Research Article

BILAYER TABLET FORMULATION OF METFORMIN HYDROCHLORIDE AND GLIPIZIDE: A NOVEL APPROACH IN THE TREATMENT OF DIABETES

J. Bagyalakshmi*, Y. Phani Krishna and T. K. Ravi.
College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, India.
*Corresponding author's E-mail: bagi_972003@yahoo.co.in

ABSTRACT

The emerging new fixed dose combination of Metformin Hydrochloride (HCl) as sustained release and Glipizide as immediate release were formulated as a bilayer matrix tablet. Metformin was formulated using Hydroxy Propyl Methyl Cellulose (HPMC) as the matrix forming polymer, and the tablets were evaluated for their physical characteristics and *in vitro* release. Three different grades of (HPMC K 4M, HPMC K15M, HPMC K100M) were used. *In vitro* release studies were carried out with a phosphate buffer of pH 6.8 using USP dissolution apparatus 2 (paddle). Tablet thus formulated using HPMC K100M provided sustained release of Metformin HCl over a period of 10 hours. Glipizide is a poorly water soluble (BCS class 2) antidiabetic drug. Due to the poor water solubility of this drug, its bioavailabilty is dissolution rate-limited. The purpose of this study is to increase the solubility of Glipizide by solid dispersion technique with sodium starch glycolate using the kneading method. The Glipizide-Sodium Starch Glycolate solid dispersion system was characterized by FT-IR and *in vitro* dissolution studies. *In-vitro* release studies were carried out with a phosphate buffer of pH 6.8 using USP dissolution apparatus 2 (paddle). Tablet thus formulated using drug and carrier at 1:8 ratio provided immediate release of Glipizide over a period of 10 minutes. SR fixed dose bilayer matrix tablets containing 500mg Metformin HCl as SR from one layer and 5mg Glipizide as IR from another layer can be prepared by solid dispersion method.

Keywords: Glipizide, Metformin hydrochloride, HPMC, bilayer tablet.

INTRODUCTION

Type 2 diabetes, a common disease that combines defects of both insulin secretion and insulin action. It is a progressive illness and most patients will eventually need more than two oral agents to maintain adequate glucose control[1]. Switching from one drug to another in a patient with poorly control 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 the combination and have been shown to further improve glycemic control when compared with monotherapy.

Metformin is the sole member of the biguanide class of medications in the United States. It replaced another biguanide, Phenformin, which was removed from the market because of a propensity for lactic acidosis in 1975[2, 3].

Metformin exerts its effects primarily by decreasing hepatic glucose output and has a comparatively lesser effect increasing insulin sensitivity. Isotope studies suggest hepatic glucose output is reduced primarily through inhibition of gluconeogenesis, which may be reduced by as much as 75%. In patients with normal renal function and who are otherwise healthy, Metformin does not increase plasma lactic acid levels or rate of turnover[4].

The major clinical effect of metformin is to decrease fasting glucose levels, thereby reducing hemoglobin A_{1c} (A1C). The degree of clinical effect varies in individual patients, but most patients experience a reduction in A1C of ~ 1.5 percentage points[5].

Lactic acidosis is a rare but potentially fatal complication of Metformin therapy. Incidence of this complication is very low: < 1 case per 100,000 treated patients[6].

Metformin is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestianl tract, and the absolute bioavailability of a single 500mg dose is reported to be 50% to 60%[7]. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occur during the initial weeks of treatment. The compound also has relatively short plasma elimination half life of 1.5 to 4.5 hours[8, 9].

Sustained-release formulations may be administered once or twice daily[10]. A sustained release formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once daily dosing of metformin. So SR formulation that releases metformin for 8 to 12 hrs may be suitable for once daily dosing. SR products are needed for metformin to prolong its duration of action and improve patient compliance[7,11].

Sulfonylureas include several medications that act on β-cells to increase insulin release. They bind to the sulfonylurea receptor on the surface of the β-cell and inhibit potassium efflux, thus depolarizing the β-cells and facilitating insulin release. First-generation agents, such as acetohexamide, chlorpropamide, and tolbutamide, have largely been replaced by second-generation

sulfonylureas, such as glyburide, glipizde, and glimipiride, which have improved safety profiles. Because sulfonylureas act by stimulating insulin release from β-cells, patients without a sufficient number of β-cells, such as those with type 1 diabetes, pancreoprivic diabetes, or later stages of type 2 diabetes, does not respond to these medications. In patients who do respond to them, insulin release may be augmented both in the fasting state and postprandially. Although potencies can vary among sulfonylureas, they tend to lower A1C to a similar extent to metformin, ~ 1.5 percentage points.

Hypoglycemia is the major detrimental effect of these agents. Because different sulfonylureas possess different pharmacotherapeutic profiles, there are differences in risk of hypoglycemic episodes among the different agents. Patients using sulfonylurea medications must be cautioned regarding the signs, symptoms, and risks of hypoglycemia while using these medications. Elderly patients may be at higher risk for hypoglycemia, and patients who frequently skip meals and experience fluctuations in activity level may not be candidates for these medications. Glyburide appears to pose a higher risk of inducing hypoglycemia than other members of this class, possibly because it has a number of active metabolites and high affinity for the sulfonylurea receptor[11].

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[12].

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 blood stream. 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.

OBJECTIVE

The main aim is to develop a bilayer formulation for the effective treatment of Type 2 Diabetes.

Present study aims at

1. Development of metformin hydrochloride as a sustained release dosage form using different excipients and enhancing the flow and compaction process, which helps in development of bilayer tablet.

2. To evaluate the potential of the solid dispersion technique for development of immediate release tablets of glipizide using Sodium Starch Glycolate as

hydrophilic carrier, which helps in the development of bilayer tablet.

MATERIALS AND METHODS

Metformin hydrochloride, Glipizide, Hydroxy propyl methyl cellulose, microcrystalline cellulose, silica gel, Magnesium stearate, sodium starch glycolate, talc.

Development of bilayer tablet of Metformin HCl and Glipizide was carried in three different stages. Sustained release layer of Metformin HCl and immediate release layer of Glipizide were prepared separately. After optimization of individual layer, the bilayer tablet was prepared using optimized formulas.

Results

Estimation of Metformin hydrochloride and Glipizide

Metformin hydrochloride and Glipizide were estimated using uv spectrophotometry at 233nm and 276 nm respectively. Phosphate buffer pH 6.8 was used in the estimation of drugs. Both drugs found to obey the Beer-Lamberts law at the concentration of 2-10 μg/ml.

Compatibilty studies

Before formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically characterized. Compatibility studies give the information needed to define the nature of the drug substances and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction between Metformin and Glipizide and with their excipients respectively. All the important peaks such as NH_2 1^0 amine stretch, aliphatic CH stretch, S=O stretch of sulphonamides, C=O stretch of amides were found to occur in the prescribed wave length which confirms that there is no interaction between the drugs and between drugs and polymers.

Tablet Formulation

Metformin hydrochloride tablets are prepared by using direct compression technique. Different grades of HPMC like HPMC K4M, HPMC K15M, and HPMC K100M were used. HPMC is mixed alkyl hydroxyalkyl cellulose ether containing methoxylhydroxypropyl 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[13].

Glipizide tablets are prepared by using kneading method of solid dispersion technique. Glipizide and sodium starch glycolate were triturated using a small volume of methanol-water (1:1) solution to obtain a thick paste,

which was kneaded for 30 min and then dried at 40°C in an oven. The dried mass was then pulverized, passed through mesh no 30. After optimization of individual layer, the bilayer tablet was prepared using optimized formulas.

Various trial formulations of Metformin hydrochloride SR tablets and Glipizide IR tablets of given in table 1 and table 2 respectively.

Table 1: Composition of Various Trial Formulations for the SR Layer Containing Metformin hydrochloride

Formulation code	F_1	F_2	F_3
Drug (mg)	500	500	500
HPMC K100M (mg)	360	-	-
HPMC K15M (mg)	-	360	-
HPMC K4M (mg)	-	-	360
Microcrystalline cellulose (mg)	125	125	125
Silica gel (mg)	5	5	5
Magnesium stearate (mg)	5	5	5
Total weight (mg)	995	995	995

Table 2: Composition of Various Trial Formulations for the IR Layer Containing Glipizide

Formulation code	F_4	F_5	F_6
Drug (mg)	5	5	5
Sodium Starch Glycolate (mg)	10	20	40
Microcrystalline cellulose (mg)	82	72	52
Talc (mg)	2	2	2
Tartrazine (mg)	1	1	1
Total weight (mg)	100	100	100

Evaluation tests

The formulated tablets were subjected for the quality control tests such as weight variation, hardness, friability, drug content uniformity, disintegration, *in-vitro* dissolution studies.

Evaluation results of Metformin hydrochloride SR tablets and Glipizide immediate release tablets were given in table 3 and table 4 respectively.

***In-vitro* dissolution study**

Dissolution study was performed as per USP Type II apparatus (Paddle type). The tablets were placed in 900 ml of dissolution medium maintain at 37.5°C. The study was carried out for 10 h. Samples absorbance was measured at 233 nm using UV-VIS Spectrophotometer

(UV 2401 PC, Shimadzu Corporation, Singapore). The percentage of Metformin hydrochloride release was calculated and the data of *in vitro* release is given in the table 5 and the graph was plotted for the percentage of drug released vs time and is depicted in figure 1. The obtained dissolution data was subjected for dissolution kinetics to know the mechanism of the drug release from the tablets and the data is given in the table 6.
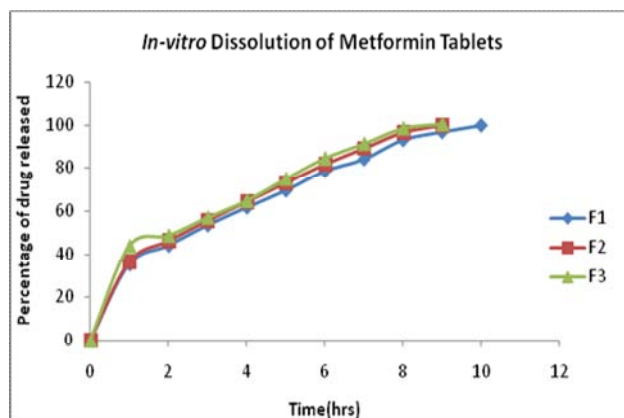

Figure 1: *In-vitro* dissolution study of Metformin hydrochloride SR (F_1, F_2, F_3) tablets

Dissolution of Glipizide from prepared tablet formulations was performed as per USP Type II apparatus. The study was carried out for 30 min. The absorbance was measured at 276 nm and percentage of Glipizide was calculated and the data is given in table 7 and 8 and the graph was plotted for the percentage of drug released vs time and is depicted in figure 2 and 3. The obtained dissolution data was subjected for dissolution kinetics to know the mechanism of the drug release from the tablets and the data is given in the table 9.
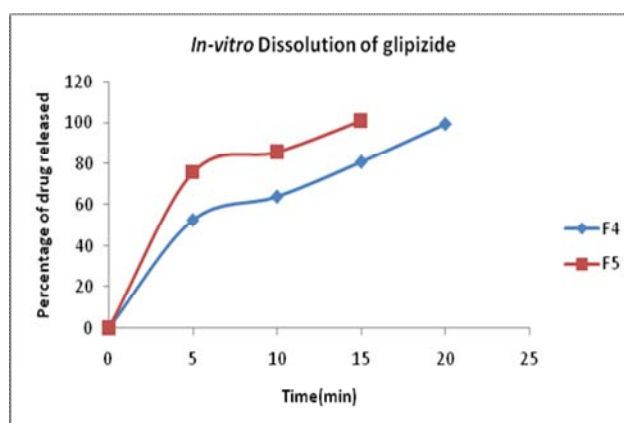

Figure 2: *In-vitro* dissolution study of Glipizide IR (F_4 & F_5) tablets

Table 3: Evaluation tests of Metformin hydrochloride sustained release tablets

S.No	Evaluation test	F_1	F_2	F_3
1	Weight range of 20 tablets	973-997mg	971-998mg	975-998mg
	Average weight	985.45mg	989mg	988mg
	Limit range (±7.5%)	936.2-1034.7	939.5-1038.4	938.6-1037.4
2	Hardness (kg/cm^2)	7	6.5	5.5
3	Friability (%)	0.46	0.59	0.52
4	Amount of drug in percentage	100%	99.2%	100.2%
5	Disintegration Time	35min	28min	20min

Table 4: Evaluation tests of Glipizide immediate release tablets

S.No	Evaluation test	F$_4$	F$_5$	F$_6$
1	Weight range of 20 tablets	92-97mg	91-97mg	92-96mg
	Average weight	95mg	96mg	95mg
	Limit range (±7.5%)	87.88 -102	88.8-103.2	87.88 -102
2	Hardness (kg/cm^2)	4	3.8	3.8
3	Friability (%)	0.48	0.63	0.57
4	Amount of drug in percentage	99.6%	103%	102%
5	Disintegration Time	40sec	28sec	15sec

Table 5: *In-vitro* dissolution test of Metformin SR tablets

Time (hrs)	Percentage Release F$_1$	Percentage Release F$_2$	Percentage Release F$_3$
1	35.3	36.4	43.7
2	44	46.08	48.6
3	53.4	55.48	56.86
4	61.6	64.2	64.66
5	69.4	72.9	74.75
6	78.4	81.6	84.3
7	83.9	88.9	91.03
8	92.8	96.3	98.14
9	96.5	99.5	100
10	99.5	-	-

Table 6: Drug release kinetics of Metformin hydrochloride Sustained Release tablets

Formulation Code	Zero order (R^2)	First order (R^2)	Higuchi's kinetics (R^2)	Korsemeyer's kinetics (R^2)
F$_1$	0.9225	0.826	0.9926	0.9886
F$_2$	0.989	0.8076	0.9928	0.989
F$_3$	0.8997	0.8305	0.9747	0.9528

Table 7: *In-vitro* dissolution test of Glipizide IR tablets (F$_4$& F$_5$)

S. No	Time (min)	Percentage Release from F$_4$	Percentage Release from F$_5$
1	5	52.8	75.8
2	10	64.2	85.6
3	15	81	100
4	20	99.6	-

Table 8: *In-vitro* Dissolution test of Glipizide IR tablets (F$_6$)

S. No	Time (min)	Percentage Release from F$_6$
1	2	46.72
2	4	62.8
3	6	73.4
4	8	88.8
5	10	100.2

Figure 3: *In-vitro* dissolution study of Glipizide IR tablets (F$_6$)

Preparation of Final Bilayer tablets

Optimized formulations of Metformin hydrochloride SR tablets and Glipizide IR tablets were selected and final bilayer tablets were prepared. Metformin layer was slightly compressed and then IR tablet powder was added and compressed together to get the final bilayer tablet. Dissolution of final bilayer tablet was also performed in the similar manner using 6.8 pH phosphate buffer and the absorbances were measured at 276 nm for the first 30 min and the rest samples were measured at 233 nm. The percentage of Metformin HCl and Glipizide release was calculated and the results were given in table 10 and 11 and the graph was plotted for the percentage of drug released vs time and is depicted in figure 4 and 5. The obtained dissolution data was subjected for dissolution kinetics to know the mechanism of the drug release from the tablets and the data is given in the table 12.
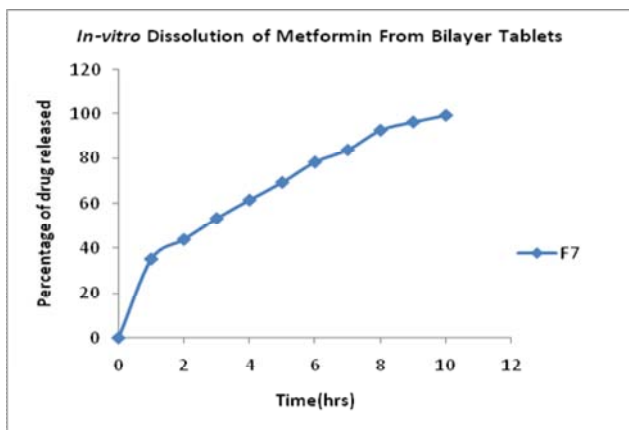
Figure 4: *In-vitro* Dissolution study of Metformin hydrochloride from Bilayer tablets
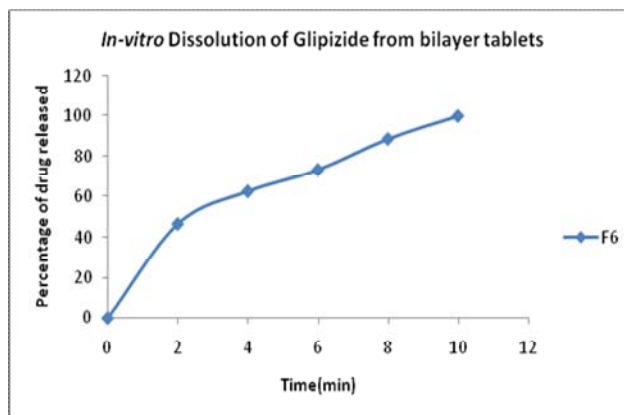

Figure 5: *In-vitro* dissolution study of Glipizide from Bilayer tablets

Table 9: Drug release kinetics of Glipizide IR tablets

Formulation Code	Zero order R^2	First order R^2	Higuchi's Plot R^2	Korsemeyer's plot R^2
F_4	0.9108	0.755	0.9591	0.9532
F_5	0.7302	0.859	0.9447	0.9561
F_6	0.9102	0.8238	0.9905	0.9908

Table 10: *In-vitro* Dissolution test of Metformin from bilayer tablets

Time (hrs)	Percentage Release of Metformin
1	35.3
2	44
3	53.4
4	61.6
5	69.4
6	78.4
7	83.9
8	92.8
9	96.5
10	99.5

Table 11: *In-vitro* Dissolution test of Glipizide from bilayer tablets

Time (min)	Percentage Release of Glipizide
2	46.72
4	62.8
6	73.4
8	88.8
10	100

Table 12: Drug release kinetics of Metformin hydrochloride and Glipizide from Bilayer tablets

Formulation F_7	Zero order R^2	First order R^2	Higuchi's Plot R^2	Korsemeyer's plot R^2
Metformin Hydrochloride	0.9225	0.826	0.9926	0.9886
Glipizide	0.9102	0.8238	0.9905	0.9908

DISCUSSION

Tablet Characteristics

The tablets of different formulations were subjected to various evaluation tests such as compatibility test, thickness, hardness, friability, and drug content. All the formulations passed the evaluation tests according to the United States of Pharmacopeia, 2000.

Release Profile of Metformin hydrochloride from SR 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 predetermined manner. 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[14]. All the formulations showed the burst release of Metformin in the initial hours, which is probably due to faster dissolution of highly water-soluble drug from the core and its diffusion out of the matrix, forming the pores for the entry of solvent molecule.

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 Korsemeyer'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 6, the kinetic parameters for Metformin HCl release from the HPMC matrix tablets were presented. As clearly indicated in table 6, the formulations did not follow zero-order or first-order release patterns.

The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation. Release of 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 Korsemeyer's equation[15] (Korsemeyer et al., 1983). For matrix tablets, as 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[16, 17] (Fassihi & Ritschel, 1993; Peppas, 1985).

All the formulations showed good linearity (R^2: 0.974 to 0.992), indicating that the diffusion is the dominant mechanism of drug release from these formulations.

Release Profile of Glipizide from IR tablets

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 Korsemeyer'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 9, the kinetic parameters for Glipizide release from the immediate release tablets are presented. . As clearly indicated in table 9, the formulations did not follow zero-order or first-order release patterns.

The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation and Korsemeyer's equation. The optimized formulation F_6 can be best expressed by Higuchi's equation

CONCLUSION

HPMC used as matrix forming polymer for the Metformin layer enables drug release for up to 9-10 hours. Among the different grades of HPMC there is significant difference in the resulting Metformin release profiles from the SR layer of the tablets was found. The formulation F_1 can be preferred as integrity was maintained.

Glipizide release shows that the dissolution rate of glipizide can be enhanced considerably by formulating it as a solid dispersion with SSG using kneading method. Incorporation of super disitnegrants in the solid dispersions played a critical role in dissolution enhancement.

SR fixed dose bilayer matrix tablets containing 500mgMetformin HCl as SR from one layer and 5mg Glipizide as IR from another layer can be successfully formulated.

REFERENCES

1. Tripathi KD. Essentials of Medical pharmacology: Jaypeee Brothers Medical Publishers Pvt, Ltd. New Delhi, India; 2004. p. 235-253.

2. Bailey CJ, Turner RC: Metformin. N Engl J Med334: 574-579, 1996.

3. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE: Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med333: 550-554, 1995.

4. DeFronzo RA, Goodman AM: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med333: 541-549, 1995.

5. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 29:1963 -1972, 2006.

6. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE: Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmeno-pausal women. Diabetes Obes Metab8: 538-554, 2006.

7. Dunn C J, Peters DH. Metformin: A review of its pharmacological properties and therapeutic use in non-insulin dependent diabetes mellitus. Drugs. 1995; 49:721-749.

8. Defang O, Shufang N, 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.

9. Scheen AJ. Clinical pharmacokinetics of metformin. Clin. Pharmacokinet. 1996; 30: 359-371.

10. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A: Efficacy, tolerability, and safety of a novel once-daily extended-release Metformin in patients with type 2 diabetes. Diabetes Care 29:759 -764, 2006.

11. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM: A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. Diabetes Care 30: 389-394, 2007.

12. Siconolfi-Baez L, Banerje MA, Lebovitz HE. Characterization and significane of sulfonylurea receptors. Diabetes Care. 1990; 13; 2-8.

13. Hogan JE. Hydroxypropyl methylcellulose sustained release technology, Drug Dev. Ind pharm.1989; 15: 975-999.

14. Mutalik S, Hiremath D. Formulation and evaluation of chitosan matrix tablets of nifedipine. The Eastern Pharmacist.2000; 2: 109-111.

15. Korsmeyer RW, Gurny R, Doelker E. Mechanism of solute release from porous hydrophilic polymers. International journal of Pharmaceutical sciences. 1983; 15: 25-35.

16. Fassihi RA, Ritschel WA. Multiple layer, direct-compression controlled-release system: In vitro and in vivo evaluation. J. Pharm Sci. 1993; 82: 750-754.

17. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. ActaHelv. 1985; 60: 110-111.

****