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Formulation and In Vitro Studies of a Fixed-Dose Combination of a Bilayer Matrix Tablet Containing Metformin HCl as Sustained Release and Glipizide as Immediate Release

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The emerging new fixed dose combination of metformin hydrocholride (HCl) as sustained release and glipizide as immediate release were formulated as a bilayer matrix tablet using hydroxy propyl methyl cellulose (HPMC) as the matrix-forming polymer, and the tablets were evaluated via in vitro studies. Three different grades of HPMC (HPMC K 4M, HPMC K 15M, and HPMC K 100M) were used. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. In vitro release studies were carried out at a phosphate buffer of pH 6.8 with 0.75% sodium lauryl sulphate w/v using the apparatus I (basket) as described in the United States Pharmacopeia (2000). The release kinetics of metformin were evaluated using the regression coefficient analysis. There was no significant difference in drug release for different viscosity grade of HPMC with the same concentration. Tablet thus formulated provided sustained release of metformin HCl over a period of 8 hours and glipizide as immediate release.

Keywords fixed dose combination; metformin HCl; glipizide; sustained releaser; matrix tablet

INTRODUCTION

Certain pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. This can be done by a regimen in which the patient follows a prescribed time schedule, but because of patient noncompliance, scrupulous adherence to a schedule often requires the assistance of a medical professional. Even those therapies that involve only two dosages, such as an immediate but rapidly declining high-level dosage combined with a prolonged low-level or moderate level dosage, either of the same drug or of two different drugs, can be a nuisance to the individual or troublesome to maintain if the individual is required to take separate unitary dosage forms. Certain pharmaceutical formulations have therefore been developed that combine both functions into a single dosage form. This simplifies the therapy and reduces or eliminates the chances of improper administration.

Type 2 diabetes is a progressive illness and most patients will eventually need more than two oral agents to maintain adequate glucose control (Tripathi, 2004). Switching from one drug to another in a patient with poorly controlled glycemia or maximizing the dosage of an existing drug is only rarely hopeful. Adding medications from different groups to the existing regimen often provides more effective glycemic control. Several of the available oral agents have been studied in combination and have been shown to further improve glycemic control when compared with monotherapy.

Metformin hydrochloride (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 (Stith et al., 1996). It improves hepatic and peripheral tissue sensitivity to insulin without the problem of serious lactic acidosis commonly found with its analog, phenformin. It has three different actions: it slows the absorption of sugar in the small intestine; it also stops the liver from converting stored sugar into blood sugar; and it helps the body use its 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 to be 50% to 60% (Dunn & Piters, 1995). 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 also has relatively short plasma elimination half-life of 1.5 to 4.5 hours (Defang, Shufang, & Wei, 2005; Scheen, 1996). 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

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would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin. In particular, SR formulation that releases metformin for 8 to 12 hours may be suitable for once-daily dosing. SR products are needed for metformin to prolong its duration of action and to improve patient compliance (Medical Economics Co., 1999; Dunn & Peters, 1995).

Glipizide is an oral antidiabetic drug of the sulfonylurea class that is used together with diet and exercise to reduce blood glucose in patients with type 2 diabetes. It stimulates the release of insulin from the pancreas, directing the body to store blood sugar (Siconolfi-Baez, 1990).

A glipizide and metformin combination is used to treat high blood sugar levels that are caused by type 2 diabetes. Normally, the pancreas releases insulin after eating to help the body store excess sugar for later use. This process occurs during normal digestion of food. In type 2 diabetes, the body does not work properly to store the excess sugar and the sugar remains in the bloodstream. Chronic high blood sugar can lead to serious health problems in the future. With two different modes of action, the combination of glipizide and metformin help the body cope with high blood sugar more efficiently.

Conventional tablets containing a fixed dose of metformin HCl and glipizide are widely available in the market. SR microcapsules of metformin by ethylcellulose are described by Balan and colleagues (2001), where metformin gave in vitro release for up to 22 hours. Defang and colleagues (2005) describe the bilayer matrix tablet and osmotic pump tablet consisting of metformin and glipizide, both as SR form. An alternative approach for effective control of blood glucose is to manufacture oral dosage forms delivering both immediate-release (IR) and SR antidiabetic drugs from single-dosage form. Based on this concept one patent was filed (Lim & Shell, 2004) where tablets containing 500 mg metformin HCl as SR and 2.10 mg of glimepiride as IR were made. Hsieh and colleagues (2006) describe one clinical study where it was shown that SR glipizide was as effective as IR dosage form of the same.

The aim of the current research work is to develop and optimize a bilayer antidiabetic matrix tablet containing metformin HCl as SR in one layer, using different grades of hydroxy propyl methyl cellulose (HPMC) by nonaqueous wet granulation method, and glipizide as IR from the remaining layer. Immediate action of glipizide will be helpful to control excess sugar, which will be maintained by metformin action later on. Thus, the developed single tablet will be sufficient instead of three to four tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy.

MATERIALS AND METHODS

Materials

Metformin HCl and glipizide were received from Deys Medical, Kolkata, India, as a donated sample. HPMC (HPMC K 4M, HPMC K 15M, and HPMC K 100M) was a gift sample received from M/S Colorcon Asia Pvt. Ltd., Mumbai, India. Starch, polyvinyl pyrrolidone K-30 (PVP K30), lactose, citric acid, sodium bicarbonate, and erythrosine lake were purchased from S. D. 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 high-performance liquid chromatography (HPLC) analysis, which were of HPLC grade.

Methods

Tablet Preparation

Nonaqueous wet granulation technology was used for granules of the SR layer containing metformin HCl whereas granules of the IR layer containing glipizide were prepared by aqueous wet granulation technology. For both the layers, granulation technology is described separately, as follows:

Granulation of the SR Layer

Detailed compositions of different trial formulations for the SR layer is given in Table 1. HPMC polymers at different ratios were blended with metformin HCl, microcrystalline cellulose (MCC), and PVP K30 in a planetary mixer for 5 minutes after passing all the materials through a mesh (1150 μm) screen. Thereafter, the powders were granulated with isopropyl alcohol, sieved using a mesh (100 μm) screen, and dried at 40°C for about 2 hours with a 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 minutes. Finally, all granules were weighed to adjust the final weight of the individual tablet taking into consideration its loss during operational handling. The final weight of each trial formulation was kept at 950 mg.

Granulation of the IR layer

Composition of the IR layer is given in table 2. The final weight of the IR layer was fixed to 200 mg. Glipizide, lactose, and erythrosine lake were passed through a mesh (1150 μm) and blended in a planetary mixer for 5 minutes so that the distribution of erythrosine lake throughout the mass was uniform. The mixture was granulated using starch paste, sieved using a mesh (100 μm) and dried at 50ºC for about 3 hours with residual moisture content of 2% to 3% w/w. The dried granules were sized by a mesh (250 μm) and mixed with citric acid, sodium bicarbonate, talcum powder, and magnesium stearate for 2 minutes.

Final Compression of Bilayer Tablets

Granules of both layers thus obtained were compressed into 1150-mg bilayer tablets to an average hardness of 7 to 8 kg/ cm^2 on a 16-station double rotary tablet punching machine (RDB3B-27; Riddhi Pharma Machinery Ltd., India) with

TABLE 1
Composition of Various Trial Formulations for the SR Layer Containing 500 mg Metformin HCl (All Quantities Given in mg)

	Formulation Code							
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCl	500	500	500	500	500	500	500	500
HPMC K 15M	150	300	360			180	180	120
HPMC K 4M				360		180		120
HPMC K 100M					360		180	120
PVPK 30	75	75	75	75	75	75	75	75
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	950	950	950	950	950	950	950	950

TABLE 2
Composition of the IR layer (Formulation code IR) Containing 5 mg Glipizide

Ingredients	Amount (mg)
Glipizide	5
Starch	20
Lactose	169
Citric acid	1
Sodium bicarbonate	2
Talcum powder	1
Magnesium stearate	1
Erythrosine lake	1
Total weight	200

19.5×8.9 mm caplet tooling at a rotational speed of 35 rpm. Formulation code for the final bilayer tablet was named F1 to F8 where composition of F1 is SR1 for the SR layer and IR1 for the IR layer (Fn = SRn+IRn, where n = 1 to 8).

Tablet Characterization

The tablets were characterized immediately after preparation. The weight variation of the tablets was evaluated on 20 tablets using an electronic balance (Sartorius GC 103). Friability was determined using 10 tablets in a Roche friabilator for 4 minutes 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 Calipter (Mitutoyo, Japan).

Drug Content Studies

Twenty tablets were taken and crushed to powder with a mortar and pestle. The exact amount of powder (around 1150 mg) was taken and diluted with methanol up to 200 ml of volumetric flask. After sonication for 15 minutes, the solution was filtered through 0.45-µm filter paper. The total amount of drug within the tablets was analyzed after appropriate dilution of the test solution by using the HPLC method as described below against the reference solution of metformin and glipizide pure powder prepared in the same procedure.

Chromatographic parameters:

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

Stock solutions of metformin HCl and glipizide were prepared in methanol as 1 mg/ml.

A seven-point standard curve was prepared for each of the analytes after appropriate dilution of stock solutions to obtain final concentrations of 0.1, 0.5, 1, 2, 5, 10, and 20 mcg/ml for metformin HCl and 0.1, 0.2, 0.5, 1, 2, 5, and 10 mcg/ml for glipizide. The standard curve was prepared taking the peak area of the analyte (metformin HCl or glipizide) versus the concentration (mcg/ml) using a weighted ($1/concentration^2$) linear least-squares regression as the mathematical model. The regression equation of the calibration curve was then used to calculate the drug content and in vitro drug release. The lowest limit of quantitation for metformin HCl and glipizide was determined from the peak signal to noise level (S/N) as 10.

Drug Release Study

Drug release from the tablet formulations was determined using the USP I (basket) apparatus (Electrolab, TDT 06P, USP XXIII). A phosphate buffer of 900 ml with a pH of 6.8 with 0.75% w/v sodium lauryl sulphate (SLS) was used as a dissolution media maintained at 37ºC (± 0.5ºC) at a rotational speed of

100 rpm. Six tablets were tested for each formulation. Dissolution Samples were analyzed by HPLC method described earlier in the section ("Drug Content Studies").

Calculation of the Theoretical Release Profile of Metformin From Bilayer Tablets

The total dose of metformin for a once-daily SR formulation was calculated by the following equation (Rawlins, 1977) using available pharmacokinetic data (Defang et al., 2005):

$$D_t = \text{Dose}\,(1 + 0.693 \times t/t_{1/2})$$

Where, D_t = total dose of drug; Dose = dose of the IR part; t = time (hr) during which the SR is desired (8 hr); and $t_{1/2}$ = half-life of the drug (3 hr).

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

Hence, the formulation should release 175.6 mg in 1 hour like conventional tablets and 46.3 mg per hour up to 8 hours thereafter.

Drug Release Kinetics

To study the mechanism of metformin release from the SR layer of 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.

$$\text{Higuchi s equation: } Q = k_H t^{1/2} \quad (3)$$

Where, Q is the amount of drug release at time t, and k_H is the Higuchi diffusion rate constant (Higuchi, 1962).

$$\text{Koresmeyer's equation: } M_t/M_\infty = Kt^n \quad (4)$$

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, 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 (Koresmeyer, Gurny, Doelker, Buri, & Peppas, 1983).

Stability Study

An accelerated stability study was conducted by storing tablets in amber bottles at ambient temperatures, 40°C and 50°C. A relative humidity of 75% was maintained throughout the study for all three temperatures. The content of the drugs and the dissolution of the drugs from the bilayer tablets were tested monthly for three months.

RESULTS AND DISCUSSION

Tablet Characteristics

The optimum weight of the IR layer was fixed to 200 mg for better release of glipizide as well as to maintain the optimum swallowable oral dosage form. An IR layer of less than 200 mg caused incomplete glipizide release due to sticking of the IR layer with the polymer of the SR layer. Erythrosine lake was used to differentiate two layers separately. Citric acid and sodium bicarbonate were used as minimally as possible to create optimum effervescence sufficient to prevent the sticking problem of the IR layer to the polymer of the SR layer. MCC, starch, and lactose were used as filler and PVPK 30 was used as a binder, whereas talc and magnesium stearate were used as lubricant. The tablets of different formulations were subjected to various evaluation tests such as thickness, hardness, friability, and drug content. The results of these parameters are given in Table 3. All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeial limit (United States Pharmacopeia, 2000) for the percentage deviation for tablets of more than 324 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 of the United States Pharmacopeia (2000). 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 (Banker & Ander, 1987). Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage of friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits (Banker & Ander, 1987).

Drug Release Study

Dissolution samples were analyzed by HPLC method described previously ("Materials and Methods"). For metformin HCl, the standard curves were linear over the concentration ranges of 0.1 to 20 mcg/ml and the correlation coefficient was 0.9995 (y = 230.61x + 23.243). For glipizide, the concentration ranges were 0.1 to 10 mcg/ml and the correlation coefficient was 0.9992 (y = 80.271x+1.989).

The lower limit of quantitation for metformin HCl was established as 50 ng/ml, its precision (CV%) and accuracy (%RE) values being 6.59% and +3.83%, respectively.

TABLE 3
Physical Properties of the Final Bilayer Tablets Containing 500 mg Metformin HCl as SR and 5 mg Glipizide as IR

Formulation Code	Weight Variation* (%)	Friability† (%)	Hardness† (kg/cm^2)	Thickness† (mm)	Drug Content*(%)	
					Glipizide	Metformin
F1	0.47 ± 0.02	0.38 ± 0.01	8.00 ± 0.25	7.45 ± 0.02	97.32 ± 0.08	98.18 ± 0.05
F2	0.69 ± 0.04	0.27 ± 0.05	8.00 ± 0.17	7.49 ± 0.04	98.41 ± 0.11	97.36 ± 0.03
F3	0.32 ± 0.04	0.42 ± 0.03	7.00 ± 0.32	7.50 ± 0.03	97.55 ± 0.23	97.75 ± 0.09
F4	0.24 ± 0.03	0.17 ± 0.04	7.00 ± 0.18	7.52 ± 0.01	98.68 ± 0.31	99.10 ± 0.23
F5	0.43 ± 0.02	0.21 ± 0.06	8.00 ± 0.27	7.48 ± 0.05	99.01 ± 0.12	98.23 ± 0.15
F6	0.21 ± 0.01	0.15 ± 0.02	8.00 ± 0.23	7.50 ± 0.02	98.75 ± 0.09	97.95 ± 0.08
F7	0.35 ± 0.05	0.19 ± 0.03	8.00 ± 0.35	7.56 ± 0.04	97.98 ± 0.05	98.13 ± 0.12
F8	0.55 ± 0.02	0.23 ± 0.04	7.00 ± 0.15	7.50 ± 0.01	97.98 ± 0.17	98.98 ± 0.14

*All values are expressed as $M \pm SE$, $n = 20$.
† All values are expressed as $M \pm SE$, $n = 10$.

The lower limit of quantitation for glipizide was established as 60 ng/ml, its precision (CV%) and accuracy (%RE) values being 5.27% and + 2.40% respectively.

Glipizide was sparingly soluble in a pH 6.8 phosphate buffer, which is why SLS (0.75% w/v) was used along with the phosphate buffer of pH 6.8 as dissolution medium for simultaneous release of metformin and glipizide. Figure 1 is the representative chromatogram of a dissolution sample showing separation of metformin HCl at 2.920 minutes and glipizide at 8.443 minutes. There is no interfering peak in the chromatogram and also the resolution between the two analyte peaks is good. Table 4 shows glipizide release from final formulations (F1 to F8). Complete glipizide release occurred within 1 hour, which supported the concept of IR from the bilayer tablet.

Complete release of metformin occurred from the bilayer tablet within 8 hours. 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/tablet) in the SR layer disintegrated slowly on dissolution medium, leading to immediate drug release. From Figure 2 it is evident that as the polymer content (HPMC K 15M) in the formulation increases, the percent of metformin release decreases, resulting in greater controlled release.

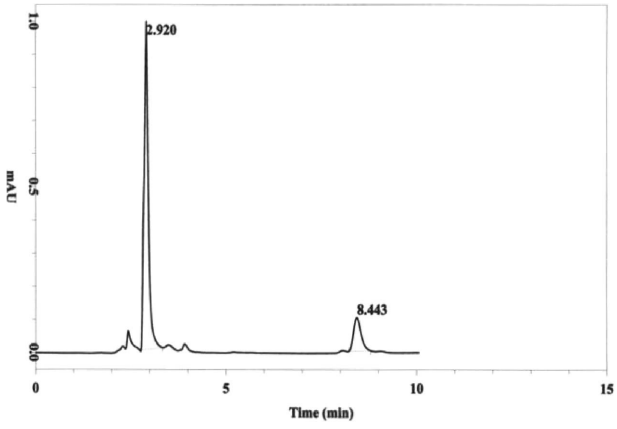

FIGURE 1. Representative chromatogram showing separation of metformin at 2.920 minutes and glipizide at 8.443 minutes.

TABLE 4
In Vitro Release of Glipizide from the Bilayer Matrix Tablets (F1–F8) after 1 Hour at a Phosphate Buffer of pH 6.8 with 0.75% SLS

Formulation Code	Glipizide Release after 1 Hour (%)
F1	92.91
F2	95.45
F3	93.75
F4	96.12
F5	94.83
F6	96.23
F7	95.59
F8	95.42

The effect of variation of polymer type (different viscosity grade) on the release profile of metformin from bilayer matrix tablets (F3, F4, and F5) is shown in Figure 3. No significant difference was observed from the matrix tablet composed of different grades of HPMC (HPMC K4M, HPMC K 15M, and HPMC K100M) when the polymer content was kept constant. This observation is in good agreement with the literature (Ford, Rubinstein, & Hogan, 1985; Bonderoni et al., 1992; Franz, Systma, Smith, & Lucisano, 1987). Figure 4 shows the effect of polymer mixture of different viscosity grades on the release profile of metformin from bilayer matrix tablets (F3, F6, F7, and F8) where no significant change in the release profile was observed.

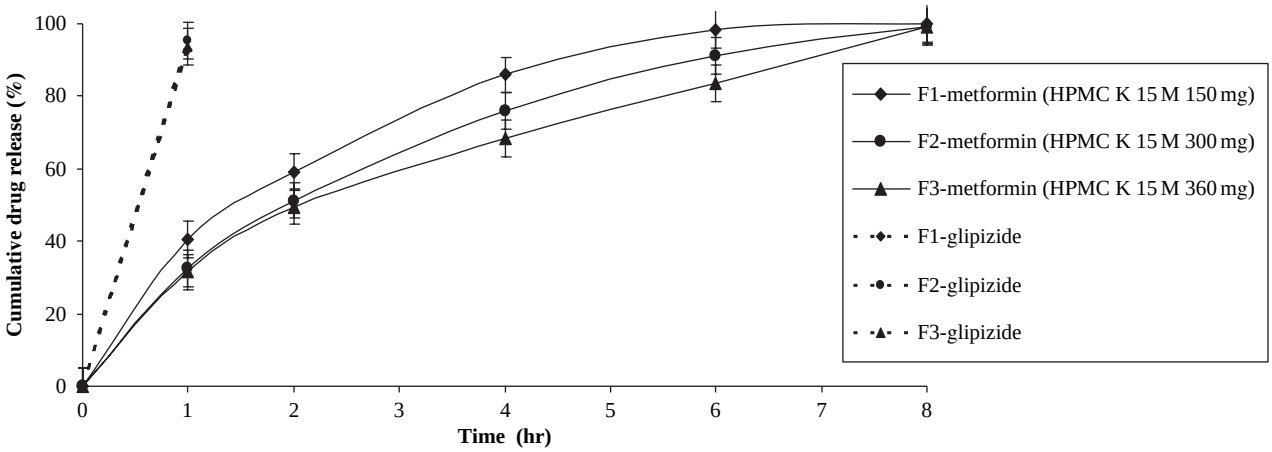

FIGURE 2. Variation in release profile of metformin with polymer content along with the release of glipizide from the bilayer matrix tablets (F1, F2, and F3; bars represent ± *SD* [*n* = 3]).

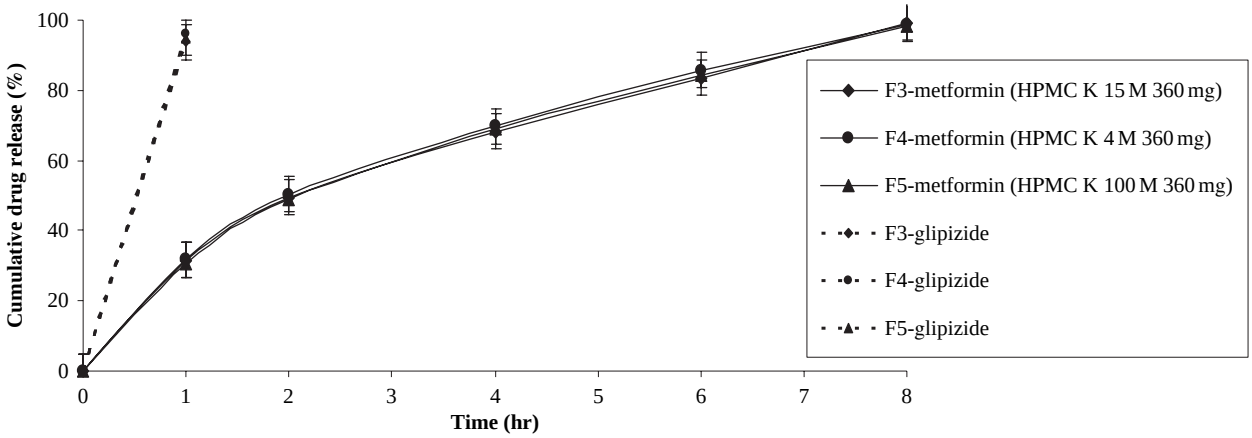

FIGURE 3. Effect of variation of polymer type (different viscosity grade) on release profile of metformin along with glipizide from the bilayer matrix tablets (F3, F4, and F5; bars represent ± *SD* [*n* = 3]).

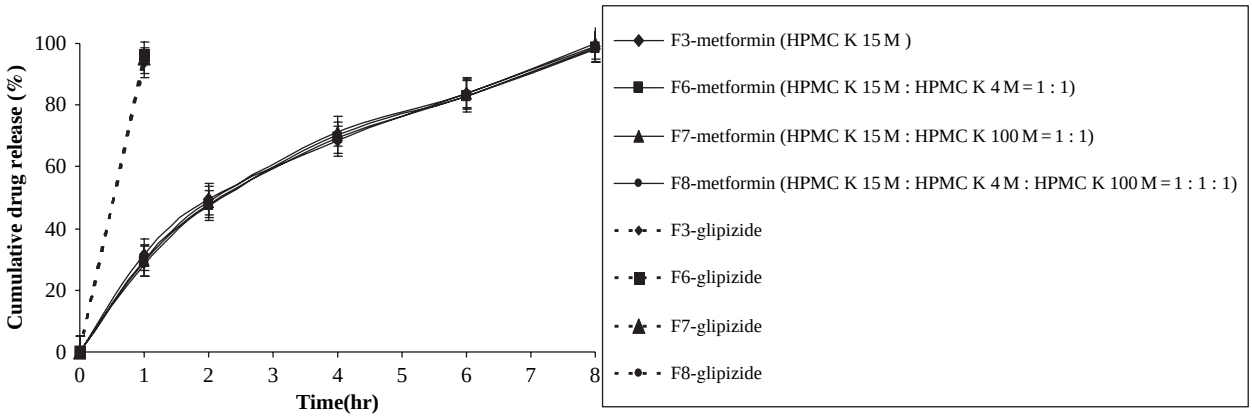

FIGURE 4. Effect of polymer mixture on release profile of metformin along with glipizide from the bilayer matrix tablets (F3, F6, F7, and F8; bars represent ± *SD* [*n* = 3]).

Metformin HCl is highly soluble in water with poor inherent compressibility. Moreover its high dose (500 mg) poses a significant challenge for developing an SR dosage form. For obtaining a desirable drug release profile, cost effectiveness, and broader regulatory acceptance, HPMC was chosen as the release-controlling polymer. 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 (Hogan, 1989).

Release Profile of Metformin from Bilayer Tablets

The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in a predetermined manner (Mutalik & Hiremath, 2000). According to the theoretical release pattern, a once-daily metformin SR formulation should release 175.6 mg in one hour and 46.3 mg per hour for up to 8 hours. Theoretically, metformin release should be 35%, 44%, 62%, 80%, and 100% in 1, 2, 4, 6, and 8 hours, respectively. In our experiments the average drug release from formulation F3 to F8 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 versus time), Higuchi's (cumulative percentage of drug released versus square root of time; 1962), and Korsmeyer's (log cumulative percentage of drug released versus log time 1983) equations, along with a zero-order (cumulative percentage of drug release versus time) pattern. In Table 5, the kinetic parameters for metformin HCl release from the HPMC matrix tablets (F1–F8) are presented. As clearly indicated from Table 5, the formulations did not follow zero-order or first-order release patterns. In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation (1962) as the plots showed high linearity (R^2: 0.996–0.999, 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 to as square root kinetics or Higuchi's kinetics. To confirm the diffusion mechanism, the data were fitted into Korsmeyer's equation (Korsemeyer et al., 1983). 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 and erosion contribute to the overall release mechanism (Fassihi & Ritschel, 1993; Peppas, 1985). In our experiments, the formulations showed good linearity (R^2: 0.992–0.999, excluding F_1), with the slope (n) ranging from 0.534 to 0.589, indicating that the diffusion is the dominant mechanism of drug release from these formulations.

Lot Reproducibility and Stability Tests

Three batches for each formulation of F3, F4, and F5 were prepared, and the dissolution rate of metformin HCl and glipizide was evaluated under the same conditions. The resulting release profiles of both drugs from these three different batches of each formulation showed no significant (standard deviation [*SD*] ± 0.06–0.19) difference in the drug release profiles,

TABLE 5
In vitro Release Kinetics (Analyzed by Regression Coefficient Method) of Metformin from the Bilayer Matrix Tablets (F1–F8)

Formulation Code	Zero-Order R^2	First-Order R^2	Higuchi R^2	Korsmeyer R^2	Korsmeyer *n*
F1	0.835	0.825	0.979	0.975	0.455
F2	0.905	0.868	0.996	0.990	0.548
F3	0.927	0.905	0.999	0.998	0.539
F4	0.919	0.899	0.997	0.997	0.534
F5	0.922	0.893	0.996	0.999	0.553
F6	0.925	0.883	0.998	0.995	0.574
F7	0.928	0.885	0.997	0.993	0.571
F8	0.931	0.874	0.996	0.992	0.589

R^2 = regression coefficient; *n* = slope.

indicating that the manufacturing process was reliable and reproducible.

The stability of metformin HCl and glipizide in these bilayer tablets was evaluated over three months at ambient temperatures of 40°C and 50°C for the F3, F4, and F5 formulations. Variation in the release profile of metformin was insignificant ($SD \pm 0.11$–1.5), as evident in Figure 5. Moreover, there was insignificant degradation (below 10%) for both drugs in three formulations, which is further confirmed by infrared spectrum of drug, polymer, and drug-polymer mixture, as shown in Figure 6.

CONCLUSION

SR fixed dose bilayer matrix tablets containing 500 mg metformin HCl as SR from one layer and 5 mg glipizide as IR from another layer have been successfully prepared by wet granulation method. HPMC used as matrix-forming polymer for the metformin layer enables desired drug release for up to 8 hours, whereas glipizide gives IR from the second layer. Among the different grades of HPMC investigated, no significant difference in the resulting metformin release profiles from the SR layer of the tablets was found. This indicates that the

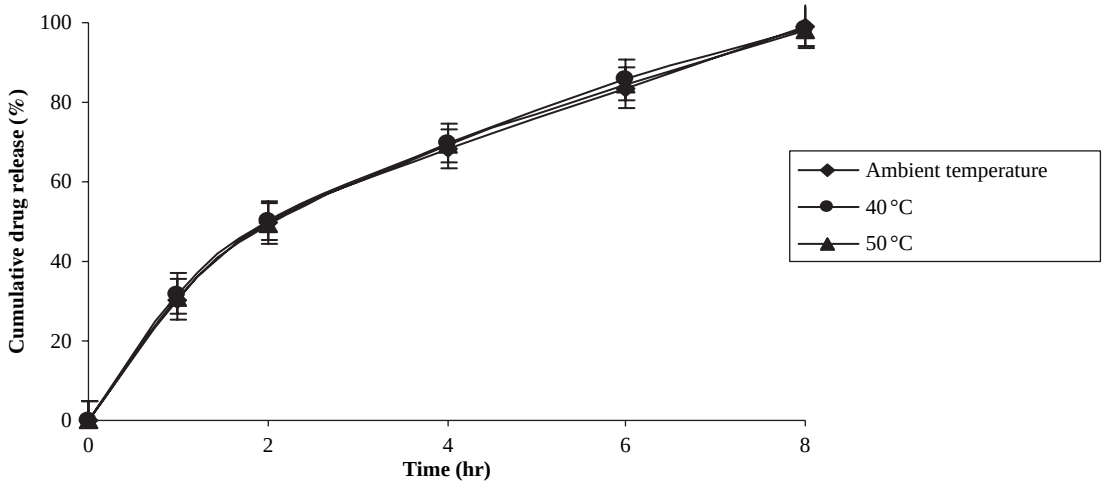

FIGURE 5. In vitro release profile showing insignificant variation in metformin release from the bilayer matrix tablets (F3, F4, and F5) with temperature (bars represent ± *SD* [*n* = 3]).

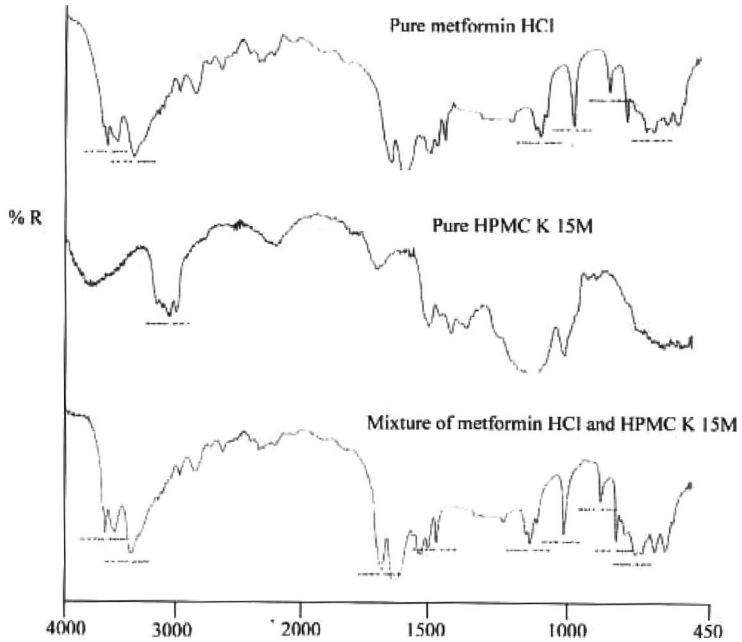

FIGURE 6. Fourier transform infrared spectra of (a) pure metformin HCl, (b) pure HPMC K 15M, and (c) mixture of metformin HCl and HPMC K 15M.

viscosity of the polymer does not affect drug release rate when the drug is water-soluble and the dose is high.

These formulations will be further tested in vivo in an animal model for their pharmacokinetic and pharmacodynamic characteristics as well as to establish optimum drug: polymer conditions leading to desired bioavailability.

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