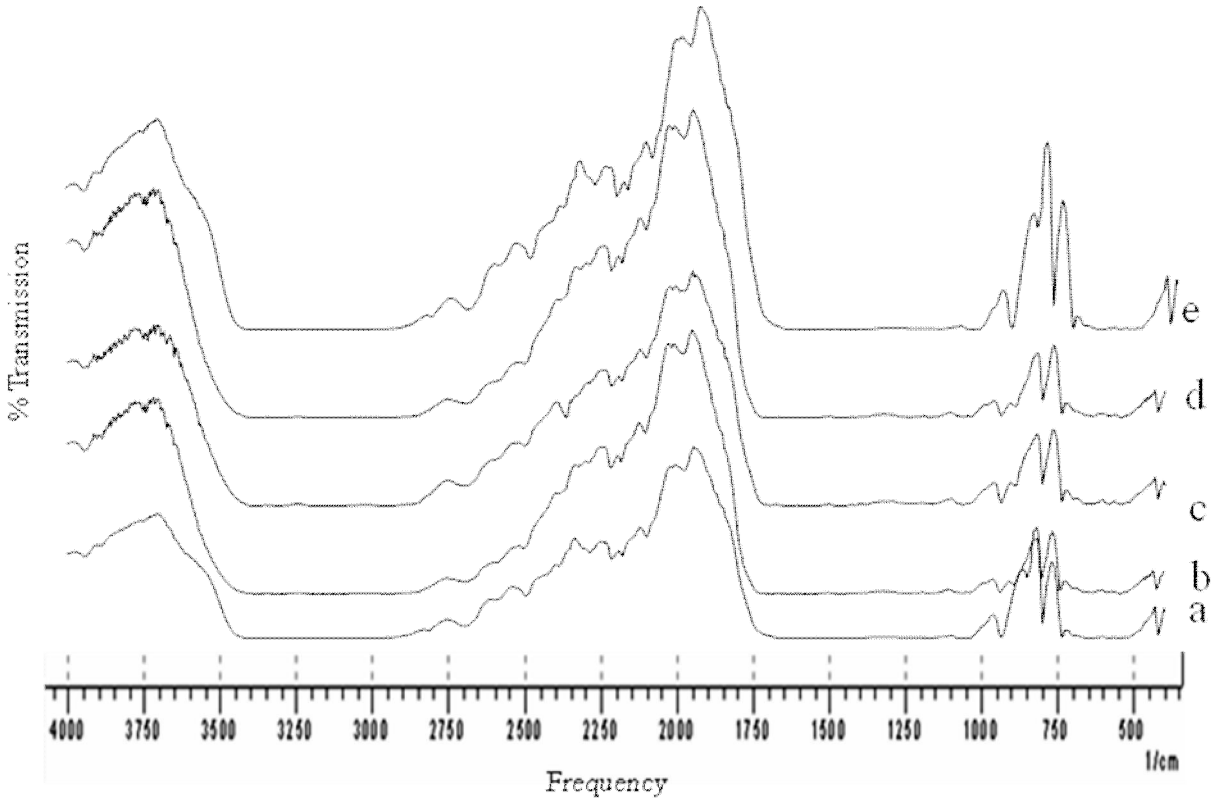

Figure2. : DSC of pure metformin hydrochloride (a), and Physical mixtures of metformin hydrochloride with HPMC K4 M (b), HPMC K15 M (c), HPMC K100 M (d), Ethyl cellulose(e) and with HPMC K100 M and ethyl cellulose(e).

Tablet characteristics:

The tablet hardness, thickness, weight variations, and friability for each formulations are presented in Table 2. In determinations of tablet weights, all formulations weights were found to be within pharmacopoeia limits. A plain punch with the same radius each time was used for all formulations in tablet pressing, and the differences in tablet radius was not significant ($P < 0.05$).

Friability value of all formulations and commercial tablets were less than 1%. and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed[27]. The average percentage deviation of all tablet formulations was found to be within the above limit, as per official pharmacopeia requirements. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95%.

Drug release studies:

The results of dissolution studies as shown in fig 3 indicate that formulations F1, F2, F3 released 47.9,2 9.6 and 23.7% of drug ,respectively, after 2h and 98.7, 97.4 and 96.6% of drug , respectively, after 10 h. whereas formulation F4 and F5 released 45.9 and 40.5% of drug ,respectively at the end of 2h,and 98.8,and 98.3% of drug , respectively, after 8 h exhibited typical diffusion profiles. The results shows that the release rate decreased as the concentration of HPMC increased. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug[28]. This indicates that drug/polymer ratio is important factors affecting the rate of release drugs from HPMC matrices Factors that may contribute to differences in drug dissolution profile as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling[29].

The dissolution profile of metformin tablets containing containing combinations of a hydrophilic polymer HPMC with a hydrophobic polymer EC in the different polymer/polymer ratio (30:70, 50:50 and70:30 respectively) while keeping the total polymer ratio 20% are shown in figure 4.

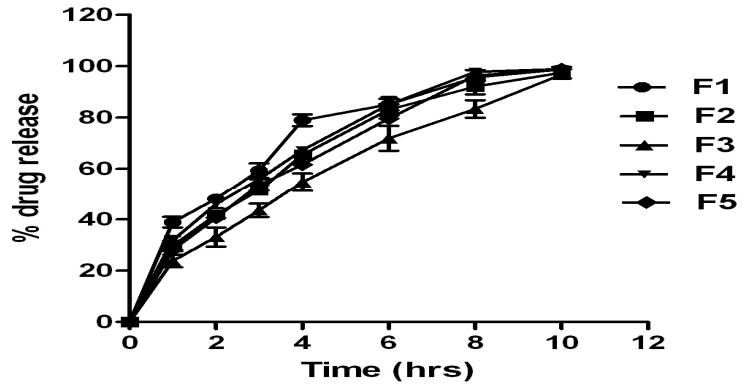

Figure 3. In vitro cumulative release of Metformin HCL from batches F-1 to F-4. Each point represents mean ± SD, n=3

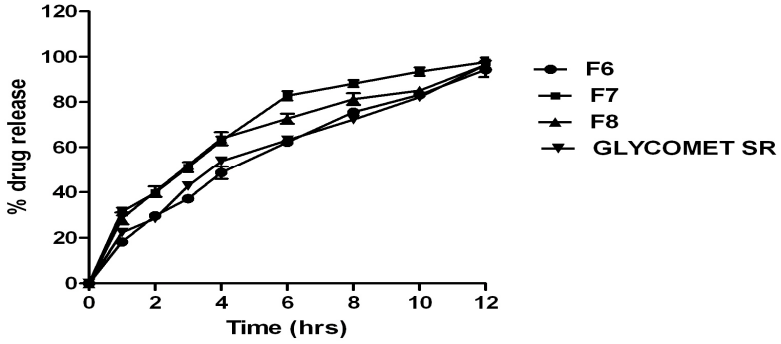

Figure 4. In vitro cumulative release of Metformin HCL from batches F6 to F8 and marketed formulation. Each point represents mean ± SD, n=3

Formulations F6, F7 and F8 released 29.7, 39.7 and 40.2% of drug, respectively, after 2h and 94.3,97.6 and 96.5% of drug, respectively, after 12 h respectively. Incorporation of ethyl cellulose resulted in extending the drug release for a period of 12 h indicating fair uniform drug release throughout the dissolution period which may attributed to decreased penetration of the solvent molecules in the presence of the hydrophobic polymer, leading to reduced diffusion of the drug from the matrix. This may be due to a more rigid complex formed by hydrophilic polymers HPMC K100 M in presence of ethyl cellulose, which helped in retaining the drug in the matrix and did not allow rapid diffusion of soluble drug from the matrix. According to penetration theory, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network.[30]

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations .The data were analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches were shown in Table 3.On analyzing regression coefficient values of all batches, it was found that formulation F1, F2, F4, F7 and F8 exhibit higuchis release kinetics whereas, Batch F3, F5and F6 followed Kosermeyr –peppas model. Marketed formulation Glycomet SR showed 28.50% at 2h and 96.52% at 12h and when compared with F5 the f_2 values found to be 73 which clearly suggest that the test and reference profile are identical.

The in vitro release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (r^2=0.98to 0.99). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation the formulations showed good linearity (r^2 = 0.98 to 0.99) with slope (n) between 0.437- 0.666 which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion.

The time taken to release 25% (t_{25}), 50% (t_{50}), and 75% (t_{75}) of drug from different formulations was determined (Table 4).Mean dissolution time (MDT) value is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. The MDT were significantly higher when the combination of HPMC with ethyl cellulose were carried out than the plain polymers, which clearly indicated sustained release nature of the combination.

The SEM images of the tablet were taken before and after dissolution. Figure 5 showed intact surface without any perforations, channels, or troughs. After dissolution, revealed many pores with increasing diameter. The solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium, which clearly indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of metformin from formulated matrix tablets.

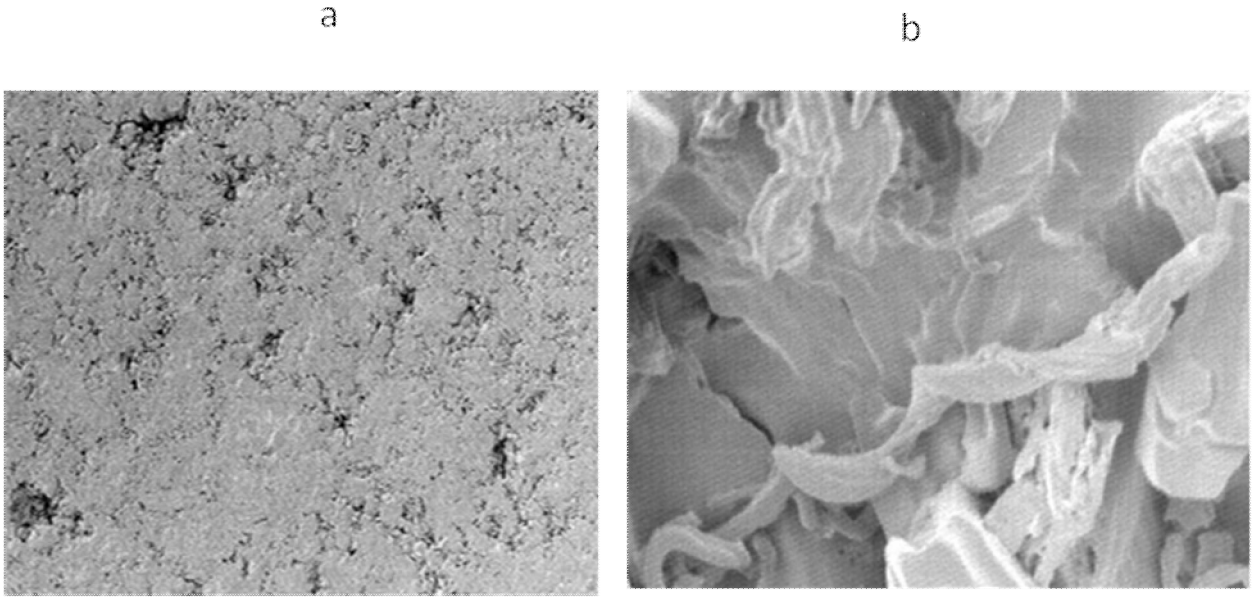

Figure 5. SEM photographs of tablet surface before dissolution (a) and after dissolution (b)

Conclusions:

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 EC could slow down the release of drug from their matrices and can be successfully employed for formulating sustained-release matrix tablets. 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.

Acknowledgments:

The authors are thankful to Universal Medicament, Nagpur, India for providing Metformin HCl as gift sample and S.K.B. College of Pharmacy, Kamptee, Nagpur, India for providing necessary facilities to carry out this work.

References:

1. Tahrani A.A, Piya M. K, Kenned A and Barnett A.H., Glycaemic control in type 2 diabetes: Targets and new therapies, Pharmacol and Therapeut., 2010, 125, 328–361.
2. Jacobson A.M., Impact of improved glycemic control on quality of life in patients with diabetes. Endocr. Pract., 2004, 10, 502−508.
3. Nathan D. M, Buse J. B, Davidson M. B, Ferrannini E, Holman R. R, and Sherwin R., Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care ,2009, 32, 193−203
4. Holman R. R, Paul S. K, Bethel M. A, Matthews D. R, and Neil H. A., 10-year follow-up of intensive glucose control in type 2 diabetes. N. Engl. J. Med, 2008, 359, 1577−1589.
5. Dunn C.J. and Peters D.H. Metformin: A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. Drugs., 1995,49,721-749.
6. Defang O, Shufang N, and Wei L., In vitro and in vivo evaluation of two extended Release preparations of combination metformin and glipizide. Drug Dev. Ind. Pharm., 2005, 31, 677–685.
7. Stepensky D, Friedman M , Srour W , Raz I , and Hoffman A., Preclinical evaluation of pharmacokinetic–pharmacodynamicrationale for oral CR metformin formulation, J. Cont. Rel,2001,71, 107–115.
8. Merkus F.W., Controlled and rate-controlled drug delivery; principal characteristics, possibilities and limitations, in Struyker-Boudier, H.A.. (eds), Rate- Controlled Drug Administration and Action, CRC Press, Boca Raton, FL, USA, 15-47, 1986
9. Colombo R, Bettini P.S, Peppas N.A., Swellable matrixes for controlled drug delivery: gel-layer behavior, mechanisms and optimal performance, Pharm. Sci. Technol. Today., 2000, 3, 198–204.
10. Hasan E.I, Amro, B.I, Arafat T, and Badwan A.A., Assessment of controlled release of hydrophillic matrix formulation for metoclopramide HCL, Eur. J. Pharm. Biopharm.,2003, 55, 339–344.
11. Winterowd J.G, Sandford P.A., Chitin and chitosan. In: Alistair, S.M. (Ed.), Food Poly-saccharides and their Applications, 1st ed. Marcel Dekker, New York, NY, 1995, 441–462.
12. Moe S.T, Draget K.I, Skjak-Braek G.S, and Alginiates O., In: Alistair, S.M. (Ed.), Food Polysaccharides and their Applications, 1st ed. Marcel Dekker, New York, NY, 1995, 245–286.
13. Lotifipour F, Nokhodchi A, Saeedi M, Norouzi-Sani S, Sharbafi J, and Siahi-Shadbad M.R., The effect of hydrophilic and lipophillic polymers and fillers on the release rate of atenolol from HPMC matrices., II Farmaco ,2004,59, 819–825.
14. Lordi N., Sustained release dosage forms. In: Lachman L, Lieberman H.A, and Kanig L.J, editors. The Theory and Practice of Industrial Pharmacy. Philadelphia: Lea and Febiger; 1986, 430–478.
15. Velasco V.M, Ford J.L, Rowe P., and Rajabi-Siahboomi A.R., Influence of drug:hydroxypropylmethylcellulose ratio, drug

and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets, J. Control., Release, 1999,57, 75-85.
16. Yan G, Li H, Zhang R and Ding D., Preparation and evaluation of a sustained release formulation of Nifedipine HPMC tablets, Drug Dev. Ind. Pharm.,2000, 26, 681-686.
17. Siepmann J, Kranz H, Bodmeier R, and Peppas NA., HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics. Pharm Res., 1999, 16,1748-1756.
18. Zhang L, Li N, Zhao F, Li K., Spectroscopic study on the interaction between methylene blue and chondroitin 4-sulphate and its analytical application. Ana. Sci. 2004, 20, 445-450.
19. Liu J, Zhang F, McGinity J.W., Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur. J .Pharm. Biopharm., 2001,52,181-190.
20. Shaikh N.A, Abidi S.E. and Block L.H., Evaluation of ethylcellulose matrix for prolonged release formulations: Water soluble drugs: acetaminophen and theophylline. Drug Dev. Ind. Pharm.,1987),13,1345-1369
21. Martin A., Micromeritics. In: Martin A, editors. Physical Pharmacy. Baltimore MD: Lippincott Williams & Wilkins; 2001, 423-454.
22. Wells J., Pharmaceutical preformulation: The physiochemical properties of drug substances. In: Aulton, M.E., editor. Pharmaceutics the science of dosage form design. London: Churchill Livingstone, 2002, 247.
23. Higuchi T., Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 1963, 2 ,1145 -1149.
24. Korsmeyer R.W, Gurny R ,and Peppas N.A., Mechanisms of solute release from porous hydrophilic polymers, Int .J .Pharm., 1983,15,25-35.
25. Costa P, Lobo J.M., Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci., 2001,13,123-133.
26. Venkatramana M.R, Kevin E, and Yihong Q., Design of pH-independent controlled release matrix tablets for acidic drugs, Int. J. Pharm.,2003,252, 81–86.
27. Banker G.S. and Anderson L.R., Tablets. In: Lachman L, Liberman H.A, and Kanig J.L, editors. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House, 1987, 293-345.
28. Skoug J.W, Mikelsons M.V, Vigneron C.N, and Stemm N.L., Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release, J. Cont. Rel., 1993 27, 227-245.
29. Wan L.S, Heng P.W, and Wong L.F.. Relationship between swelling and drug release in a hydrophilic matrix, Drug Dev. Ind., Pharm., 1993, 19, 1201-1210.
30. Leuenberger H, Rohera B.D, Haas C., Percolation Theory – a novel approach to solid dosage form design, Int. J. Pharm., 1987, 38, 109-115.

*****