Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Pharmacia Sinica, 2014, 5(5):18-26

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Formulation of once a day controlled release Metformin HCl matrix tablets

S. Vidyadhara*, R. L. C. Sasidhar, A. Ramu, T. Balakrishna and T. Sravani

Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, A. P., India

---

ABSTRACT

An oral controlled matrix tablet of Metformin HCl was formulated by hydrophilic polymer such as hydroxy propyl methyl cellulose K_{100} M (HPMC K_{100} M) as rate retarding polymer along with pharmaceutically acceptable electrolytes. Electrolytes such as aluminium hydroxide, magnesium carbonate and sodium carbonate were used at different concentrations (40 to 60 mg / tablet) in various formulations, while the ratio of drug and polymer were maintained constantly. In this work, a attempt was made for in-situ interactions between drug and electrolytes to control the release of highly water soluble drug from oral hydrophilic monolithic system. These electrolytes were used to monitor matrix swelling and gel properties. Electrolytes at higher concentrations exhibited greater retardation in drug release from than in low concentrations for controlled release of the drug. The results indicated that the drug released at a controlled rate were due to differential swelling rate and matrix stiffening and provides a uniform gel layer. These findings indicated that the swelling and gel formation in the presence of ionisable species within the hydrophilic matrices provide an attractive alternative for controlled drug delivery from a monolithic system. Accelerated stability studies were carried out as per ICH guidelines for some selected formulations, which indicated that these formulations were stable at accelerated storage conditions.

Key words: Metformin HCl, HPMC K_{100} M, Aluminium Hydroxide, Magnesium Carbonate, Sodium Carbonate.

INTRODUCTION

Oral drug delivery is the most widely utilized routes for administration of drugs, which has been explored for systemic delivery via various pharmaceutical products as different dosage form. [1] In long-term therapy for the treatment of chronic disorders, conventional formulations are required to be administered frequently in multiple dosage regimens, and therefore have several undesirable effects. Hence, in order to reduce the drawback associated with multiple dosing, controlled or sustained release solid unit dosage forms as tablets were developed. [2] They often produce better patient compliance, maintain uniform drug therapeutic level, are cost-effective, have broad regulatory acceptance, reduce dose as well as side-effects, and increase the safety margin for high-potency therapeutic agents [3] .

In this new era various hydrophilic polymers have been investigated and are widely used in the design of complex controlled release systems [4-6]. The polymers used in the design of controlled release of a drug include nonionic hydroxypropyl methylcellulose (HPMC K100 M). The major challenge in the development of new controlled release devices is to achieve optimal drug concentration at the site of action. To achieve optimal drug concentration at the site of action, liberation of the drug from the device must be controlled as accurately as possible [7]. The dissolution in a monolithic matrix for linear drug release over a prolonged period of time is not easily achievable and

still remains a challenge. The limitation of a hydrophilic polymer may be circumvented through modification of physical and chemical infrastructure of the polymeric gel system by using electrolytes.

In the present investigation, studies were under taken for design and development of oral controlled release drug delivery system of Metformin HCl by matrix diffusion technique. It is an oral hypoglycemic agent, chemically it is 1, 1–dimethyl biguanide derivative,acts by suppressing hepatic gluconeogenesis [8].

It is a white, crystalline powder and hygroscopic in nature. MH is freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in dichloromethane [9]. Metformin HCl is readily absorbed from the gastrointestinal tract, having oral bioavailability of 50-60%, Peak plasma concentration (Cmax) is reached within 1-3hrs with immediate-release and 4-8hrs with extended release. Plasma protein binding of Metformin HCl is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Metformin HCl is not metabolized and excreted as unchanged form in urine, having elimination half life of 2-6 hrs. Based on these physiochemical, biopharmaceutical properties and rationale of clinical efficacy Metformin HCl was selected as drug candidate for developing controlled release matrix tablet formulations [10].

Thus the aim of this work was to provide and expand on a means to design, formulate and develop a novel oral monolithic, controlled release tablet dosage forms of a drug that may be tailored to provide quasi steady state drug release over an extended period of time [11]. The rationale behind the mechanism and dynamics of electrolytes induced matrix stiffening and structural changes to the gel is the basis of controlled drug release has also been elucidated.

MATERIALS AND METHODS

Materials

Metformin HCl and Hydroxy Propyl Methyl Cellulose K100 M **(**Commercially procured from Yarrow chem. Ltd., Mumbai), Aluminium Hydroxide (Commercially procured from Loba Chemicals., Ltd., Mumbai), Sodium Carbonate and Magnesium Carbonate (Commercially procured from Qualigens Fine Chemicals, Mumbai), Micro Crystalline Cellulose (Commercially procured from Colorcon Chemicals Asia Pvt., Ltd., Mumbai), Talc and Magnesium Stearate (Commercially procured from S.D Fine Chem, Ltd., Mumbai).

PREPARATION OF MATRIX TABLETS

Metformin HCl controlled release matrix tablets were prepared by wet granulation method using Isopropanol as granulating fluid. The controlled release matrix tablets formulations consisted of a polymer, drug and electrolytes. The ratio of drug and polymer were maintained constant while the electrolyte concentration was varied. The weight of all formulations was maintained uniformly by using MCC as diluent. The materials were individually weighed, and prepared as damp mass by using isopropyl alcohol as granulating fluid. The damp mass was passed through sieve no.18 and the granules obtained were dried at 60^0C using tray drier. The prepared granules were evaluated for flow properties such as angle of repose and compressibility index. The dried granules were again passed through sieve no.40. The prepared granules were lubricated with talc and magnesium stearate and were compressed as matrix tablets with 8mm flat punches by using clit-10 station mini press. To minimize the processing variables, all batches of tablets were compressed under identical conditions. The compositions of various Metformin HCl matrix tablets were given in table 1.

EVALUATION OF PHYSICAL PARAMETERS

The physical parameters such as hardness, friability weight uniformity and drug content were evaluated for the prepared matrix tablets as per the specifications of official compendium [12]. The Precompressional parameters evaluated and the post compressional parameters were given in tables 2 and 3.

Determination of Swelling Index:

The swelling behavior of matrix tablets were measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using 6.8 p^H phosphate buffer as dissolution medium at 37 ± 0.5^0C. After 0.5, 1, 2, 4, 6 and 8 hrs each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated

by using the following formula [13]. The swelling index for various selected formulations of Metformin HCl matrix tablets were given in table 5.

$$\textbf{Swelling index} = \frac{(\text{Wet weight of tablet} - \text{Dry weight of tablet})}{\text{Dry weight of tablet}}$$

***In Vitro* Dissolution Studies**

Dissolution studies for each matrix tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA DS 8000), equipped with paddles (USP apparatus II method) employing 900ml of 6.8 p^H phosphate buffer as dissolution medium.[14] Samples were withdrawn at regular intervals up to 12 hrs. Fresh volume of the medium was replaced with the withdrawn volume to maintain sink conditions and constant volume was maintained throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 233nm subsequently various dissolution parameters were analyzed based on the equations, first order constant, Higuchi constant, and the Korser-Mayer Peppas constant respectively. The following are the equations used:

$$\text{In } Q = k.\ t \qquad 1$$

$$Q = k.\ t \qquad 2$$

$$M_t / M_\infty = kt^n \qquad 3$$

Where Q in the equation (1) is cumulative percent drug remained, while Q in the equation (2) is cumulative amount of drug released, t is the release time and k is the constant incorporating the structural and geometrical characteristics of the release device. If the value of n =0.45 indicates case I (Fickian) diffusion or square root of time kinetics, 0.45<n<0.89 indicates anomalous (non Fickian, drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, n=0.89 indicates case II transport and n>0.89 indicates super case II transport. Linear regression analysis was performed for all these equations and regression coefficients (r) are determined.

RESULTS AND DISCUSSION

The present study was under taken for design and evaluation of the controlled release matrix tablets of Metformin Hydrochloride with controlled release grade polymer HPMC K100M by employing electrolytes as drug release retardants.

All batches of tablets were produced under similar conditions to avoid processing variables. The compositions of various matrix tablets were given in table-1. These tablets were preliminarily evaluated for various physical parameters such as weight uniformity, hardness, friability and drug content.

All batches of tablets with different electrolyte compositions were within the weight range of 1000 ± 3 mg. The hardness of all the tablet formulations was in the range of 4.0-4.8 kg/cm^2. Friability loss of the tablet formulations were found to be negligible and were in the range of 0.1 - 0.2% w/w. Drug content estimated for all the tablet formulations were highly uniform with less than 2.5% variation. Drug content was also the same in case of matrix tablets containing electrolytes. All the matrix tablets were prepared under identical conditions and were found to be stable. The results of physical parameters evaluated for various matrix tablets were given in table 2-3

From the *in vitro* dissolution studies, the results showed that greater inhibition of drug release rate of Metformin. The dissolution profiles of various matrix tablets were shown in figures 1-2 and then their corresponding kinetic data was shown in table-4. The drug release from the matrix tablet formulations was extended up to 12hrs in majority of the formulations. By the incorporation of electrolyte into hydrophilic monolithic tablet matrices, it was possible to reduce the release rate of drug over an extended period of time. The inclusion of electrolytes with in a swollen matrix for controlling the release rate of metformin may lead to the formation of free base of metformin and fundamental structural changes in gel boundary, thus including the textual variations in the swollen matrix. Formulations M6, M9 and M12 containing highest proportion of electrolytes extended the drug release over a period of 12 hrs.

Table 1: Composition of Metformin HCl Matrix Tablets

Ingredients (mg/tab)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Metformin Hcl	750	750	750	750	750	750	750	750	750	750	750	750
HPMCK100M	100	150	200	200	200	200	200	200	200	200	200	200
Aluminium Hydroxide	-	-	-	40	50	60	-	-	-	-	-	-
Magnesium Carbonate	-	-	-	-	-	-	40	50	60	-	-	-
Sodium Carbonate	-	-	-	-	-	-	-	-	-	40	50	60
Isopropanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
MCC	140	90	40	-	-	-	-	-	-	-	-	-
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Total Tablet Weight (gm)	1	1	1	1	1	1	1	1	1	1	1	1

Table 2: Flow properties of Granules of Metformin HCl matrix tablets

S. No	Formulation code	Angle of repose(º)	Compressibility index%
1.	M1	22.34	12.17
2.	M2	24.54	11.87
3.	M3	23.18	11.41
4.	M4	23.30	15.77
5.	M5	22.80	11.14
6.	M6	22.57	13.63
7.	M7	21.74	12.27
8.	M8	24.62	12.37
9.	M9	23.74	13.42
10.	M10	22.34	12.17
11.	M11	24.54	11.87
12.	M12	23.18	11.41

Table 3: Physical Parameters of Metformin HCl Matrix Tablets

S. No	Formulation code	Wt uniformity (mg)	Hardness (kg/cm^2)	Friability (% w/w)	Drug content (mg/tab)
1.	M1	997±3.0	4.0±0.3	0.12	749.2±0.5
2.	M2	998±3.0	4.5±0.3	0.18	750.4±0.5
3.	M3	997±2.0	4.5±0.3	0.17	749.9±0.2
4.	M4	1000±3.0	4.5±0.3	0.18	749.8±0.3
5.	M5	1001±2.0	4.5±0.3	0.14	750.2±0.5
6.	M6	1002±2.0	4.5±0.3	0.15	750.5±0.2
7.	M7	996±4.0	4.0±0.3	0.13	749.9±0.4
8.	M8	997±4.0	4.5±0.3	0.15	750.5±0.3
9.	M9	999±3.0	4.6±0.3	0.18	750.4±0.2
10.	M10	1000±3.0	4.6±0.3	0.12	749.2±0.5
11.	M11	998±3.0	4.8±0.3	0.18	750.4±0.5
12.	M12	997±2.0	4.5±0.3	0.17	749.9±0.2

Table 4: Dissolution Parameters of Metformin HCl Matrix Tablets

Formulation Code	Zero order		First order		Higuchi		Peppas	
	K	R^2	K (hr $^{-1}$)	R^2	K(mg/hr$^{1/2}$)	R^2	N	R^2
M1	11.47	0.641	0.554	0.974	265.66	0.947	0.508	0.960
M2	9.14	0.630	0.451	0.982	243.85	0.949	0.524	0.960
M3	7.41	0.630	0.319	0.984	218.81	0.964	0.523	0.966
M4	7.19	0.644	0.266	0.985	211.31	0.978	0.508	0.979
M5	7.19	0.722	0.228	0.993	216.73	0.983	0.558	0.980
M6	6.92	0.767	0.194	0.990	210.73	0.993	0.562	0.990
M7	7.02	0.645	0.236	0.980	206.43	0.976	0.515	0.970
M8	6.90	0.685	0.203	0.992	205.26	0.981	0.534	0.977
M9	6.81	0.722	0.187	0.992	206.71	0.989	0.549	0.980
M10	7.28	0.681	0.244	0.998	217.03	0.972	0.545	0.973
M11	7.06	0.728	0.208	0.997	212.99	0.985	0.730	0.983
M12	6.91	0.786	0.177	0.998	212.71	0.989	0.601	0.984

Table 5: Swelling Index of Metformin HCl Matrix Tablets

S.No	Time (hrs)	Formulations		
		M6	M9	M12
1	1	92.98	84.84	80.19
2	2	130.07	120.93	111.36
3	4	162.36	155.14	150.75
4	6	180.59	173.48	165.92
5	8	193.28	185.02	175.77

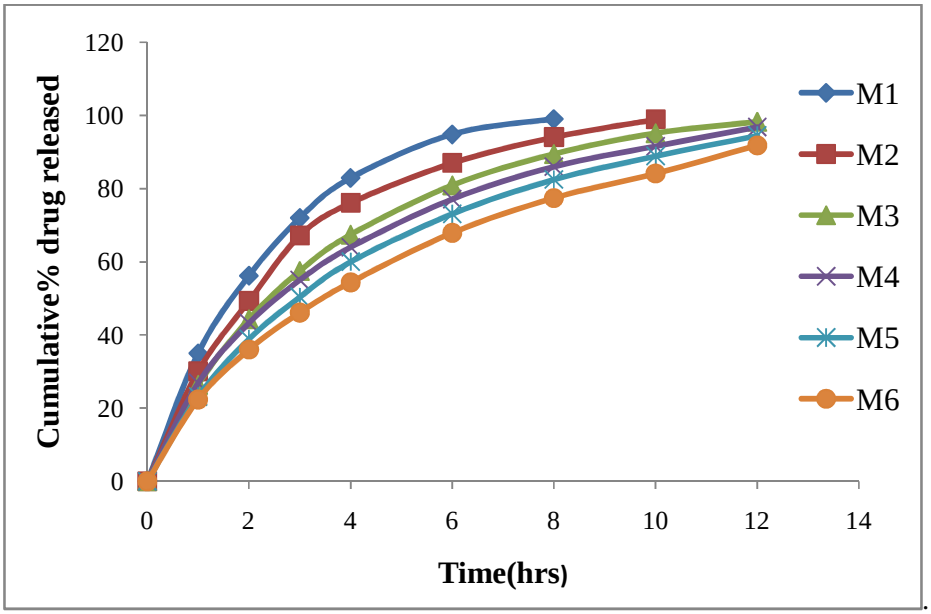


Figure 1: Drug Release Profiles of Metformin HCl Matrix Tablets

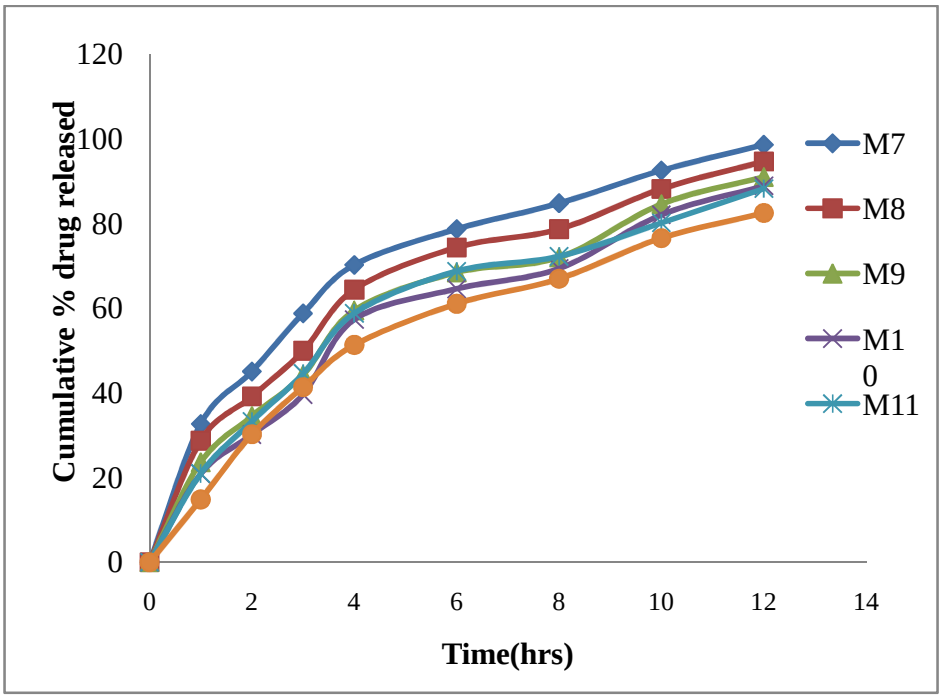
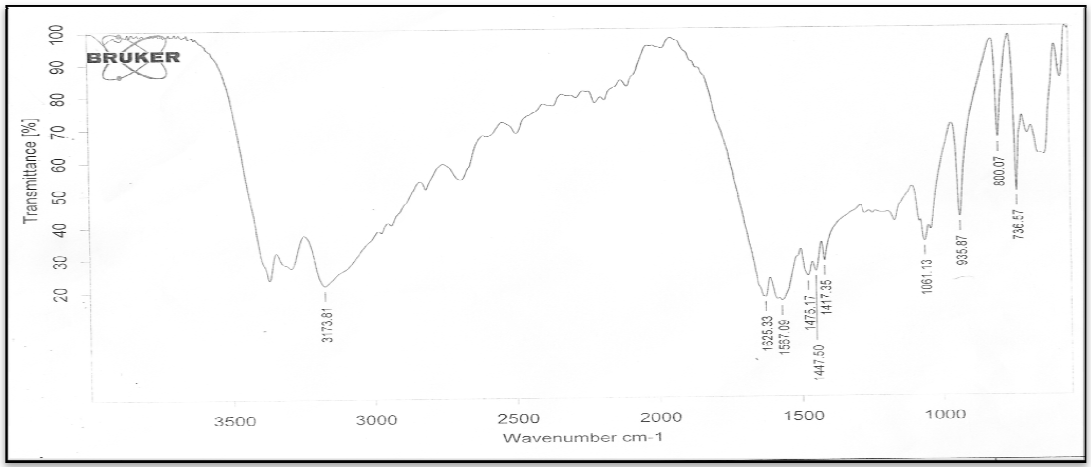
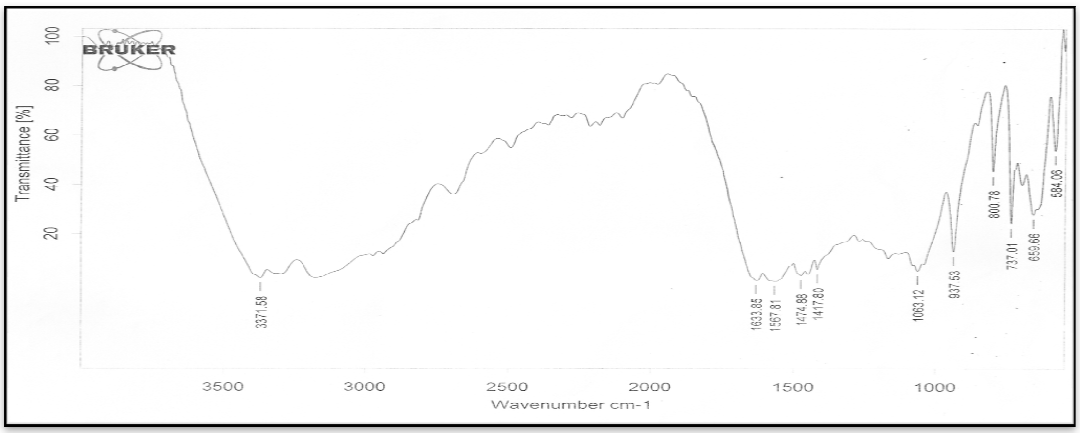


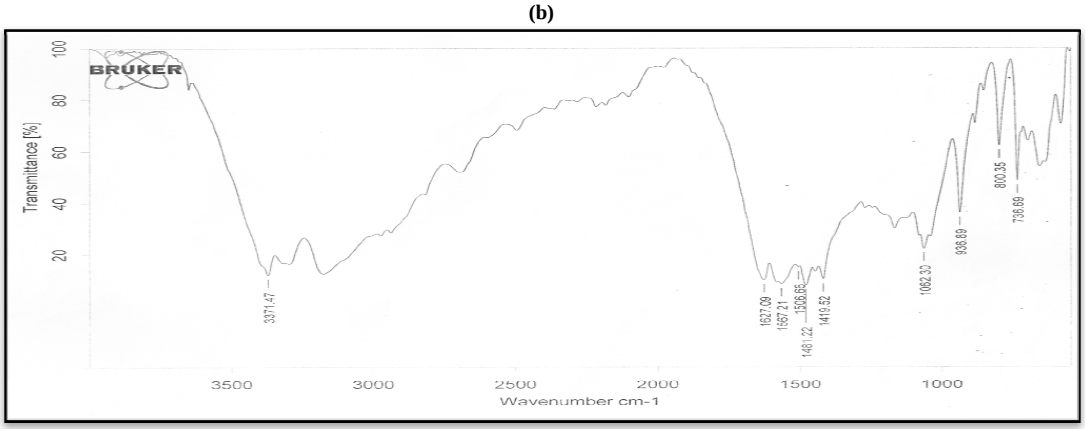
Figure 2: Drug Release Profiles of Metformin HCl Matrix Tablets


BRUKER
Transmittance [%]
100
90
80
70
60
50
40
30
20
3173.81
1325.33
1557.09
1475.17
1447.50
1417.35
1061.13
935.87
800.07
736.57
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

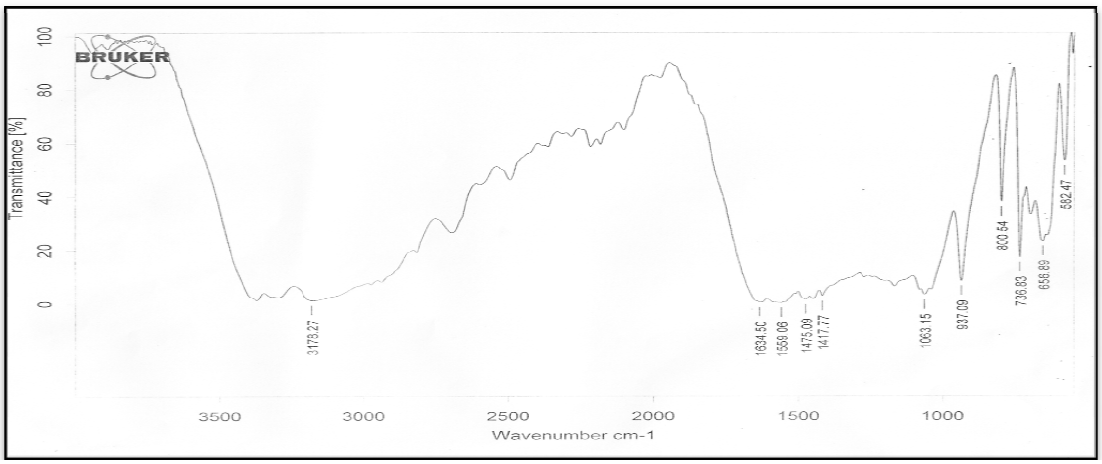
(a)


BRUKER
Transmittance [%]
100
80
60
40
20
3371.58
1633.86
1557.81
1474.88
1417.80
1063.12
937.53
800.78
737.01
659.66
584.08
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

(b)

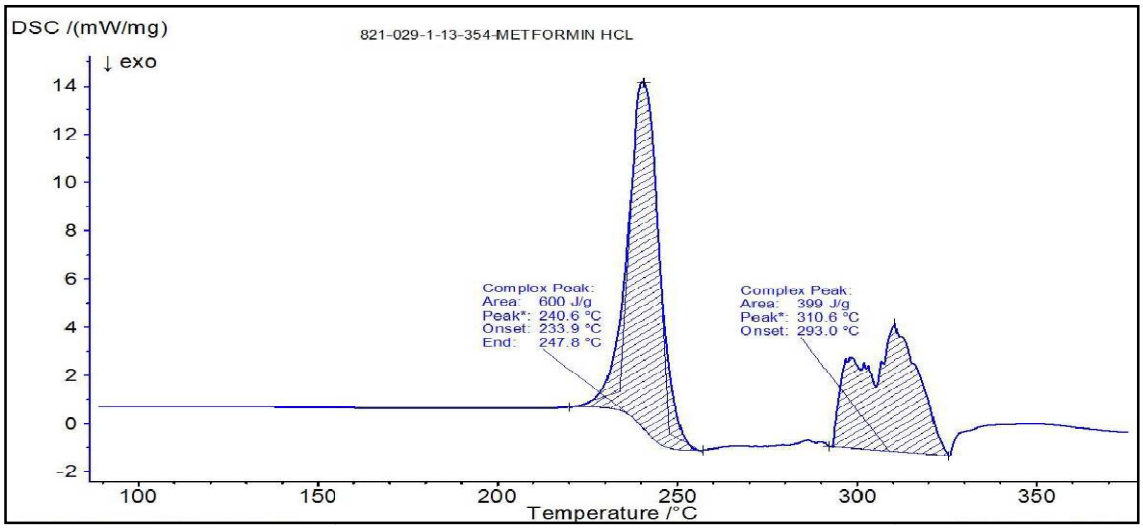

BRUKER
Transmittance [%]
100
80
60
40
20
3371.47
1627.09
1567.21
1506.65
1481.22
1419.92
1062.50
938.69
800.35
736.69
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

(c)

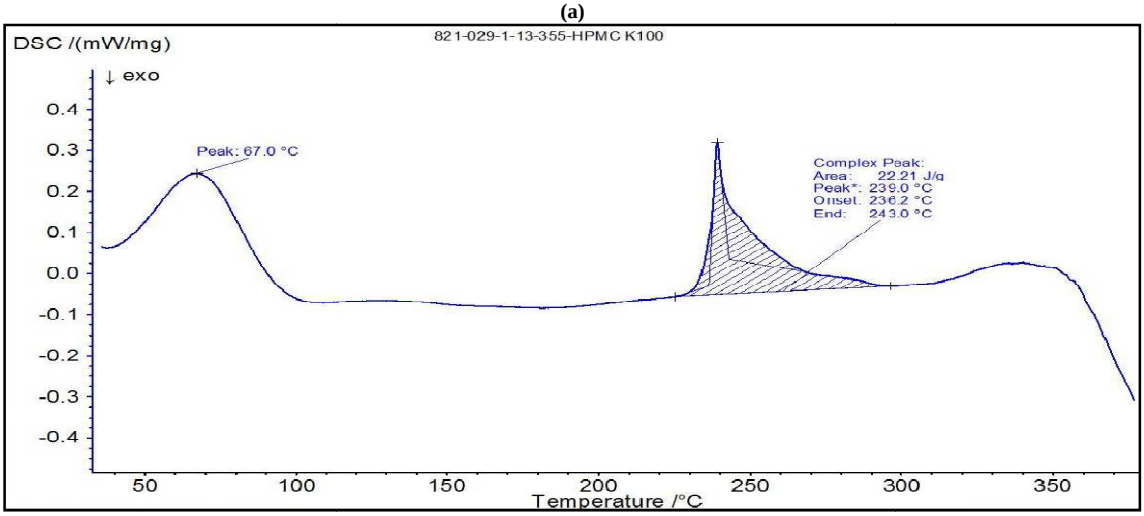


(d)

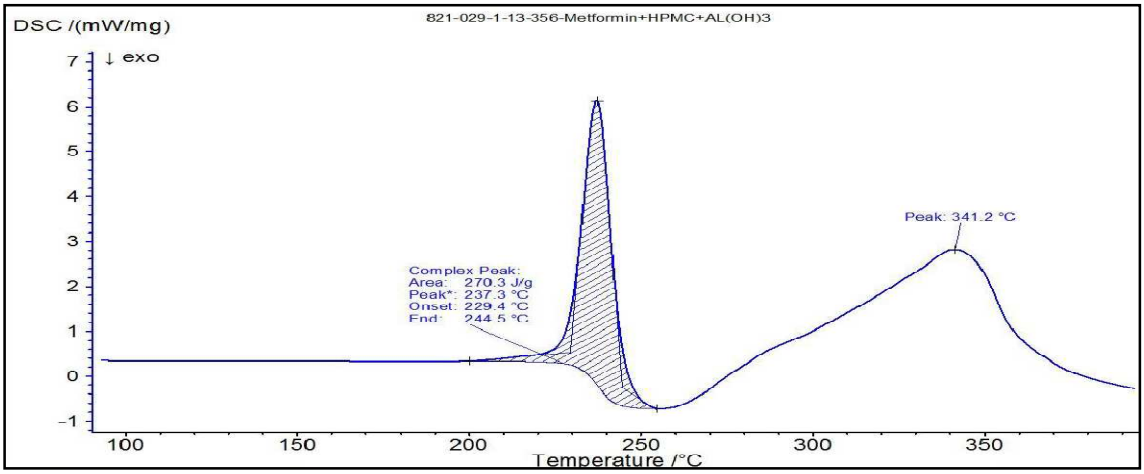
Figure 6: FTIR Spectra of a) Pure drug b) M6 c) M9 d) M12



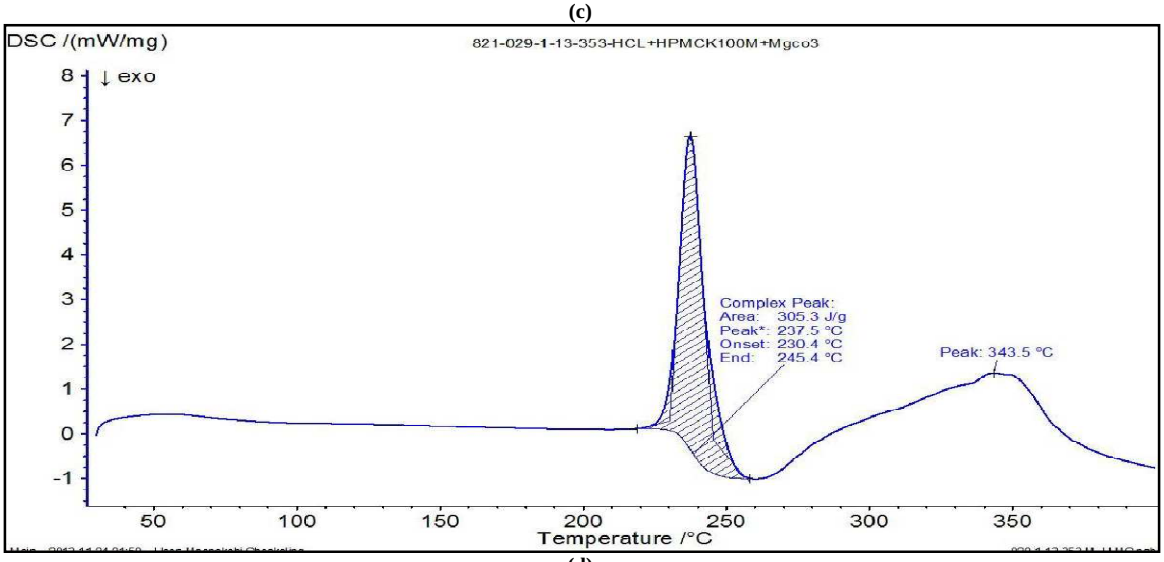
(a)



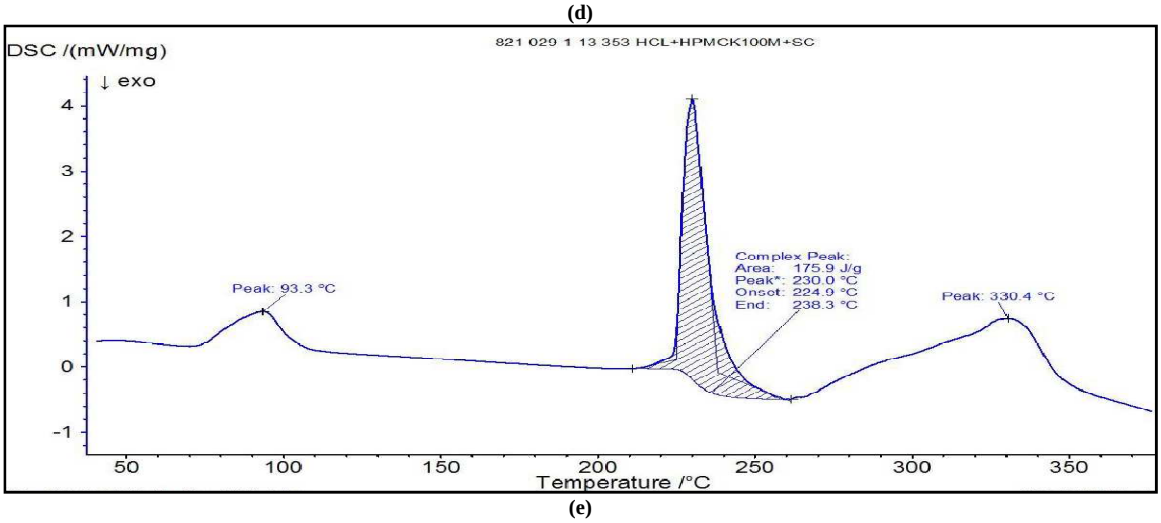
(b)



(c)



(d)



(e)

Figure 7: DSC Thermograms (a) Pure Drug (b) HPMC K100 M (c) M6 (d) M9 (e)M12

It appears that electrolyte induced buffer threshold within the matrix place an essential role in effective interaction with drug and textural changes. Further it may be due to higher p^{Ka} values of electrolytes, which can display higher buffer threshold for maintaining suitable p^{H} values greater than 7.0 might exert better and desired control on drug

release from matrix tablet. The following mechanism may prevail during the period of drug release from the swollen intragel structure. As the dissolution medium enters the periphery of the tablet, there is a rapid electrolyte water interaction with significant chemical reaction through electrolyte solubilisation and subsequent events that may lead to both initial suppression and later enhancement of polymer swelling. During this infiltration process, the electrolyte present in the gel boundary could have been converted to chloride form (for example sodium carbonate and sodium chloride) due to which the hydrochloride form of metformin HCl lead to the formation of free base of Metformin.

The formation of free base might cause matrix stiffening. The passive and actively formed electrolytes within the gel matrix would compete for water leading to dehydration of polymer molecules, thus leading to suppression of initial swelling which was seen up to 2 to 3 hours with formulations containing high concentration of electrolytes. After 3 hours the water attracted by electrolytes in to the polymer matrix could result in solubilising the drug molecules which would diffuse by penetration of leading to enhancement of swelling. The swelling index characteristics of various matrix tablets were given in table-5. From these alterations and mechanisms of intragel changes, it appears possibility to inhibit drug dissolution rate. This inhibition in dissolution rate appears to be a time-dependent phenomenon. Since as more water enters the gel matrix layer- by- layer, the electrolytes and their by products are diluted and any drug base may revert to its hydrochloride form, which is subsequently released.

CONCLUSION

This work has provided a novel and a simple approach to formulate controlled release formulations for delivery of metformin HCl over an extended time period. An important feature of this system the potential for generating constant drug release. The formulations M6, M9 & M12 were found to extend the drug release over an extended period of time. Hence these formulations were found to be suitable for once a day matrix tablet administration for treating the depression patients.

Acknowledgements
The authors express their gratitude to Dr. Reddy labs, Hyderabad, and MS/Colorcon Asia limited, Mumbai, for providing the gift samples. The authors are thankful to the management of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur for providing the facilities to carry out the research work.

REFERENCES

[1] Chien YW. Concepts and system design for Rate-controlled drug delivery. *In: Novel Drug Delivery Systems*. 2 nd ed. New York: Marcel Dekker, **1992**, pp 1-38.
[2] Singh BN, Kim KH, *J Control Release*, **2000**, 63, 235-59.
[3] Brazel CS, Peppas NA, *Mater Res Soc Symp Proc*,**1994**, 331, 211-6.
[4] HayashidaT, Kikumaru K, Tomoyukio. US Patent No., 593 694, **1997**.
[5] Conte U, La Manna A, Maggi L. US Patent No., US 5, **1997,** 626 874.
[6] Fassihis R, Yang L. US Patent No., US 5, **1998**, 783 212.
[7] Siepmann J, Ainaouli A, Vergnaud JM, Bodmeler R. *J Pharm SCI*, **1998**, 87, 827.
[8] Klip A and Leiter La, *Diabetes Care*, **1990**, 13, 696-704.
[9] Dunn CJ and Peters DH. *In Drugs*, **1996**, 49, 721-749.
[10] Scheeri Aj, Clinical Pharmacokinetics of Metformin. *Clin Pharmacokinetic*, **1996**, 30, 359-71.
[11] Vidyadhara S, Babu JR, Krishna TB. *Asian J Pharm*, **2011**, 5, 28-32.
[12] Vidyadhara S, Umamaheshwar Rao V, Siva Prasad S, Babu Naik M, Sravani T. *Current Trends in Bio Technology and Pharmacy*, **2013**, 7, 665-672.
[13] Pillay V, Fassihi R.US Patent Appl, **1998,** 09/037 096.
[14] Vidyadhara S, Rao PR, Prasad JA, *Indian J Pharm Sci*, **2004**, 66, 188-92.