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Sustained Release of Metformin HCl from Hydroxy Propyl Methyl Cellulose Matrices: Formulation and *in vitro* Evaluation

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Sustained release formulation of metformin HCl presents significant challenges due to its poor inherent compressibility, high dose and high water solubility. Sustained release matrix tablets of metformin HCl were formulated using different grades of hydroxy propyl methyl cellulose (HPMC) (HPMC K 4 M, HPMC K 15 M and HPMC K 100 M) by non-aqueous wet granulation method. The granules were evaluated for angle of repose, bulk density, compressibility index and total porosity. The tablets were subjected to thickness, weight variation test, drug content, hardness and friability. *in vitro* release studies were carried out at 0.1 N HCl and phosphate buffer of pH 6.8 using the apparatus I (basket) equipment as described in the USP 24/NF dissolution monograph. The granules showed satisfactory flow properties, compressibility and drug content. There was no significant difference in drug release for different viscosity grade of HPMC with same concentration. Release kinetics was evaluated using the regression coefficient analysis. All the formulations exhibited diffusion-dominated drug release and followed Higuchi release kinetics. Tablet thus formulated provided sustained release of metformin HCl over a period of 8 h.

Key Words: Metformin HCl, Hydroxy propyl methyl cellulose, Sustained release, Matrix tablet.

INTRODUCTION

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations.

Hydrophilic polymer matrix is widely used for formulating a SR dosage form[1-4]. There have been many studies demonstrating that the drug release profile from a hydrophilic matrix tablet is influenced by the viscosity of the gel layer formed due to its polymer hydration[5,6]. Various other factors like water-solubility and particle size of the drug, particle size and type of the polymer, type of diluents used and temperature of the release media are also responsible factors for effective drug release[7-9].

HPMC is the widely used swellable polymers used to prolong drug release due to its rapid hydration, good compression and gelling characteristics along with its ease of use, availability and low toxicity. It regulates the release of drug by controlling the swelling and cross-linking[10,11].

Metformin HCl is an orally administered biguanide, which is widely used in the management of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action[12]. It improves hepatic and peripheral tissue sensitivity to insulin without the problem of serious lactic acidosis commonly found with its analogue, phenformin. It has three different actions; (a) it slows the absorption of sugar in our small intestine; (b) it also stops our liver from converting stored sugar into blood sugar and (c) it helps our body use our natural insulin more efficiently. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract and the absolute bioavailability of a single 500 mg dose is reported[13] to be 50-60 %. 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. The compound has also relatively short plasma elimination half-life of 1.5 to 4.5 h[14,15]. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. Sustained release formulation that would maintain plasma levels of drug for 8-12 h might be sufficient for once daily dosing for metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance[13,16].

Palmer *et al.*[17] of Colorcon Ltd., UK has described the method for preparation of metformin HCl 500 mg extended release tablet by direct compression method. But in commercial scale it creates problem of powder flow ability from hoper to compression machine followed by weight variation, content uniformity, hardness and friability due to poor inherent compressibility of metformin HCl.

Sustained release microcapsules of metformin by ethylcellulose had been described by Balan *et al.*[14] where metformin gave *in vitro* release for up to 22 h. But preparation of microcapsules in commercial scale and optimization of drug release rate is troublesome. Defang *et al.*[15] described the bilayer matrix tablet and osmotic pump tablet consisting metformin and glipizide both as SR form. The aim of this investigation was to formulate a sustained release matrix tablet of metformin HCl, a water soluble drug from a HPMC matrix using different grades of HPMC by non-aqueous wet granulation method and optimization of formulation parameters through *in vitro* release of the drug from the matrix.

EXPERIMENTAL

Metformin HCl was received from Deys Medical, Kolkata, India as donation. Hydroxypropyl methyl cellulose (HPMC K 4 M, HPMC K 15 M and HPMC K 100 M) was a gift sample received from M/s Colorcon Asia Pvt. Ltd., Mumbai, India. Microcrystalline cellulose (MCC) and PVP K30 (polyvinyl pyrrolidone K30) were purchased from SD Fine Chemicals Ltd., Mumbai, India. Magnesium stearate and talc were procured from Mohanlal Dayaram and Company, Hyderabad, India. All other chemicals/reagents used were of analytical grade, except for those used in HPLC analysis, which were of HPLC grade (Merck India Ltd., Bombay).

Preparations of matrix tablets: Sustained release matrix tablets, each containing 500 mg of metformin HCl were prepared by conventional non-aqueous wet granulation method employing HPMC of different grades as matrix forming polymer. The detailed compositions of those tablet formulations are given in Table-1. HPMC polymer at different ratio was blended with metformin HCl, MCC and PVP K30 in a planetary mixer for 5 min after passing all the materials through a mesh (1150 μm). There after the powders were granulated with isopropyl alcohol, sieved using a mesh (100 μm) and dried at 50 ºC for about 2 h with residual moisture content of 2 to 3 % w/w. The dried granules were sized by a mesh (250 μm) and mixed with magnesium stearate and talc for 2 min. All granules were weighed finally to adjust the final weight of individual tablet considering its loss during operational handling.

TABLE-1
COMPOSITION OF VARIOUS FORMULATION OF
METFORMIN SUSTAINED RELEASE MATRIX TABLET

Ingredients	Formulation code							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Metformin HCl	500	500	500	500	500	500	500	500
HPMC K 15 M	150	300	360	–	–	180	180	120
HPMC K 4 M	–	–	–	360	–	180	–	120
HPMC K 100 M	–	–	–	–	360	–	180	120
PVPK 30	100	100	100	100	100	100	100	100
MCC	215	65	5	5	5	5	5	5
Talcum powder	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight	975	975	975	975	975	975	975	975

(All quantities given in mg)

Granules thus obtained were compressed into 975 mg tablets to average hardness of 7 to 8 kg/sq.cm on an 8 station rotary tablet machine (CIP Machineries Pvt. Ltd., Ahmedabad, India) with 19.5 × 8.9 mm caplet tooling at a rotational speed of 72 rpm.

Evaluation of granules

Angle of repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. Angle of repose was calculated using the following equation[18]

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

where, h and r are the height and radius of the powder cone.

Bulk density: Booth loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each trial formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas[19]

LBD = Weight of the powder/volume of the packing

TBD = Weight of the powder/tapped volume of the packing

Compressibility index: The compressibility index of the granules was determined by Carr's compressibility index[20]

$$\text{Carr's index (\%)} = [(TBD - LBD) \times 100]/TBD$$

Total porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V)[21]

$$\text{Porosity (\%)} = (V_{bulk} - V)/V_{bulk} \times 100$$

Tablet characterization: The tablets were characterized immediately after preparation. The weight variation of the tablets was evaluated on 20 tablets according to official method[22] using an electronic balance (Sartorius GC 103). Friability was determined using 10 tablets in a Roche friabilator for 4 min at a speed of 25 rpm. For each formulation the hardness of 10 tablets was also evaluated using a Monsanto hardness tester (Campbell electronics, India). The thickness of the tablets was measured on 10 tablets with a vernier caliper (Mitutoyo, Japan).

Drug content studies: 20 Tablets were taken and crushed to powder with mortar and pestle. Exact amount of powder equivalent to 100 mg metformin was taken and diluted with methanol up to 100 mL of volumetric flask. After sonication for 15 min, solution was filtered through 0.45 μm filter paper. The total amount of drug within the tablets was analyzed after appropriate dilution of test solution by using the HPLC method as

described above against the reference solution of metformin pure powder prepared in the same procedure. The drug extracted from the tablets was intact; no degradation products were detected in the extraction solution with the HPLC method.

Drug release study: Drug release from 6 tablets of each formulation was determined using the USP I (basket) apparatus (Electrolab, TDT 06P, USP XXIII) where 900 mL of 0.1 N HCl and phosphate buffer of pH 6.8 were used as dissolution media maintained at 37 ºC (± 0.5 ºC) at a paddle rotation speed of 100 rpm. 5 mL of aliquot were withdrawn at 1, 2, 4 and 8 h. with replacement of 5 mL fresh media. The release rates from the tablets were conducted in a dissolution medium of 0.1 N HCl for 2 h and thereafter in phosphate buffer of pH 6.8 for 6 h. Solution samples were analyzed by high performance liquid chromatography (HPLC) method as described below:

Column:	Hypersil BDS C18 (250 × 4.6 mm, 5 µm particle size)
Mobile phase:	10 m mol phosphate buffer of pH 6.0: Acetonitrile = 50: 50 (v/v)
Detector:	UV detection with 232 nm
Loop size:	20 µL

Calculation of theoretical release profile of metformin from sustained release formulations: The total dose of metformin for once-daily sustained release formulation was calculated by the following equation[23] using available pharmacokinetic data[15]:

$$D_t = \text{Dose}\ (1 + 0.693 \times t/t_{½})$$

where, D_t = total dose of drug; Dose = dose of the immediate release part; t = time (h) during which the sustained release is desired (8 h); $t_{½}$ = half-life of the drug (4 h).

$$D_t = 175.6\ (1 + (0.693 \times 8)/3) \cong 500$$

Hence, the formulation should release 175.6 mg in 1 h like conventional tablets and 46.3 mg per h up to 8 h there after.

Release kinetics: To study the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations:

$$\text{Zero-order equation: } Q_t = Q_0 + k_0 t \quad (1)$$

where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k_0 is the zero order release rate.

$$\text{First-order equation: } \ln Q_t = \ln Q_0 + k_1 t \quad (2)$$

where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

$$\text{Higuchi's equation}[24]\text{: } Q = k_H t^{½} \quad (3)$$

where, Q is the amount of drug release at time t and k_H is the Higuchi diffusion rate constant.

Koresmeyer *et al.*[25] equation: $M_t/M_\infty = Kt^n$ (4)

where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time and k is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the drug release mechanism.

RESULTS AND DISCUSSION

Metformin HCl is highly water soluble with poor inherent compressibility. Moreover its high dose (500 mg) poses a significant challenge for developing a sustained release dosage form. For obtaining a desirable drug release profile, cost effectiveness and broader regulatory acceptance HPMC was chosen as release controlling polymer.

Evaluation of granules: Granulation is the key process in the production of tablet dosage form involving the sustained release of a drug from coated or matrix-type particles. Physical properties such as specific surface area, shape, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous system[26].

The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index and total porosity (Table-2). The results of angle of repose (< 30) indicate good flow properties of granules[20,21]. This was further supported by lower compressibility index values (Table-2). Generally compressibility index values up to 15 % result in good to excellent flow properties[20]. Granule density, porosity and hardness are

TABLE-2
PROPERTIES OF THE GRANULATION

Formulation code	Angle of repose	Loose bulk density (g/mL)	Tapped bulk density (g/mL)	Compressibility index (%)	Total porosity (%)
F_1	29.32 ± 0.02	0.459 ± 0.04	0.532 ± 0.04	13.74 ± 0.03	25.48 ± 0.02
F_2	27.19 ± 0.03	0.436 ± 0.03	0.507 ± 0.02	14.02 ± 0.05	28.37 ± 0.03
F_3	26.65 ± 0.03	0.415 ± 0.05	0.486 ± 0.03	14.62 ± 0.02	24.31 ± 0.05
F_4	26.15 ± 0.02	0.420 ± 0.02	0.491 ± 0.05	14.48 ± 0.02	29.57 ± 0.03
F_5	26.55 ± 0.01	0.411 ± 0.06	0.483 ± 0.01	14.92 ± 0.03	27.22 ± 0.04
F_6	25.32 ± 0.02	0.427 ± 0.02	0.504 ± 0.03	15.29 ± 0.01	25.19 ± 0.04
F_7	26.54 ± 0.03	0.409 ± 0.02	0.480 ± 0.03	14.80 ± 0.02	30.40 ± 0.03
F_8	26.49 ± 0.04	0.417 ± 0.04	0.495 ± 0.04	15.78 ± 0.04	31.25 ± 0.05

All values are expressed as mean ± SE (Standard error), n = 6

often interrelated properties. In addition granule density may influence compressibility, tablet porosity, dissolution and other properties. The percentage porosity values ranged from 24.31 to 31.25 % indicating that the packing of the granules may range from close to loose packing and also confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26 % shows that the particles in the powders are of greatly different sizes and a value greater than 48 % shows that particles in the powder are in the form aggregates or flocculates[21]. All these results indicate that the granules processed satisfactory flow properties and compressibility.

Tablet characteristics and drug content: The tablets of different formulations were subjected to various evaluation tests such as thickness, hardness, friability and drug content test. The results of these parameters are given in Table-3. All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is ± 5 %. The average percentage deviation of all tablet formulations was found to be within the above limit and hence all formulations passed the uniformity of weight as per official requirements[22]. Good uniformity in drug content was found among different batches of tablets and the percentage of drug content was more than 95 %. Tablet hardness is not an absolute indicator of strength[26]. Another measure of a tablet's strength is friability. Conventional compressed tablet that lose less than 1 % of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations for all the formulations was below 1 %, indicating that the friability is within the prescribed limits[26].

TABLE-3
PHYSICAL PROPERTIES OF METFORMIN HCl 500 mg SR TABLETS

Formulation code	Weight variation† (%)	Friability‡ (%)	Hardness‡ (Kg/cm^2)	Thickness‡ (mm)	Drug content† (%)
F_1	0.50 ± 0.01	0.51 ± 0.01	7.00 ± 0.21	6.65 ± 0.02	97.85 ± 0.09
F_2	0.73 ± 0.02	0.62 ± 0.05	8.00 ± 0.15	6.63 ± 0.04	98.12 ± 0.05
F_3	0.58 ± 0.03	0.36 ± 0.03	8.00 ± 0.14	6.64 ± 0.03	96.98 ± 0.10
F_4	0.64 ± 0.04	0.17 ± 0.04	8.00 ± 0.34	6.64 ± 0.01	98.53 ± 0.15
F_5	0.83 ± 0.03	0.25 ± 0.06	7.00 ± 0.28	6.63 ± 0.05	96.65 ± 0.07
F_6	0.70 ± 0.04	0.11 ± 0.02	8.00 ± 0.19	6.65 ± 0.02	97.93 ± 0.12
F_7	0.39 ± 0.01	0.09 ± 0.03	8.00 ± 0.30	6.65 ± 0.04	98.02 ± 0.06
F_8	0.85 ± 0.03	0.19 ± 0.04	7.00 ± 0.33	6.64 ± 0.01	97.23 ± 0.11

†All values are expressed as mean ± SE (Standard error), n = 20.
‡All values are expressed as mean ± SE (Standard error), n = 10.

Dissolution studies

Dissolution samples were analyzed by HPLC method described earlier. The chromatogram showed the separation of metformin HCl at 2.367 min. Complete drug release of metformin occurred from bi-layer tablet within 8 h. HPMC is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content and the solubility of HPMC is pH independent[27].

The amount of HPMC polymer in the formulation was found to affect the metformin release rate significantly. Tablets prepared with smaller amounts of HPMC (75 mg per tablet) in the SR layer disintegrated slowly on dissolution medium leading to immediate drug release. From Fig. 1, it is evident that as the polymer content (HPMC K 15 M) in the formulation increases, the % of metformin release decreases and results more controlled release. The effect of variation of polymer type (different viscosity grade) on release profile of metformin from bi-layer matrix tablets (F_3, F_4 and F_5) is shown in Fig. 2. No significant difference was observed from the matrix tablet composed of different grades of HPMC (HPMC K 4 M, HPMC K 15 M and HPMC K 100 M) when the polymer content was kept constant. This observation is in good agreement with the literature[28-30]. Fig. 3 shows the effect of polymer mixture of different viscosity grades on release profile of metformin from bi-layer matrix tablets (F_3, F_6, F_7 and F_8) where no significant change in the release profile was observed.

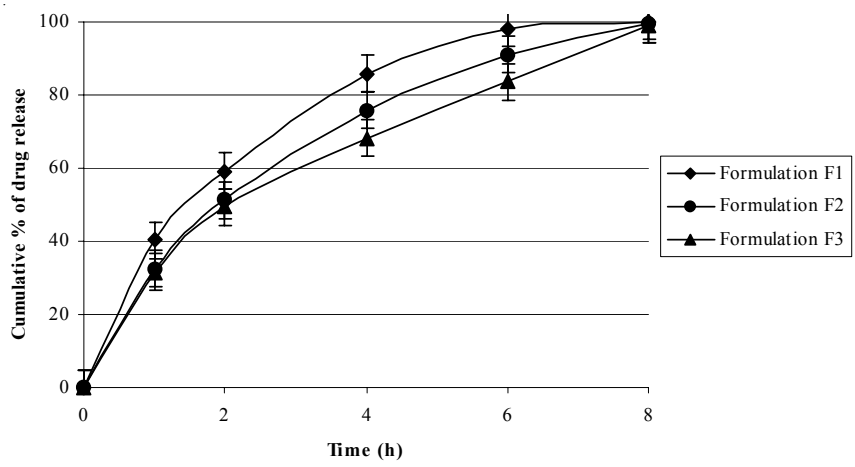

Fig. 1. Variation in release profile of metformin with polymer content from bi-layer matrix tablets (F_1, F_2 and F_3). Bars represent ± SD (n = 6)

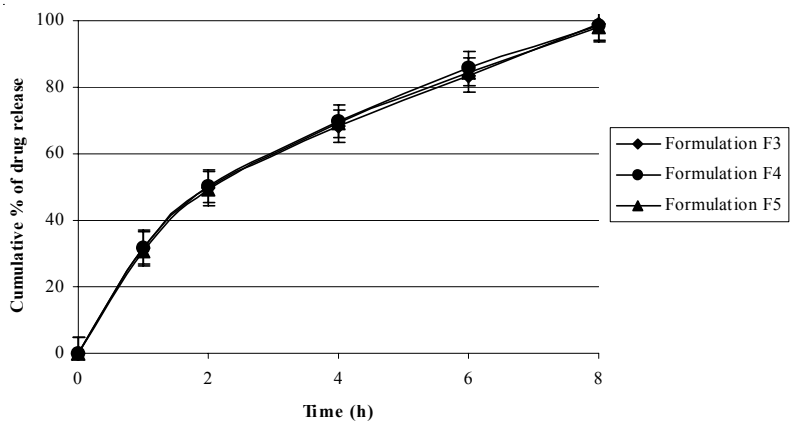

Fig. 2. Effect of variation of polymer type (different viscosity grade) on release profile of metformin from bi-layer matrix tablets (F_3, F_4 and F_5). Bars represent ± SD (n = 6)

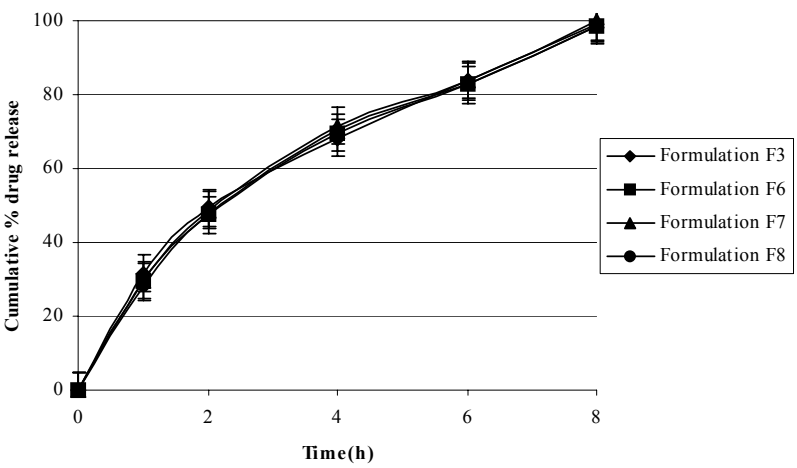

Fig. 3. Effect of polymer mixture on release profile of metformin from bi-layer matrix tablets (F_3, F_6, F_7 and F_8). Bars represent ± SD (n = 6)

The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain the whether it releases the drug in a predetermined manner[31]. According to the theoretical release pattern, a once daily metformin sustained-release formulation should release 175.6 mg in 1 h and 46.3 mg/h up to 8 h. Theoretically the metformin release should be 35, 44, 62, 80 and 100 % in 1, 2, 4, 6 and 8 h, respectively. In present experiments the average drug release from formulation F_3 to F_8 simulates the theoretical drug release. All the formulations showed the burst release (175.6 mg) of metformin in the initial hours, which

is probably due to faster dissolution of the highly water soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecule.

Drug release kinetics

To know the mechanism of drug release from these formulations, the data were treated according to first order (log cumulative percentage of drug released *vs.* time), Higuchi's (cumulative percentage of drug released *vs.* square root of time) and Korsmeyer *et al.*'s (log cumulative percentage of drug released *vs.* log time) equations along with zero order (cumulative percentage of drug release *vs.* time) pattern. In Table-4, the kinetic parameters for metformin HCl release from the HPMC matrix tablets (F_1-F_8) are presented. As clearly indicated from Table-4, the formulations did not follow zero-order or first-order release pattern. In present experiments the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation as the plots showed high linearity (R^2: 0.994 to 0.999, excluding F_1). Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square root kinetics or Higuchi's kinetics. To confirm the diffusion mechanism, the data were fitted into Korsmeyer *et al.*'s equation. For matrix tablets, an n value of near 0.5 indicates diffusion control and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion

TABLE-4
In vitro RELEASE KINETICS (ANALYSED BY REGRESSION COEFFICIENT METHOD) OF METFORMIN HCL FROM DIFFERENT TRIAL FORMULATIONS

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer	
				R^2	n
F_1	0.833	0.826	0.978	0.973	0.456
F_2	0.902	0.866	0.994	0.989	0.546
F_3	0.924	0.907	0.998	0.996	0.538
F_4	0.918	0.898	0.999	0.995	0.535
F_5	0.923	0.894	0.998	0.994	0.552
F_6	0.923	0.88	0.996	0.994	0.572
F_7	0.926	0.883	0.996	0.991	0.570
F_8	0.929	0.878	0.995	0.990	0.587

R^2 = Regression coefficient; n = Slope.

and erosion contribute to the overall release mechanism[32,33]. In present experiments the formulations showed good linearity (R^2: 0.989 to 0.996, excluding F_1), with slope (n) ranging from 0.535 to 0.587 indicating that the diffusion is the dominant mechanism of drug release from these formulations.

Conclusions

An extended release matrix tablet for metformin HCl, a potent candidate for oral treatment of type II diabetes, has been successfully prepared by the non-aqueous wet granulation method using different viscosity grade of HPMC that enabled desired drug release up to 8 h. This formulation will be further tested *in vivo* in an animal model for its pharmacokinetic and pharmacodynamic characteristics.

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REFERENCES

1. S. Vidyadhara, P.R. Rao and J.A. Prasad, *Indian J. Pharm. Sci.*, **66**, 188 (2004).
2. K.R. Reddy, S. Mutalik and S. Reddy, *AAPS Pharm. Sci. Tech.*, **4**, 1 (2003).
3. A.D. Mohammed, L.F. James, H.R. Michael, E.H. John and R.S.R. Ali, *Pharm. Dev. Tech.*, **4**, 313 (1999).
4. B.J. Lee, S.G. Ryu and J.H. Cui, *Drug Dev. Ind. Pharm.*, **25**, 493 (1999).
5. P.I. Lee, *J. Contr. Rel.*, **2**, 277 (1985).
6. P. Colombo, *Adv. Drug Del. Rev.*, **11**, 37 (1993).
7. D.L. Wise, Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, New York, p. 1 (2000).
8. N. Shufang, P. Weisan, L. Xiaodong and W. Xueming, *Drug Dev. Ind. Pharm.*, **30**, 627 (2004).
9. M. Levina and R.S.R. Ali, *J. Pharm. Sci.*, **93**, 2746 (2004).
10. Y.W. Chien, Novel Drug Delivery Systems, Marcel Dekker, New York (1992).
11. M.N.V.R. Kumar and N. Kumar, *Drug Dev. Ind. Pharm.*, **27**, 1 (2001).
12. B.J. Stith, M.L. Goalstone, R. Espinoza, C. Mossel, D. Roberts and N. Wiernsperger, *Endocrinology*, **137**, 2990 (1996).
13. C.J. Dunn and D.H. Peters, *Drugs*, **49**, 721 (1995).
14. G. Balan, P. Timmins, D.S. Greene and P.H. Marathe, *J. Pharm. Sci.*, **8**, 1176 (2001).
15. O. Defang, N. Shufang and L. Wei, *Drug Dev. Ind. Pharm.*, **31**, 677 (2005).
16. N.J. Montvale, Physicians' Desk Reference, edn. 53 (1999).
17. P. Fiona, L. Marina, R.S. Ali, Poster Reprint, Controlled Release Society Annual Meeting (June 2005).
18. J. Cooper and C. Gunn, Tutorial Pharmacy, CBS Publishers and Distributor, New Delhi, p. 211 (1986).
19. D. Shah, Y. Shah and M. Rampradhan, *Drug Dev. Ind. Pharm.*, **23**, 567 (1997).

20. M.E. Aulton and T.I. Wells, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone, London (1988).
21. A. Martin, Physical Pharmacy, Lippincott Williams & Wilkins, Baltimore, p. 423 (2001).
22. Pharmacopoeia of India, Ministry of Health and Family Welfare, Government of India, Controller of Publications, New Delhi (1996).
23. E.A. Rawlins, Bentley's Text Book of Pharmaceutics, Cassell and Collier Macmillan, London (1977).
24. W.I. Higuchi, *J. Pharm. Sci.*, **51**, 802 (1962).
25. R.W. Korsmeyer, R. Gurny, E.M. Doelker, P. Buri and N.A. Peppas, *Int. J. Pharm.*, **15**, 25 (1983).
26. L. Lachman, H.A. Liberman, The Theory Practice of Industrial Pharmacy, Varghese Publishing House, Mumbai, p. 293 (1987).
27. J.E. Hogan, *Drug Dev. Ind. Pharm.*, **15**, 975 (1989).
28. J.L. Ford, M.H. Rubinstein and J.E. Hogan, *Int. J. Pharm.*, **24**, 327, (1985).
29. M.C. Bonderoni, C. Caramella, M.E. Sangalli, U. Conte, R.M. Hernadez and J.L. Pedraz, *J. Contr. Rel.*, **18**, 205 (1992).
30. R.M. Franz, J.A. Systma, B.P. Smith and L.J. Lucisano, *J. Contr. Rel.*, **5**, 159 (1987).
31. S. Mutalik and D. Hiremath, *The Eastern Pharmacist*, **2**, 109, (2000).
32. R.A. Fassihi and W.A. Ritschel, *J. Pharm Sci.*, **82**, 750 (1993).
33. N.A. Peppas, *Pharm. Acta Helv.*, **60**, 110 (1985).

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