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FORMULATION AND EVALUATION OF BILAYERED TABLET OF METFORMIN HYDROCHLORIDE AND GLIMEPIRIDE

GHANSHYAM PATEL[1], Dr. RAGIN SHAH[1], BHAVIN BHIMANI[2], RAJENDRA PATEL[2] Dr. UPENDRA PATEL[2], DHIREN DASLANIYA[1]

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1. **Dept. of Pharmaceutics, JJT University, Jhunjunu, Rajasthan.**
2. **Dept. of Pharmaceutics, Arihant School of Pharmacy and Bio research institute, Gujarat.**

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Corresponding Author

Mr. Ghanshyam Patel

Dept. of Pharmaceutics, JJT University, Jhunjunu, Rajasthan.

Abstract

An attempt was to formulate Pharmaceutical equivalent bilayer tablet of Anti-diabetic by using the wet granulation method. In this formula one layer provide the loading dose by immediate drug release and another layer provide maintenance dose up to 10 hrs by extended release. The drug excipient computability study was carried out with FTIR study, there was no interaction found. Immediate release fraction was formulated by using cross carmellose sodium (CCS) as a disintegrating agent and sustained release fraction was formulated by using hydroxy propyl methyl cellulose (HPMC) as a rate controlling polymer. The granules were evaluated for angle of repose, bulk density, tapped density and compressibility index showed satisfactory results. The prepared bilayer tablets were evaluated as thickness, hardness, friability and *in-vitro* release studies. *In-vitro* dissolution study was carried out for 10 hrs using USP dissolution apparatus type II with 0.1 N HCl and 6.8 pH phosphate buffer as dissolution medium. From the Kinetic study of dissolution profile all batches were depicted for release mechanism of sustained release. Stability study was carried out for the optimized formulation at 40°C/75% RH for 1 month, the result shows that there was no significant change in physical and chemical parameter of the tablet.

INTRODUCTION

In the present scenario of pharmaceutical drug delivery system conventional pharmaceutical dosage forms are being replaced by new drug delivery systems. These are having edge over conventional systems in terms of many biopharmaceutical parameters and patient compliance. The development in the field of API, excipients and tableting machines or processing equipments during the past decade has made tablet manufacturing a science and tablets the most commonly used dosage form. Combination of one or more active ingredients gains importance in recent years to treat the various forms of diseases or to get the different therapeutic actions particularly from solid oral dosage form. In some cases, when two or more drugs are given simultaneously then incompatibility comes into action.[1,2,3] A drug interaction is a situation in which a substance affects the activity of a drug, i.e. the effects are increased, decreased and they produce a new effect that neither produces on its own. Typically, interaction between drugs comes to mind. A contemporary example of a drug interaction used as an advantage is the co-administration of carbidopa with levodopa (available as Carbidopa/levodopa). Levodopa is used in the management of Parkinson's disease and must reach the brain in an un-metabolized state to be beneficial. When given by itself, levodopa is metabolized in the peripheral tissues outside the brain, which decreases the effectiveness of the drug and increases the risk of adverse effects. However, since carbidopa inhibits the peripheral metabolism of levodopa, the co-administration of carbidopa with levodopa allows more levodopa to reach the brain un-metabolized and also reduces the risk of side effects.[4,5] Drug interactions may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion (ADME) of a drug. Alternatively, drug interactions may be the result of the pharmacodynamic properties of the drug, e.g. the co-administration of a receptor antagonist and an agonist for the same receptor.[6]

Lack of compliance is generally observed with long-term treatment of chronic diseases. Patient compliance is affected by

a combination of several factors, like awareness of disease process, patient faith in therapy and his understanding of the need to adhere to a strict treatment schedule also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and systemic side effects of the dosage form play role.[7] The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system. The magnitude of these fluctuations depends on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less. By reducing the total amount of drug, decrease in systemic or local side effects is observed. This would also lead to greater economy. Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues or organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration.[8, 9, 10]

The objective of the study is to formulate bilayer tablets consisting of Glimepiride as an immediate release layer and Metformin HCl as a sustained release layer. The immediate release layer was prepared using super disintegrant croscarmellose sodium and sustained release layer was prepared using matrix polymer hydroxypropylmethylcellulose (HPMC). [11, 12]

MATERIALS AND METHOD

Materials

Metformin HCl and Glimepiride were procured as a gift sample respectively from Abhilash chemicals PVT. Ltd. and IPCA Laboratories Ltd. Cross Carmelose sodium and HPMC of various grades were obtained as a gift sample from Colorcon PVT Ltd., Goa. All other chemicals were used of analytical grade and purchased from SD fine Chemicals.

Method

FORMULATION OF SUSTAINED RELEASE LAYER OF METFORMIN HCl GRANULES

Sifted Metformin HCl, Lactose Monohydrated, HPMC K100M, HPMC K15M CR, Lactose Monohydrated through sieve no. # 40. Mix the above sifted materials in Rapid Mixer Granulator for 5 mins at Impeller rpm 150. Dissolve PVP K-30 in 80 ml Isopropyl alcohol. Granulate above

mixture with binder PVP K-30 solution at Impeller rpm 150 and kneading for 2 mins at Impeller rpm 150 and chopper rpm 1500. Dried the granules in Fluid Bed dryer at 60°C until LOD 1.5 to 2.5 % w/w. Pass the granules through sieve no.# 20 in oscillating granulator and then mix with Aerosil for 5 mins in Cage blender. Finally lubricate with Magnesium Stearate for 3 mins in Cage blender. Composition of Metformin HCl Granules seen in Table 1.[13]

Preparation of Glimepiride Tablets

Glimepiride passed through sieve no. #40. Pass Microcrystalline cellulose through sieve no. #40 and Lake of Ethrosine through sieve no. #100 and mix in polybag.. Mix above both mixture in Polybag for 5 mins. Add Cross Carmelose Sodium in above mixture and shake for 5 mins. Dissolve PVP K-30 in 60 ml Isopropyl alcohol and 40 ml Dichlorometheline. Granulate above mixture with binder PVPK-30 solution. Finally lubricate with Magnesium Stearate for 3 min. in Cage blender. Composition of Glimepiride Tablet seen in Table 2.[14]

As previously reported procedure granules of Metformin HCl layer and Glimepiride layer were prepared separately and composition of combine layer seen in Table 3.

EVALUATION OF BI-LAYER TABLET

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture etc. Prepared tablet was evaluated for thickness, weight variation, hardness and friability as per IP' 2007 and results are shown in Table 4.

DRUG CONTENT ESTIMATION

Standard Solution: Weigh 25 mg of Metformin HCl and 25 mg of glimepiride, transfer them in 100 ml volumetric flask, made volume up to 100 ml with the diluents to prepare stock solution. From this stock solution pipette out 5 ml and dilute it up to 50 ml to prepare standard solution. Sample solution was prepared from powder of 20 tablets and equivalent weight was dissolved and checks out using HPLC method and result shown in Table 5.[15]

***IN- VITRO* DRUG RELEASE**

In-vitro drug release studies of the prepared bilayer tablets were conducted for a period of 24 hrs using USP XXIV type-I apparatus basket at 40°C ± 0.5°C and 75% ± 5%RH and 100 RPM speed. The dissolution studied

was carried out in duplicate for 12 hrs (initial 2 hrs with 0.1 N HCl and rest 10 hrs in pH citro phosphate buffer) under sink condition. At 5,10,15,30,45 mins and 1,3,5,7,10 hrs interval samples of 10 ml were withdrawn from the dissolution medium and replaced with freshed medium to maintain the sink conditions. After filtration the samples were analyzed by a HPLC method. The total content of the both drug in the sample was calculated using appropriate method constructed from reference standard. *In-vitro* drug releases of different batches of combination are shown in Figure 1, Figure 2 and data shown in Table 6.[16]

RELEASE KINETIC

The dissolution data obtained was fitted to various kinetic models like Zero order, First order, Higuchi, Hixson Crowell and the result are given in Table 7 and Release mechanism in Table 8.

STABILITY STUDY OF BI-LAYER TABLET

The bi-layer tablets were stored at 40° ± 5°C temperature and 75% ± 5% RH in stability chamber. Samples were withdrawn at 1 month time intervals and evaluated for drug content, weight variation, hardness, thickness and friability and result were shown in Table 9.[17]

RESULT AND DISCUSSION

EVALUATION OF PHYSICAL PARAMETER FOR BILAYER TABLET

In the bilayer tablet, white colored part made up of Metformin HCl SR layer while pink color part made up of glimepiride IR layer. Tablets are capsule shaped with breakline one side. Prepared bilayer tablet were evaluated for average weight, hardness, thickness and friability. Result of Physical parameter for bilayer tablet was shown in Table 4.

The bilayer tablets passes the weight variation test, thickness of the tablets was found within range and friability of the tablets was found less than 1% for both 100 and 200 revolutions.

ASSAY AND CONTENT UNIFORMITY OF BILAYER TABLET

Tablets were passed the both assay and content uniformity test.

***IN-VITRO* RELEASE STUDY**

The release rate of Bilayer tablet was determined using the USP XXIV dissolution testing apparatus II (Paddle). The

dissolution test was performed using 900 mL of 0.1N HCl and 50 rpm for 45 mins and then it is replace with pH6.8 phosphate buffer upto 10 hrs at 37±0.5^{0}C. Result of *in-vitro* release study was show in Table 6.

Dissolution rate study of different batches revealed that glimepiride release from all the tablets was rapid, reaching 95% within 45 mins. Hence they pass the dissolution tolerance limits according to IP. According to IP, a once daily Metformin HCl extended release formulation should release drug NMT 25%-40% in 3 hrs 40%-70% and in 5 hrs NLT 80% in 10 hrs in pH 6.8 Phosphate buffer. The batches B6 was found within IP limit. Dissolution pattern of batches varies with varying in the percentage of polymer.

KINETIC MODELING OF DISSOLUTION DATA

The kinetics of the dissolution data were well fitted to zero order, first order, Higuchi model, Hixson-Crowell and korsmeyer-peppas model as evident from regression coefficients. Here all formulation follows Higuchi release kinetics as depicted in Table 7. In case of the controlled release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. To find out release mechanism the *in-vitro* release data were fitted in korsmeyer-peppas equation where *n* is a factor, which indicates the mechanism of the release. The release exponent *n* was determined and given in Table 8. For all batches it was found that n value was greater than 0.45 and less than 1.0 which indicates anomalous transport mechanism.

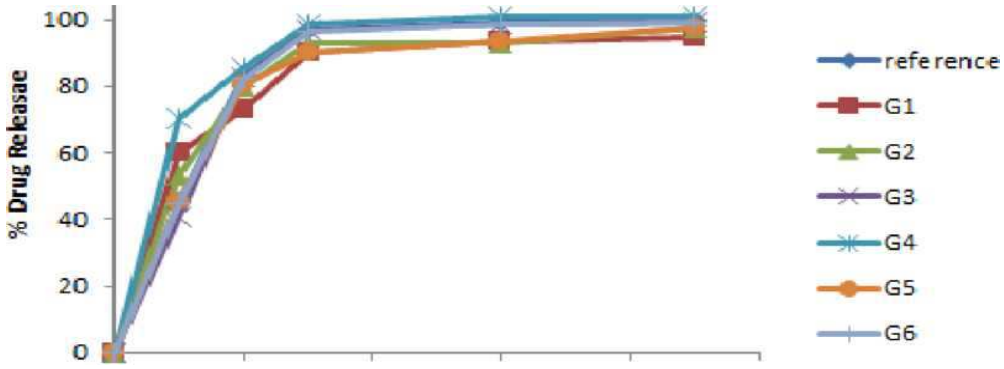
Stability studies of optimized Batch

Stability study was done to see the effect of temperature and humidity on tablets. Tablets were evaluated periodically (initial 1 month) for appearance, hardness, friability drug content and *In-vitro* drug release. The results of the stability study for the optimized batch was given in Table 9.

SUMMARY AND CONCLUSION

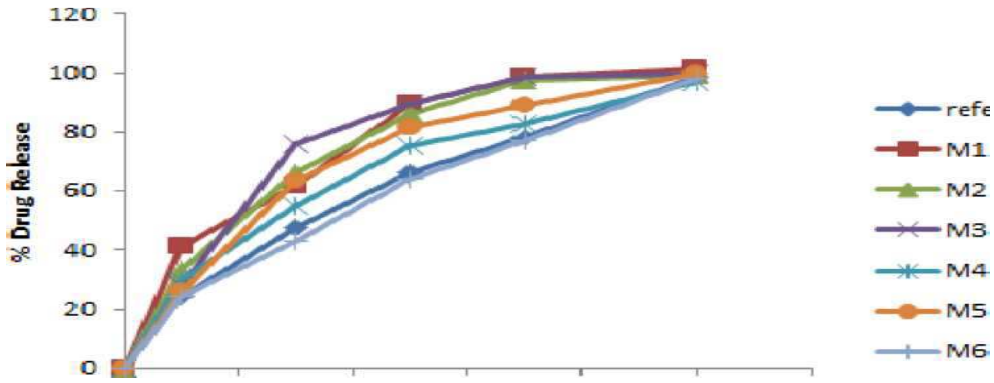
The present investigation was carried out to design and optimize Bilayer tablet for Metformin HCl and Glimepiride. Bilayer tablet containing barrier layer Metformin HCl sustained release tablet and immediate release Glimepiride tablet was successfully prepared by Wet granulation method. HPMC K100M was used as matrix forming polymers for Metformin HCl sustained

release tablet which drug release up to 10 hrs, whereas crosscarmellose sodium was used as super disintegrant for immediate release of Glimepiride . The initial burst release of Metformin HCl was controlled by subsequent drug release and matrix integrity was maintained by HPMC K100M.The results obtained in this study showed that the profile and kinetics of drug release were function of polymer type, polymer grade and polymer concentration for sustained release of Metformin HCl. Thus, an attempt made to design an effective formulation was feasible with the advantages of sustained release and immediate release action with a minimum amount of dose for Antidiabetic patients.



Time (Mins)

Figure 1 *In- vitro* drug release of Glimepiride (Immediate release layer)



Time (hrs)

Figure 2: *In- vitro* drug release of Metformin HCl (Sustained release layer).

Table 1

Composition of Metformin HCl Granules

Sr. No.	Ingredients	Batch M1	Batch M2	Batch M3	Batch M4	Batch M5	Batch M6
1.	Metformin HCl	500	500	500	500	500	500
2.	HPMC K15M CR	105	140	175	--	--	--
3.	HPMCK100M	--	--	--	105	140	180
4.	Lactose	95	60	25	90	55	15
5.	Monohydrated PVP K-30	5	5	5	10	10	10
6.	Isopropyl	QS.	QS.	QS.	QS.	QS.	QS.
7.	Aerosil	2	2	2	2	2	2
8.	Mg. Stearate	3	3	3	3	3	3
	Total	710	710	710	710	710	710

Table 2

Composition of Glimepiride Tablet

Sr. No.	Ingredients (in mg.)	Batch G1	Batch G2	Batch G3	Batch G4	Batch G5	Batch G6
1.	Glimepiride	1	1	1	1	1	1
2.	Microcrystalline cellulose	83.50	81.50	79.50	77.50	75.50	73.50
3.	Cross Carmelose Sodium	2	4	6	8	10	8
4.	PVP K 30	2	2	2	2	2	2
5.	Iso propyl alcohol	QS.	QS.	QS.	QS.	QS.	QS.
6.	Dichlorometheline	QS.	QS.	QS.	QS.	QS.	QS.
7.	Lake of erythrosine(color)	0.5	0.5	0.5	0.5	0.5	0.5
8.	Magnesium Stearate	2	2	2	2	2	2
	Total	90	90	90	90	90	90

Table 3

Composition of Bilayer tablet of Metformin HCl and Glimepiride

Sr. No.	Batch no.	Batch B1	Batch B2	Batch B3	Batch B4	Batch B5	Batch B6
1.	Metformin HCl granules	710	710	710	710	710	710
2.	Glimepiride Tablets	90	90	90	90	90	90
3.	Total Weight	800	800	800	800	800	800

Table 4

Evaluation of Physical parameter for Bilayer tablet

Batch	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
B1	802±0.72	4.30±0.2	6.6± 0.14	0.92±0.005
B2	805± 0.71	4.25±0.3	6.5 ± 0.13	0.95±0.002
B3	808±0.73	4.30±0.2	6.3 ± 0.15	0.94±0.004
B4	800±0.72	4.30±0.5	7.4 ± 0.16	0.95±0.001
B5	801± 0.71	4.28±0.5	7.1 ± 0.14	0.80±0.004
B6	802±0.73	4.35±0.2	6.7 ± 0.14	0.91±0.003

Table 5

Assay of bilayer Tablet.

Batch	% Metformin HCl (n =3)	% Glimepiride (n =3)
B1	101.3±5.24	99.71±1.25
B2	98.5±6.45	98.45±1.10
B3	103.1±5.23	99.32±1.32
B4	102.3±4.35	98.33±1.33
B5	98.4±2.42	99.33±2.11
B6	97.3±4.05	99.33±2.10

*value expressed as mean (n) ± S.D

Table 6

***In-vitro Drug* release study of Bilayer tablet**

	% Drug release of Glimepiride in 0.1N HCl						
Time (in mins)	Marketed	B1	B2	B3	B4	B5	B6
5	45.09	60.09	53.22	40.5	70.32	45.10	44.79
10	83.45	73.00	79.82	82.92	85.65	80.50	82.15
15	96.9	90.00	92.89	97.02	98.89	90.00	96.56
30	99.12	93.33	93.17	98.39	101	93.33	98.80
45	100	94.83	97.36	99.14	101.1	97.75	99.25
	% Drug release of Metformin HCl in pH 6.8 phosphate buffer						
Time (in hrs)	Marketed	B1	B2	B3	B4	B5	B6
1	24.27	41.50	33.25	28.25	30.18	26.17	24.51
3	47.48	61.58	66.15	75.80	55.10	63.68	42.81
5	66.50	89.56	86. 15	89.30	75.58	81.86	63.80
7	77.96	98.70	97.50	98.45	82.68	89.10	77.20
10	98.50	101.6	99.10	99.60	96.70	99.80	98.05

Table 7

Kinetic study of dissolution data of all batches

Coefficient of determination (R^2)

Batch	Zero order	Higuchi	First order	Hixson Crowell	K-peppas
Batch B1	0.960	0.978	0.812	0.923	0.960
Batch B2	0.934	0.983	0.873	0.869	0.933
Batch B3	0.924	0.971	0.854	0.852	0.924
Batch B4	0.909	0.964	0.849	0.934	0.909
Batch B5	0.957	0.984	0.847	0.911	0.957
Batch B6	0.928	0.946	0.782	0.926	0.928

Table 8

Release mechanism follow by dosage form as per k-peppas model

Batch	**n value**	**Release mechanism**
Batch B1	0.5251	Anomalous diffusion
Batch B2	0.5186	Anomalous diffusion
Batch B3	0.4865	Anomalous diffusion
Batch B4	0.4522	Fickian diffusion
Batch B5	0.5102	Anomalous diffusion
Batch B6	0.4727	Anomalous diffusion

Table 9

Stability data of B6 at accelerated (40±2°C & 75±5% RH) conditions

Test	Initial	1 Month
Appearance	White and pink color, capsule shape tablet with break line one side.	No Change in appearance
Hardness (kg/cm)	6.8±0.14	6.7±0.11
Thickness (mm)	4.30±0.2	4.32±0.3
Friability (%)	0.91 %	0.93%
Assay for Glimepiride	98.5%	99.25%
Assay for Metformin HCl	98.45%	95.45%

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