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Research Article

FORMULATION AND EVALUATION OF IMMEDIATE AND SUSTAINED RELEASE BILAYERED TABLET WITH GLIBENCLAMIDE AND METFORMIN HYDROCHLORIDE

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ABSTRACT

The aim of the present research work is to develop bilayer tablet dosage form containing combination of immediate and sustained release layer prepared using Glibenclamide and Metformin Hydrochloride respectively for the treatment of Type-11 diabetes mellitus. Immediate release of glibenclamide granules was prepared with different superdisintegrant. Metformin hydrochloride sustained release granules were prepared by non-aqueous wet granulation technique. Both pre-compression and post compression parameters were analyzed for all the tablets. Bilayer tablets was formulated using croscarmellose sodium for immediate release of Glibenclamide showed 99.94% of release in 30 minutes and using hydrophilic HPMC K100 and hydrophobic Ethyl cellulose in the ratio of 1:1 released 99.90% of Metformin hydrochloride for the period of 13 hours. From this research work it is evident that the formulated bilayer tablet has ability to release the Glibenclamide immediately and Metformin hydrochloride for longer period of time, which can be used for treatment of type11 diabetes mellitus compared to Marketed formulation.

Keywords: Metformin Hydrochloride, Glibenclamide, Sustained release.

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INTRODUCTION

Metformin hydrochloride is a highly water soluble hypoglycemic agent in the treatment of Type-1(Non insulin dependent) diabetes mellitus, affecting elevated plasminogen activator (PAI) levels both in Hypertriglyceridemia and in non insulin dependent diabetes[1].The drawbacks being high dose[2](1.5-2 g/day), low bioavailability (40-60 %), short biological half life (0.9-2.6 hour) requires repeated administration of high doses to maintain effective plasma concentrations[3]. Bioavailability decreases as the dose increases, suggesting some form of saturable absorption process and need for twice to three times a administration which can also reduce patient compliance and bringer more successful therapy[4].

Glibenclamide is a second generation sulphonyl urea capable of stimulating insulin release,but are not capable of acting on insulin resistance, and Metformin hydrochloride able to act on insulin resistance, whereas they are not able to stimulate insulin secretion[5].Rationale for combination of Glibenclamide with Metformin hydrochloride suggests the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin resistance condition. 5mg of Glibenclamide and 500mg of Metformin hydrochloride is suitable for the treatment of Type-11 diabetes mellitus at any time of the progression of the disease. 5mg of Glibenclamide is required to reduce the hyperglycemic effect and 500 mg of

Metformin hydrochloride is required to sustain the normal glycemic level for the Type-11 diabetic patient[6']

Therefore an object to produce a bilayer tablet with two different release profiles with Glibenclamide as immediate release layer and Metformin hydrochloride as a sustain release layer to provide a desired pharmacokinetic and therapeutic action.

MATERIALS AND METHODS

Metformin hydrochloride and Glibenclamide as gift sample from Biocon, Bangalore. HPMC K100 from Rolex laboratory reagent, Mumbai. Ethyl cellulose and Povidone (PVP-K30), microcrystalline cellulose, Aerosil and Magnesium stearate, Lactose anhydrous, Manitol and talc were purchased from Chemspure, Chennai.

Preparation of immediate release granules

Mixing all the powdered polymer ingredients with Glibenclamide passing through sieve no.40 using binder solution dissolving PVP K-30 in water to get granules dried 50^0c with moisture content not more than 1% adding lubricants at the final stage 12 formulations were prepared (Table-1).

Preparation of sustained release granules

The drug Metformin hydrochloride 500 mg/tablet along with other polymers Sunset yellow mixed. The binder solution dissolving PVP K-30 in iso propyl alcohol dried at 50^0c till moisture content reached upto 2 % at the last added Lubricants (Table-2). To characterize flow of granules subjected to Angle of repose, Bulk and tapped density, compressibility index and Hausner's ratio.

Evaluation of bilayer tablets

Drug content of both drugs in bilayer tablets were measured by separating both layer and measured individually.

Triturating 20 tablets weighing about 20 mg of glibenclamide shaken with 40 ml of 0.1M Methanolic hydrochloric acid. Heat the solution gently and then centrifuged. Extraction procedure was repeated with three further quantities of each 20 ml of 0.1M methanolic hydrochloric acid. Combined extracts and add sufficient 0.1M methanolic hydrochloric acid to produced 100ml. Measure the solution at absorbance 300 nm using 0.1M methanolic hydrochloric acid heated to the same degree as blank.

Table 1: Formulation of Glibenclamide immediate release layer.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Glibenclamide	*5*	*5*	*5*	*5*	*5*	*5*	*5*	*5*	*5*	*5*	*5*	*5*
Sodium starch glycolate	6	8	10	12	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	6	8	10	12	-	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	-	-	6	8	10	12
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	73	73	73	71	71	71	69	69	69	67	67	67
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
Lactose	50	50	50	50	50	50	50	50	50	50	50	50
Aerosil	02	02	02	02	02	02	02	02	02	02	02	02
Magnesium Stearate	04	04	04	04	04	04	04	04	04	04	04	04

Table 2: Formulation of Metformin Hydrochloride sustained release layer

Ingredients	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27
Metformin Hcl	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K100	100	125	150	175	200	-	-	-	-	-	50	50	100	100	100
Ethylcellulose	-	-	-	-	-	100	125	150	175	200	100	100	100	100	100
Microcrystallinecellulose	160	135	110	85	60	160	135	110	85	60	110	110	60	55	50
PVP K30	20	20	20	20	20	20	20	20	20	20	20	20	20	25	30
Talc	08	08	08	08	08	08	08	08	08	08	08	08	08	08	08
Aerosil	04	04	04	04	04	04	04	04	04	04	04	04	04	04	04
Magnesiumstearate	08	08	08	08	08	08	08	08	08	08	08	08	08	08	08
Isopropyl alcohol	qs	Qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

Metformin hydrochloride (0.1 gm) from crushing of 20 tablets shaken with 70 ml of water for 15 minutes and then diluted with 100 ml of water. Further diluted 10 ml to 100 ml with water and measured absorbance of resulting solution at 233 nm.

***In-vitro* disintegration test**

Six immediate release glibenclamide tablets selected randomly from each formulation carried out in 0.1NHcl buffer at 37±0.5^{0}c until the complete disintegration of the tablet with no palpable mass in the apparatus measured in seconds.

Wetting time and water absorption ratio

A tablet was placed in the wet tissue paper placed in a dish containing 6 ml of water and the time of complete wetting was measured and water absorption ratio calculated.

$$R = \frac{100(w_a - w_b)}{w_b}$$

where w_a=Weight after water absorption.

w_b=Weight before water absorption.

In vitro dissolution test

In vitro dissolution studies using USP paddle dissolution apparatus. 900ml with pH1.2 Hcl buffer at 50 rpm for first two hours and replaced 900ml of 6.8 Phosphate buffer at 37±0.5^{0}c withdrawn suitable volume of medium and replaced with fresh medium at specific time intervals. Absorbance measured at 300nm for Glibenclamide and 233nm for Metformin hydrochloride.

Kinetic analysis of dissolution data

The rate and mechanism of release of drug analyzed fitting the dissolution data into Zero order equation, first order equation and Higuchi model and Korsmeyer equation.

In vivo studies

Four adult male rats weighed average weight of 200 gm checked for their blood glucose level. Bilayer tablet administered to rats dose of 1gm/kg body weight by oro gastric tube intubation method. 0.5 ml blood samples were withdrawn from retro orbital of rat at 0.5, 4, 8 and 12 hours time intervals. The pharmacokinetic parameters of bilayer tablet of Marketed sample and the formulation F28 was shown in Table 5.

Stability studies

This is to determine for physical, chemical, therapeutics and toxicological specifications. Stability studies conducted for optimized bilayer tablets .The preliminary stability of the optimized batch as per ICH guidelines and stability protocol of glibenclamide immediate and metformin hydrochloride sustained release tablets as long term study 25^0±2^{0}C/60% RH±5% and for intermediate as 30^0±2^{0}c/60% RH±5% and also for Accelerated 40^{0}C±2^{0}c/75% RH±5%.Testing

Table 3: Evaluation parameters of immediate release layer tablets

Formulation	Weight variation (mg)±S.D	Friability %	Hardness (Kg /cm²)	Thickness (mm)	Disintegration Time(sec)	Drug content In %
F1	201.6±0.57	0.26	4.23±0.15	4.94±0.12	348±1.00	93.40
F2	201.3±0.57	0.43	4.13±0.20	5.00±0.07	92.3±2.51	97.80
F3	202.0±1.00	0.75	4.00±0.20	5.01±0.24	47.6±1.53	103.80
F4	201.3±1.52	0.86	4.16±0.21	5.19±0.06	191.3±1.53	97.80
F5	201.3±1.52	0.31	4.00±0.20	5.17±0.05	80.3±0.58	95.80
F6	201.0±1.73	0.54	4.10±0.17	5.08±0.19	46.3±1.53	99.20
F7	199.3±3.51	0.81	4.16±0.06	5.17±0.06	180±1.00	95.60
F8	197.6±3.21	0.94	4.20±0.17	5.17±0.05	79.3±4.50	98.80
F9	199.6±1.52	0.33	4.20±0.10	5.01±0.10	29.3±0.58	97.80
F10	201.3±1.15	0.45	3.96±0.21	4.93±0.03	101.6±1.53	99.80
F11	199.3±2.51	0.63	4.06±0.15	5.12±0.09	76.3±1.53	97.80
F12	200.0±3.00	0.87	4.10±0.10	5.21±0.08	26±1.00	99.90

Table 4: Evaluation parameters of sustained release layer tablets

Formulations	Weight variation (mg)±S.D.	Friability in %	Hardness (kg /cm²)	Thickness (mm)	Drug content (%)
F13	800.3±0.59	1.10	3.53±0.06	6.23±0.03	99.80
F14	800.6±1.53	1.07	3.70±0.10	6.04±0.02	101.20
F15	799.6±0.58	0.96	3.96±0.15	6.01±0.01	101.00
F16	799.3±0.58	0.91	4.10±0.10	6.10±0.01	99.90
F17	801.6±2.31	0.75	4.33±0.17	5.99±0.01	98.90
F18	801.3±0.58	1.03	4.00±0.00	6.21±0.01	100.60
F19	799.6±1.15	1.00	3.93±0.15	6.07±0.02	100.10
F20	802.0±1.73	0.87	4.10±0.10	6.02±0.02	101.40
F21	799.3±2.08	0.64	4.53±0.05	6.10±0.01	101.30
F22	799.6±2.51	0.37	5.10±0.10	6.02±0.02	101.50
F23	800.3±1.53	0.87	4.23±0.15	6.07±0.02	101.60
F24	800.6±0.58	0.71	4.80±0.10	5.98±0.12	99.70
F25	803.3±2.51	0.63	5.03±0.05	6.19±0.01	100.80
F26	803.0±3.46	0.66	5.30±0.10	6.02±0.02	102.10
F27	799.3±0.58	0.59	5.43±0.06	6.08±0.01	100.90

Table 5: Pharmacokinetic parameters of bilayer tablet of Marketed sample and F28

FORMULATION	**AUC_{0-t} µg.hr/ml**	**$AUMC_{0-t}$ µg.hr²/ml**	**C_{max} µg/ml**	**T_{max} hrs**
Marketed sample				
a)Glibenclamide	a)16	a)8	a)64	a) 0.5
b)Metformin Hcl	b)25	b)184	b)3.1	b) 8
F28				
a)Glibenclamide	a)17	a)8	a)67	a) 0.5
b)Metformin HCL	b)24	b)180	b)3.0	b) 8

parameters were after a period of 60 days for Hardness, Friability and Drug content.

RESULTS AND DISCUSSIONS

Glibenclamide and Metformin Hydrochloride analysed by IR spectra. The mixture of Metformin hydrochloride and polymers HPMC K-100 and Ethylcellulose and mixture of Glibenclamide and superdisintegrants (Sodium starch glycolate ,Crospovidone and croscarmellose sodium) characterized by IR. The results confirmed identification of samples which are compared with the reference standard. Differential scanning calorimetry was done for the mixture of drug and excipients. The spectra showed exothermic peak at 170^{0}c. The presence of Glibenclamide and thermal curve for Metformin hydrochloride exhibited a sharp endothermal effect at 221.6^{0}c in Fig-1.

The percentage of carr's index was 6.26-11.74 % indicates excellent flow character for immediate release release formulations F1-F12.The sustained release release formulations F13-F27 was 0.62-9.35% except formulations F16, F17, F20, F21 and F22 were 20.44, 24.73, 16.75 and 20.91. Hausner's ratio for immediate release formulations F1-F12 were 1.06-1.13.In sustained release formulations F13-F27 were 1.01-1.32.The weight variation of tablets in the immediate release formulations F1-F12 were 199.3±2.51 to 202.0±1.00 and sustained release formulations F13-F27 were 799.3±0.58 to 803.0±3.46 to be within the limit (±5%).The friability of immediate release formulations F1-F12 were ranging from 0.26-0.94%w/w and for sustained release formulations F13-F27 were ranging from 0.37-1.10%w/w. Hardness for the formulations

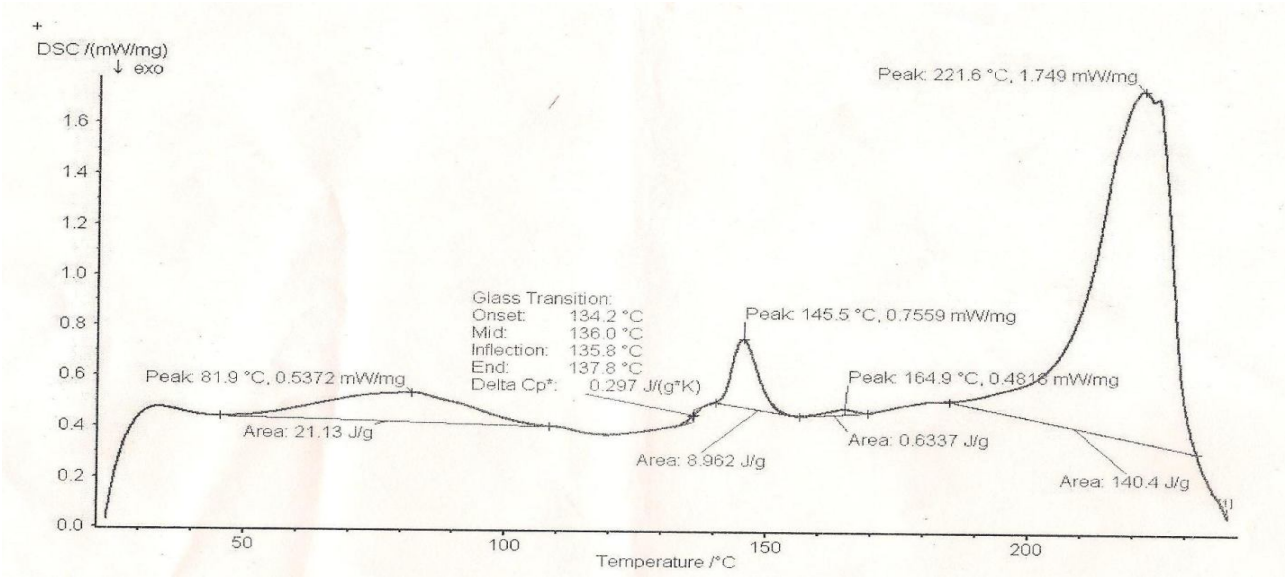

Fig 1: DSC Spectra of mixture of Metformin Hydrochloride, Glibenclamide, HPMC K100, Ethyl cellulose and excipients

The bulk and tapped density of the formulations F1-F12 in immediate release granules 0.308-0.334 gm/ml and 0.341-0.373 gm/ml. Formulations F13-F27 sustained release granules bulk density 0.143-0.160 gm/ ml and tapped density 0.154-0.190 gm/ml. The angle of repose of formulation F1-F12 immediate release granules was found between 25^0-30^0 showed excellent flow characters. Formulations F13-F27 sustained release granules produced excellent flow character except F16, F17 and F22 of sustained release formulations lies between 31^0 - 35^0.depicts good flow characters.

F1-F12 ranged from 3.96±0.21 to 4.23±0.15 kg/cm^2 and for F13-F27 ranged from 3.53±0.06 to 5.43±0.06 kg/cm^2 which were within the limit. The thickness of the formulations F1-F12 and sustained release layer tablets F13-F27 ranged from 4.93±0.03-5.21±0.08 mm and 5.98±0.12 - 6.23±0.03 mm respectively.

In the immediate release formulations wetting time and water absorption ratio for the formulation F12prepared with Croscarmellose sodium was 36 seconds and 35 respectively represented in figure 4. From this observation cros carmellose sodium provides less wetting time and water

absorption ratio compared with sodium starch glycolate and crospovidone due to its wicking nature and fibrous structure of croscarmellose sodium. The disintegration time for formulations F1-F12 was compared that indicates the formulation F12 containing croscarmellose sodium 12mg/tablet disintegrated the fastest time in 26 seconds with no mass left and had good hardness.

The drug content of the immediate release formulations F1-F12 and for sustained release formulations F13-F27 were found to be between 93.40-103.80% and 98.90-102.10% respectively. In the dissolution study of immediate release layer formulations F1-F12 revealed.The formulations F1, F4, F7 and F10 released 77.53, 95.36, 94.65 and 98.69% of Glibenclamide respectively. F2, F5, F8 and F11 released 80.81, 89.71, 98.42 and 99.85 % of Glibenclamide and F3, F6, F9 and F12 released 93.88, 95.49, 97.44, 99.91% of Glibenclamide released respectively in 30 minutes dissolution period. From the observations F12 prepared with Croscarmellose sodium 12 mg/tablet released the drug faster than other formulations in the immediate release layer formulations. As the concentration of superdisintegrants increases there was no increase in the release percentage of the drug.

with HPMC K100 alone could not able to sustain the release not more than 7 hours. The formulations F18, F19, F20, F21 and F22 prepared with Ethyl cellulose could not able to sustain the drug release for not more than 8 hours. The formulations F23, F24 and F25 prepared with combination of hydrophilic HPMC K100 and hydrophobic Ethyl cellulose at different polymer ratio (1:2) was able to sustain the drug release for 12 hours. The formulations F23, F24 and F25 were released 99.85, 99.88 and 99.69% of Metformin hydrochloride respectively.

Formulations F26 and F27 the effect of drug release on varying the concentration of PVP K30. Sustained release layer formulation F26 and F27 prepared with 25 and 30 mg of PVP K30 and polymer ratio 1:1 was released 99.46% and 99.85% of drug. Hence PVP K30 shows an effect on drug release. In the increase in concentration of PVP K30 release of the drug from the tablet is decreased by increasing the binding and hardness properties of the tablet.1:1 polymer ratio of HPMC K100 and ethylcellulose was the optimum concentration for retarding Metformin hydrochloride release which sustains the drug release more than 12 hours.

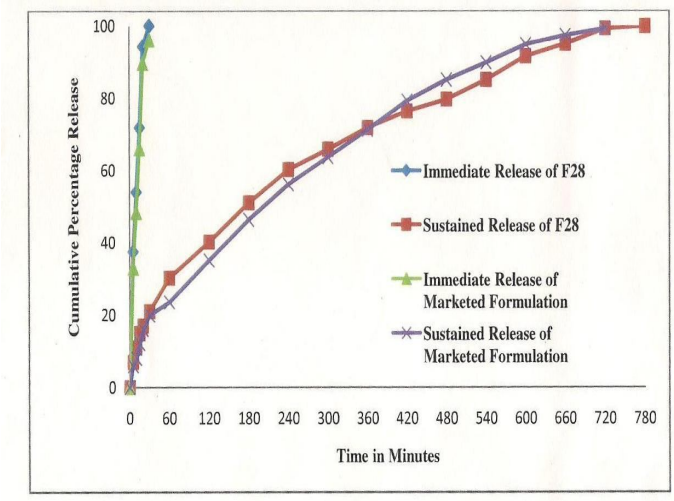

Fig 2: Comparative invitro dissolution of optimizes bilayer tablet F28 Vs Marketed Formulation

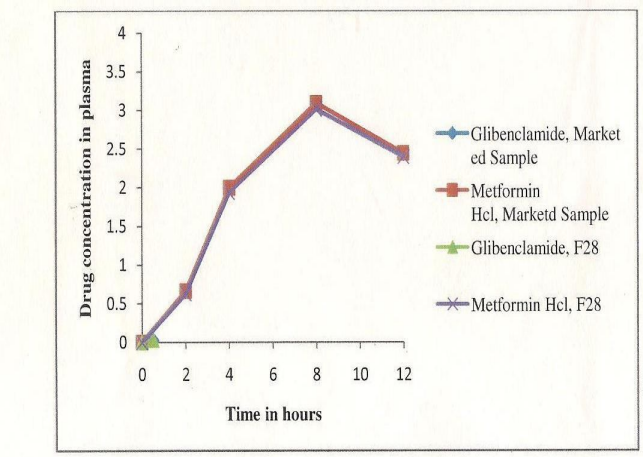

Fig 3. In-vivo release plot of F28 and Marketed product

In dissolution study data of sustained release formulations containing Metformin F13-F27 release percentage of drug in 12 hours time period F13, F14, F15, F16 and F17 prepared

In the optimized sustained release formulation F27 calculated regression coefficients for Zero order, First order and Higuchi model, Korsmeyer peppas and Hixson crowell were found to

be 0.932, 0.782, 0.998, 0.996 and 0.963 respectively. Therefore the release kinetics fits Higuchi model. The result of the invitro dissolution data were fitted to Korsmeyer-peppas equation which characterizes the transport mechanism. The value of release exponent 'n' for the optimized formulation was 0.510 indicated releases governed by anomalous transport (Non fickian) diffusion.

Stability studies were performed at $40^0c \pm 2^0c/75\%$ RH for a specified time period and analysed for weight variation, Hardness, Friability, Thickness, Drug content and invitro dissolution after a period of 30 and 60 days. The formulation showed acceptable limit only. The overall results showed that the formulation is stable for a period of 60 days.

CONCLUSION

The present research work was carried out using the combination of Glibenclamide 5mg for immediate effect in Hyperglycemia and 500 mg of Metformin hydrochloride to sustain the glycemic level for the effective therapy in Type11 diabetes mellitus. The dissolution data for the formulation F27 was fitted to Higuchi model described the mechanism as anomalous (Non fickan) diffusion.

Bilayer tablets F28 was formulated using croscarmellose sodium for immediate release of Glibenclamide showed 99.94% of release in 30 minutes and using hydrophilic HPMC K100 and hydrophobic Ethyl cellulose in the ratio of 1:1 released 99.90% of Metformin hydrochloride for the period of 13 hours. The in vivo study showed the bioavailability of the drug glibenclamide and metformin hydrochloride in plasma for the period of 30 minutes and 12 hours respectively.

From this research work it is evident that the formulated bilayer tablet has ability to release the Glibenclamide immediately and sustain Metformin hydrochloride for longer period of time, which can be used for treatment of type11 diabetes mellitus compared to Marketed formulation.

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