Research Article

Formulation and Evaluation of Sustain Release Bilayer Tablets of Metformin and Gliclazide

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ABSTRACT

The main objective of the present work was to develop sustained release bilayer tablets of gliclazide and metformin using HPMC K4M and HPMCK100LV. The tablets were evaluated for physical characteristics like hardness, weight variation, and friability. Invitro release of drug was performed using 7.4 pH phosphate buffer and dissolution was done for 10hrs. All the physical characters were acceptable and within limits.

Keywords: Gliclazide, Metformin, HPMC K4M, HPMCK100LV, bilayer tablets.

INTRODUCTION[1, 2]

In recent times, various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk, the addition of one agent may potentiate effects of other agent. Using low dosage of two different agents minimizes the clinical and metabolic side effects that occur with maximal dosage of individual component of the combined tablet and thus dose of the single components can be reduced[1]. Bilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles improves patient compliance, prolongs the drugs action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level. As non insulin dependent diabetes mellitus is a progressive disorder, and although oral monotherapy is often initially successful, it is associated with a high secondary failure rate, which contributes to the development of long term diabetic complications resulting from persistent insulin, accumulating evidence suggests that combination therapy using oral antidiabetic agents with different mechanisms of action may be highly effective in achieving and maintaining target blood glucose levels. Low –dose combination therapy may be associated with fewer side effects than higher-dose monotherapy and may achieve similar or better glycaemic control. A therapeutic approach that addresses both underlying defects in diabetes viz insulin deficiency and insulin resistance, is gliclazide plus metformin. Where gliclazide belongs to sulfonylurea group of oral hypolgycaemic agents. It is metabolized in the liver. It appears in the blood within 1-2 hrs and peak level is achieved in 4-6 hrs .The plasma $t_{1/2}$ is 8-12 hrs and its duration of action is 12 hrs .it is indicated for insulin dependent diabetes mellitus. It stimulates insulin secretion by pancreatic beta cells. In the long term it reduces hepatic gluconeogenesis, and increases insulin effects by acting at the receptor or post receptor sites. Metformin is a currently available oral hypoglyceamic agent that acts predominantly by inhibiting glucose release. As patients with non-insulin independent diabetes often have excess hepatic glucose output, use of metformin is effective in lowering glycosylated hemoglobin (HbA_{1c}) by 1-2% when used as monotherapy or in combination with other blood –glucose lowering agents .It is extensively plasma protein bound (more than 90%).Addition of gliclazide to metformin therapy gives an additive glucose lowering effect. Similarly, addition of metformin to sulfonylurea therapy gives an addictive response, both with respect to glucose lowering and lipid-lowering effects .Hermann et al showed that in most patients with newly diagnosed type 2 diabetes, blood glucose levels could be controlled with combined sulfonylurea – metformin therapy similar findings were found in UKPDS. So the two drugs were chosen to formulate the sustain release tablet.

MATERIALS AND METHODS

MATERIAL

Gliclazide and Metformin were procured as gift samples from Bliss Pharma, Palghar Maharashtra HPMC K4M, HPMC K100LV, Magnesium stearate, MCC, talc, PVP K30, IPA were obtained from the college laboratory at Shri Guru Ram Rai Institute of Technology.

METHOD

The formulation was made by wet granulation using HPMC K4M and HPMC K100M as polymers and sodium bicarbonate as a gas generating agent and PVP K30 as a binding agent. For formulation of tablets: drug, HPMC K4M, HPMC K100M, MCC were sifted through mesh 100. The paste of PVP K 30 in isopropyl alcohol was used as granulating agent. The granules were then dried in a conventional hot air oven at 45^0C the granules further passed through sieve 40. Magnesium stearate and talc were added as a lubricant and the granules were compressed into tablets.

EVALUATION[3-10]

Evaluation of powder blend

BULK DENSITY (Db)

It is the ratio of the total mass of powder to the bulk volume of powder .It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/Vb$$

Where,
M- is the mass of powder
Vb-is the bulk volume of the powder (ml)

TAPPED DENSITY

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes was noted less than 2% (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = = M/Vt$$

M- is the mass of powder
Vb-is the tapped volume of the powder (ml)

CARR'S INDEX

It indicates powder flow properties. It is expressed in percentage and is given where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

HAUSNERS RATIO

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula where, Dt is the tapped density. Db is the bulk density. Lower Hausnerr ratio (<1.25) indicates better flow properties of powder.

ANGLE OF REPOSE

The friction forces in a losse powder can be measured by the angle of repose .It is an indiThe friction forces in a losse powder can be measured by the angle of repose .It is an indicative of the flow properties of the powder it is defined as maximum angle possible the surface of the pile of powder and the horizontal plane between.

$$Tan(a) = h/r$$

Where, a is the angle of repose h is the height in (cms) r is the radius in (cms)
The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Evaluation of tablets

a) Hardness

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. The hardness of tablet was determined using Monsanto hardness tester. It is expressed in kg/cm^2.

b) Friability

The friability of tablets was determined using Roche fribilator. It is expressed in percentage. Twenty tablets were weighed and transferred into the fribilator. The fribilator was operated at 25 rpm for 4 minutes or run upto revolutions. The tablet were weighed again, the % friability was then calculated.

c) Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually to check variation.

d) Uniformity of weight

Weight of contents of 20 capsules were

determined and average weight was calculated. Requirements are met if not more than two of the individual weights deviate from the average weight by more than 10 % and none deviates by more than20%.

e) In vitro dissolution studies

In vitro dissolution studies were carried out using USP type I dissolution apparatus tablet was introduced in the dissolution media. The dissolution was carried out in 900 ml 0.1 N HCl for 2 hrs at 37ºC ± 0.5ºC at a speed of 75 rpm and subsequently the dissolution media was replaced with phosphate buffer pH 7.48 for 10 hrs. At predetermined time intervals, 10 ml samples were withdrawn. Every time the sample withdrawn was replaced by fresh dissolution media maintained at the same temperature. The samples removed were filtered, dilutedand analyzed spectrophotometrically at 232nm.

RESULTS AND DISCUSSIONS

EVALUATION OF GRANULES AND TABLETS

The granules of bilayer tablets were evaluated for their flow properties. The bulk density was within the range of 0.46 to 0.52 gm/cm^3.Tapped density ranged between 0.50to 0.64 gm/cm^{3}angle of repose was within the range of 24.5 to 30.1. Compressibility index was found to be 9.09 to 20.31 and hausners ratio ranged from 1.16 to 1.25 for granules of different formulations.

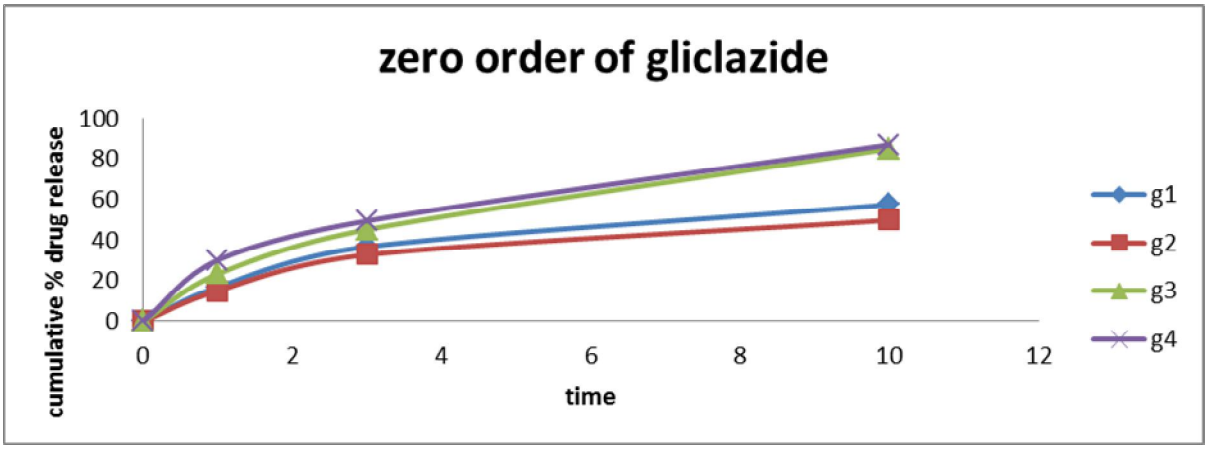

Fig. 1: Zero order release of gliclazide

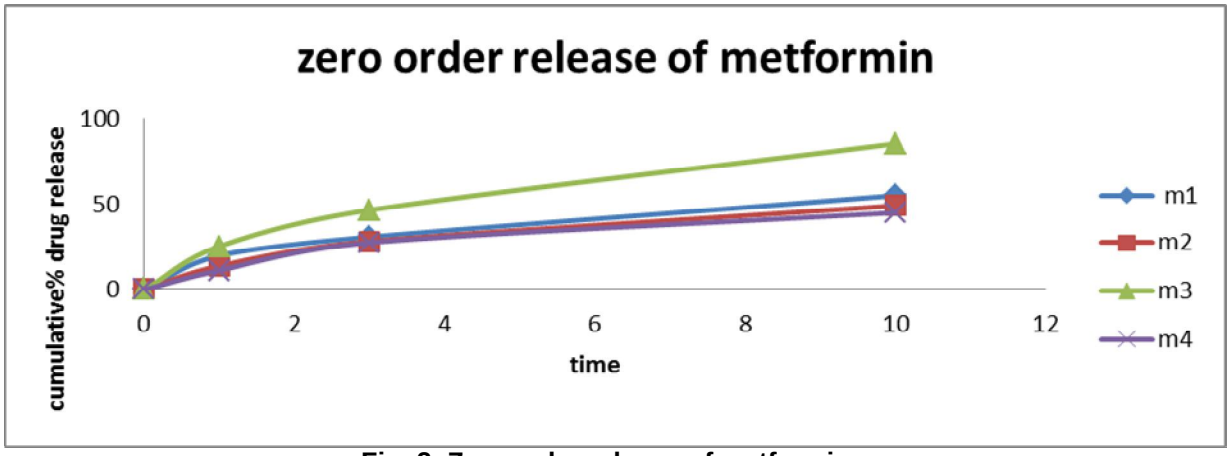

Fig. 2: Zero order release of metformin

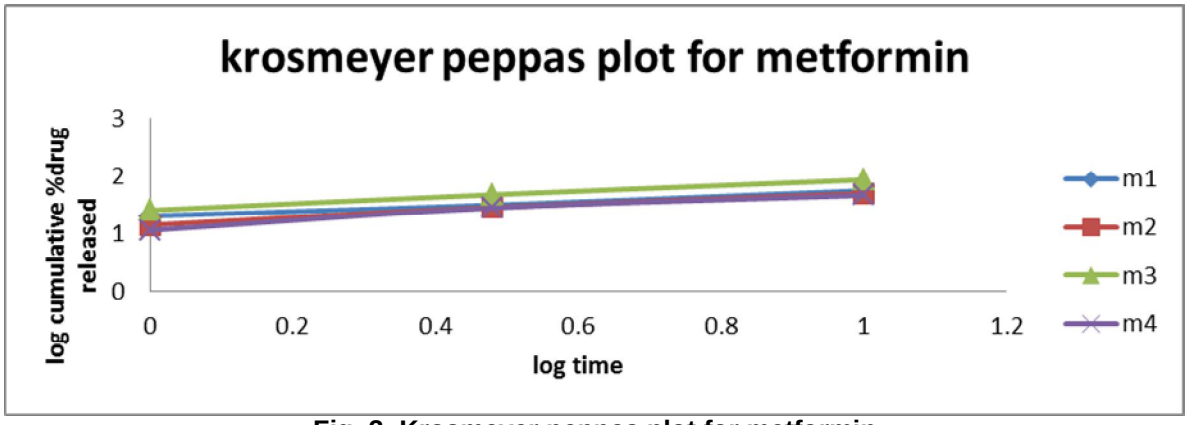

Fig. 3: Krosmeyer peppas plot for metformin

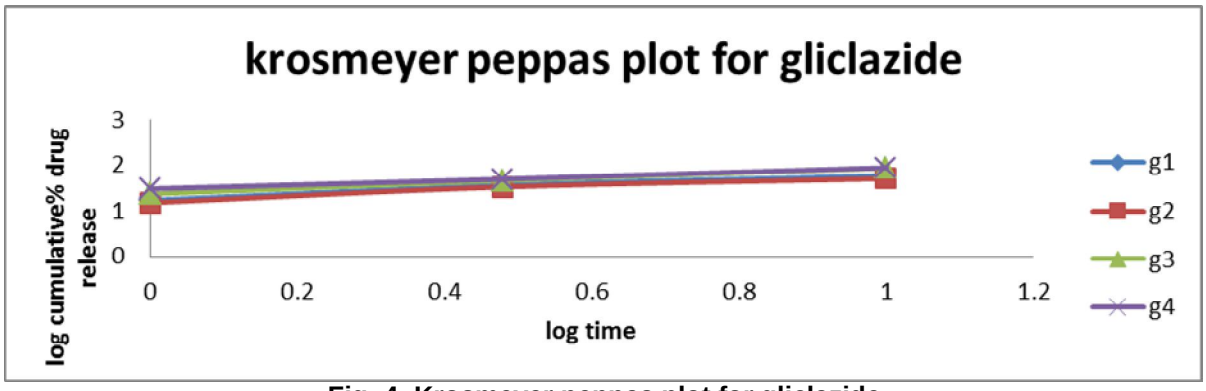

Fig. 4: Krosmeyer peppas plot for gliclazide

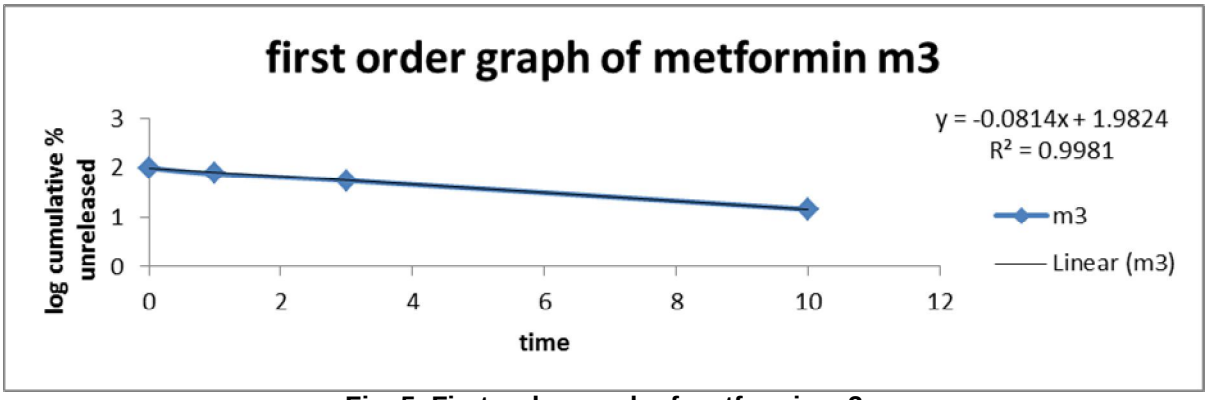

Fig. 5: First order graph of metformin m3

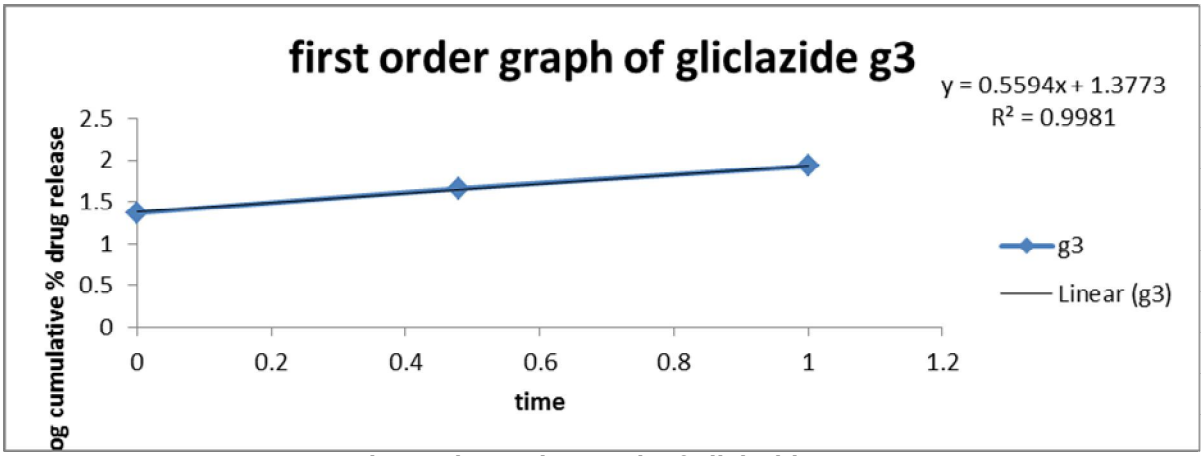

Fig. 6: First order graph of gliclazide g3

Table 1: Formulation chart for preparation of Metformin S R

	F1	F2	F3	F4
DRUG	500	500	500	500
HPMC K4M	20	30	10	25
HPMC K100LV	30	30	50	35
MCC	62.5	62.5	62.5	62.5
MAGNESIUM STEARATE	8.25	8.25	8.25	8.25
TALC	8.25	8.25	8.25	8.25
PVP K30	30	30	30	30
IPA	QS	QS	QS	QS

Table 2: Formulation chart for preparation of Gliclazide S R

DRUG	30	30	30	30
HPMC K4	2	4	7	8
HPMC K100	15	13	10	9
MCC	45	45	45	45
TALC	2	2	2	2
MAGNESIUM STEARATE	2	2	2	2
PVP K 30	4	4	4	4
IPA	QS	QS	QS	QS

Table 3: Evaluation of granules of Metformin

Formulation metformin	Angle of repose	Bulk density	Tapped density	Carr's index	Hauseners ratio
M1	29.1+,-0.13	0.47 +,- 0.02	0.58 +,-0.02	18.96+,-.13	1.23
M2	30 +,- 0.28	0.51+,- 0.02	0.64 +,-0.04	20.31+,-0.04	1.25
M3	24.5 +,- 0.19	0.48+,-0.02	0.57 +,-0.01	15.78+,-0.11	1.18
M4	27.8 +,- 0.16	0.50+,-0.02	0.55 +,- 0.01	9.09 +,- 0.15	1.14

Table 4: Evaluation of granules of Gliclazide

Formulation gliclazide	Angle of repose	Bulk density	Tapped density	Carr's index	Hauseners ratio
G1	29.2+,-0.21	0.50+,-0.01	0.57+,-0.01	12.28+,-0.05	1.17
G2	25.9+,-0.23	0.46+,-0.01	0.54+,-0.01	14.81+,-0.13	1.2
G3	30.01+,-0.11	0.52+,-0.01	0.59+,-0.01	16.95+,-0.19	1.24
G4	26.7+,-0.18	0.49+,-0.02	0.50+,-0.01	19.01+,-0.1	1.16

Table 5: Formulation

Formulations metformin	Drug release in 1 hr	Drug release in 3 hrs	Drug release in 10 hrs
M1	19.79	30.75	60.91
M2	25.39	47.21	82.04
M3	32.51	41.8	88.69
M4	34.03	58.75	92.04
Formulations gliclazide	Drug release in 1 hr	Drug release in 3 hrs	Drug release in 10 hrs
G1	16.8	36.68	57.47
G2	14.99	32.79	48.99
G3	23.29	45.21	85.03
G4	30.91	49.50	86.78

Table 6: Evaluation of tablets

	M1, G1	M2, G2	M3, G3	M4, G4
Weight variation mg	754	758	760	758
Thickness (mm)	6	6.1	6.1	6.2
Hardness	8.5	8.6	8	8.1
Friability	.79	.57	.679	.5

CONCLUSION

Formulations M3, G3 has been selected as best formulation among all the other formulations. Formulation M3 G3 provides better invitro release from layer 1 as well as 2. The data obtained from invitro release study were fitted to various mathematical models like Higuchi, Peppas model, first order, the best fit model in all the cases. The release was found to be non – fickian as the n value for m3 and g3 was found to be 0.52, 0.51. The formulation was found to follow first order.

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