Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Formulation and Evaluation of Bilayer Tablets of Metformin Hydrochloride

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ARTICLE HISTORY

Received: 1-Jul-2011

Accepted: 10-Aug-2011

Available online 10-Nov-2011

Keywords:

Bilayer tablets, Metformin, *In vitro* studies, stability testing.

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ABSTRACT

The objective of the work was to design a controlled release oral dosage form of metformin bilayer tablet. In this formulation the loading dose was incorporated in the immediate release layer so that the minimum effective concentration may be attained within a shorter period of time after this the maintenance dose level will be taken over by the drug release from the second layer of the bilayer tablet. Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.The Bilayer tablets of Metformin HCL were prepared by direct compression method. F_{10} is considered to be the optimized formulation with the desired drug release. The polymers which have been used in the best formulation (F10) are HPMC K_4M and SCMC, Starch, Croscarmelose sodium, Crospovidone. The granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, hausner's ratio and moisture content. The tablets were subjected to weight variation, thickness, hardness, friability, drug content and invitro release studies. The results of FTIR analysis of pure drug, drug – excipients mixtures and tablet formulations showed that there was no physical and chemical interaction of drug with the other excipients.The stability studies of optimized formulation F_{10} at 25°C/60 % RH, 30°C / 75% RH, 40°C/75% RH for 3 months did not show any variation in the tested parameters and release also. The TG/DTA analysis reveals that there is a weak intermolecular interaction between drug and excipients. The phenomenon of drug release shown that the release of optimized formulation F10 is controlled by swelling mediated diffusion. By using the sustained release dosage form incidents of both local and systemic adverse effect can be reduced.

INTRODUCTION

Tablets are composed of two layers of granulation compressed together. Bilayer tablets require fewer materials than compression coated tablets, weight less, and may be thinner. Monograms and other distinctive marking may be impressed in the surface of the bilayer tablets[1]. Colouring the separate layers provide many possibilities for unique tablet identity.Blood level of a drug can be held at consistent therapeutic level for improved drug delivery, accuracy, safety and reduce side effects. Reduction of adverse side effect can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced[2].

Metformin HCL (N,N-dimethylimidodicarbonimidic diamide) is an oral anti-diabetic drug. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function and evidence suggest it may be the best choice for people with heart failure . It is also used in the treatment of polycystic ovary syndrome[3-5].

Bilayer tablets readily lend themselves to repeat action products. Where in one layer on layered tablet provides the initial dose , rapidly disintegrate in the stomach the other layer are insoluble in gastric media but released in the intestinal environment. The combined use of this also reduces the use of large amount of drug and frequency of dosing for the diabetic effect. Metformin HCL is an oral anti diabetic drug used in management of type-2 diabetes. During this long term therapy, sometimes lactic acidosis may be happened. It produces severe effect to the patient. To avoid its unusual problem of metformin effects, we designed the bilayer sustained release tablets. The tablets produced by this attempt not produce dose dumping and slow release of medicament avoids lactic acidosis. The half-life of metformin is 4-8hrs hence are suitable candidates for the design of sustained release drug delivery system[6-10].

MATERIALS AND METHODS

Metformin HCL was obtained as gift sample from Sun pharmaceuticalLtd, Vadodara, India. Hydroxy propyl methyl cellulose (HPMC K_4M), Croscarmellose sodium, Crospovidone from Vigro chem, India. Sodium carboxy methyl cellulose Microcrystalline cellulose were purchased from Himedia Labs, Mumbai. The bilayer tablets were prepared by directcompression.

Formulation of Bilayer Tablets

Preformulation Studies [11, 12]

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined

Table No. 1 : Composition of immediate release layer of metformin HCL

S.No	Ingredients	Category	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Metformin HCL	Active ingredient	150	150	150	150	150	150
2	Microcrystalline cellulose	Diluent	5	10	5	-	-	-
3	Cross carmellose sodium	Superdisintegrant	-	-	-	5	-	5
4	Cross povidone	Superdisintegrant	-	-	-	-	5	5
5	Magnesium stearate	Lubricant	3	3	3	3	3	3
6	Talc	Glidant	2	2	2	2	2	2

with excipients. It is the first step in the rational development of dosage forms. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms. The use of preformulation parameters (I.R spectrum, drug – excipients compatibility studies, Angle of repose, Bulk density and tapped density, Hausner ratio and Carr's index and Loss on drying) maximizes the changes in formulating an acceptable, safe, efficacious and stable product. The drug (Metformin HCL) in powder form and granules were subjected to the following physical test for 3 times and average values were noted.

Preparation of immediate release layer of Metformin HCL

Metformin HCL immediate release tablets were prepared by using direct compression method. The Microcrystalline cellulose,Croscarmellose sodium,Cros povidone powder and the active ingredient were mixed homogenously. Magnesium stearate and talc were added as a lubricant (Table No. 1.).

Preparation of extended release layer of Metformin HCL

Metformin HCL sustained release layer were prepared by using direct compression method. The Hydroxyl propyl methyl cellulose (HPMC),Sodium carboxy methyl cellulose(SCMC), Soluble starch, Lactose and the active ingredient were mixed homogenously. Magnesium stearate and talc were added as a lubricant (Table No. 2.).

Table No. 2: Composition of sustained release layer of metformin HCL

S.No	Ingredients	Category	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
1	Metformin HCL	Active ingredient	350	350	350	350	350	350	350	350	350	350
2	HPMC K4M	Polymer	60	70	80	70	70	70	70	70	70	70
3	SCMC	Polymer	-	-	-	5	10	15	10	10	10	10
4	MCC	Diluent	-	-	-	-	-	-	10	20	-	-
5	Starch(dried)	Diluent	-	-	-	-	-	-	-	-	5	10
6	Lactose	Diluent	10	10	10	5	5	5	5	5	5	5
7	Magnesium stearate	Lubricant	3	3	3	3	3	3	3	3	3	3
8	Talc	Glidant	2	2	2	2	2	2	2	2	2	2

Tablet Compression

The bilayer tablet compression was made using 10mm punch in a 16 station rotary tablet machine. In this, sustained release metformin granules were introduced first in to the die cavity and a slight precompression was made so that the layer was uniformly distributed, afterthat immediate release metformin granules were added and a final compression was made.

Evaluation of Tablets [13-14]

a) Thickness and Diameter

The thickness and diameter of the tablets were carried out using vernier caliper (Mitutoyo corps, Japan). Five tablets were used for the above test from each batch and results were expressed in millimeter.

b) Hardness test

Tablets require a certain amount of strength, or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by "Monsanto hardness tester". Five tablets from each batch were used for hardness studies and results were expressed in Kg/cm^2.

(c) Weight variation test

Twenty tablets were selected at random individually weighed in a single pan electronic balance (Ax, shimadzu – corporation, Japan) and the average weight was calculated. The uniformity of weight was determined according to I.P specification. As per I.P not more than two of individual weight would deviate from average weight by more than 5% and none deviate more than twice that percentage.

(d) Friability test

The friability of the tablets were determined by Roche friabilator. In this apparatus, the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of six inches with each revolution. Pre-weighed 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

$$Friability = \frac{Weight\ \ loss}{Weight\ of\ tablets\ before\ operation} \times 100$$

(e) *In vitro* dissolution Studies by U.V spectrophotometer

In vitro drug release studies of Metformin HCL was studied using dissolution apparatus USP XXI Rotating basket method. pH 1.2 (0.1N HCL) buffer 900 ml was used as the dissolution medium.Tablet was placed in a basket and rotated at a speed of 50 rpm maintained at a temperature of 37±0.5°C. One ml of the sample was withdrawn at periodic time interval of 5,10,15,20,25,30mins and was made up to 10ml with 0.1 N HCL buffer solution. One ml of fresh dissolution medium was replaced after each time of withdrawn of sample. Followed by study in simulated intestinal fluid (pH 7.4 Phosphate buffer solution) used in 900 ml dissolution medium.The dissolution samples 1 ml were collected at an interval of 1,2,3,4,5 upto 24 hrs with replacement of equal volume of fresh dissolution medium.The sample was made upto 10 ml with pH 7.4 buffer solution and its absorbance was measured at 232 nm.The amount of drug was calculated using standard graph.

(f) Content Uniformity Test

Standard preparation:

Prepare a solution of USP Metformin Hydrochloride in water having a known concentration of about 10 µg per ml.

Sample preparation of Metformin HCL

One tablet was finely powered and dissolved in 70 ml of water and then shaken by mechanical means for 15mts, dilute with water to volume, and filter, discarding the first 20 ml of the filtrate. Dilute 10ml of the filtrate with water to 100ml, and 10ml of the resulting solution with water to 100ml and measured the absorbance at 232nm.

Stability Studies [15]

As per *in vitro* release formulation F_{10} was found to be desirable than other formulations. Hence it was chosen for stability studies. The tablets were packed and kept in different temperatures for 3 months at 4°C, 40°C / 60% relative humidity and 60°C/ 75% relative humidity. At the interval of 1 month tablets were withdrawn and evaluated for physical properties like thickness, hardness, diameter, friability, weight variation and content uniformity. *In vitro* drug release is also carried out.

TG / DTA studies

For the optimized formulation F10 Thermogravimetry / Differential thermal analysis were performed to characterize drug – excipients compatibility. The TG/DTA thermograms of pure drug and mixture recorded in a TG/DTA analyzer (SDT Q 600 , India) at a heating rate of 20°C/min from 0 to 500°C in an nitrogen atmosphere.

Data Analysis [15]

To analyze the mechanism of release, the best formulation was subjected to some statistical tests.

Results of the data were fitted into the following equation.

- Zero order equation
- First order equation
- Higuchi plot
- Peppas plot.

RESULTS AND DISCUSSION

The present study was undertaken to formulate Metformin HCL Bilayer tablets. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time. The short biological half-life and dosing frequency more than one per day make the drug an ideal candidate for sustained release.

The tablets prepared in the present study by direct compression method have advantages over those prepared by wet granulation in terms of time and energy consumption, thus making it possible to formulate tablets at a lower cost. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery.

The study involved pre-formulation of drugs and granules, formulation and processing development along with evaluation of the tablets.

Pre-formulation Study of Drug

The Metformin HCL was subjected to drug-excipients compatibility study with excipients like hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, microcrystalline cellulose, croscarmellose sodium, cros povidone, starch, talc and magnesium stearate. The mixtures shown to have no colour change.

The angle of repose for pure drug was very less and hence the poor flow of the pure drug was exhibited. Also the carr's index of the pure drug was found to be high, confirming that the drug has poor flow properties and compressibility.

Good flow of powders / granules is essential in tableting because the compressibility & flow properties of the drugs likely to influence the compression process in the preparation of tablets. In view of this the formulation were prepared by direct compression technique to improve the flow as well as compressability.

Table No. 3: Preformulation study data of the pure drug.

S.No	Parameters	Values obtained
1.	Angle of repose (θ)	10.34 ± 0.002
2.	Loss on drying (%)	0.415 ± 0.005
3.	Bulk density (gm/ml)	0.3175 ± 0.006
4.	Tap density (gm/ml)	0.4358 ± 0.003
5.	Hausner ratio	1.5 ± 0.002
6.	Carr's index	27.16 ± 0.561

*Values mentioned are average of 3 determinations.

Evaluation of Powder Blend

The prepared granules of the formulations were evaluated for the parameters like bulk density, tap density, compressibility index, hausner ratio, angle of repose and loss on drying.

- After granulation, angle of repose was improved.
- Hausner ratio was found to be 1.2 (or) less than 1.2.
- Carr's index was found to be in the range of 12 – 16.
- All these values indicated that the granules have good flow property and hence the granulation process has improved the flow property.

IR Report

When FT IR Spectrum of Metformin HCL (pure drug), excipients and optimized formulation of Metformin HCL bilayer tablets (F10) were compared, therewere no major changes in the position of the spectrum. It indicates absence of physical and chemical interaction among active component Metformin HCL and excipients. So the bilayer tablets of Metformin HCL has no interaction with added excipients.

In Vitro Release of Immediate Release Layer

In formulation F_1,F_2,F_3 formulations microcrystalline cellulose was used in concentration of 5,10,15mg and the release was found to be 38.44%, 52.85% and 60.06% respectively. Hence, to get more release it was decided to alter the formulation further. In F_4 formulation only croscarmellose 5mg was used and release was found to be 74.47%. In F_5 formulation only crospovidone 5mg was used and release was found to be 86.49%. In F_6 formulation, combination 5mg of croscarmellose sodium and 5mg of cros povidone were used and release was found to be 97.30% at 30 min. The percentage of drug release increased with combination of super disintegrants like croscarmellose sodium and crospovidone which may be due to its strong swelling property and highly porous structure of the cros povidone.

In Vitro Release of Sustained Release Layer

In F_1, F_2, F_3 formulation HPMC K4M in various concentration 60,70,80 mg was used and release was found to be at the end of 24th hrs 32.13%, 41.14% and 37.23% respectively. In F_1 and F_3 the release was in lower side. HPMC itself fail to retard the release of drug through the matrix because of its solubility in stomach pH. So in further formulations SCMC was used along with HPMC. HPMC K4M 70 mg (F_2 formulation) was selected for further formulation. In F_4, F_5 and F_6 formulations SCMC was used in the concentration of 5, 10, 15 mg and release was found to be 48.85%, 64.27% and 55.25% respectively. In F_5 formulation release at the end of 24th hrs 64.27%. So SCMC 10 mg was selected in other formulation. In F_7 and F_8 HPMC K4M 70 mg, SCMC 10 mg addition to MCC 10 mg and 20 mg was used and release was found to be 69.47% and 74.57% respectively. In F_9 formulation HPMC K4M 70 mg ,SCMC 10 mg instead of MCC starch was included in the concentration of 5mg and release was found to be 83.59%.As the expected release was 90% by USP limit. So F_9 formulation was slightly altered. In F_{10} formulation HPMC K4M 70 mg ,SCMC 10 mg and starch 10 mg was included and the release was found to be 97.60%.The *invitro* release pattern of sustained release layer of Metformin HCL was found to be satisfactory as per USP limit. Hence, the formulation F_{10} is the optimized one.

Evaluation of Tablets

The thickness and diameter were found in the range of 6.0 ± 0.024 to 6.5 ± 0.048 and 10.2 ± 0.047 to 10.9 ± 0.048 respectively.Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within the I.P limit. Mostly, the variation was within ± 5%. The hardness of the different formulations ranged from 4-7 kg / cm^2. All the formulations exhibited less than 1% friability. The content uniformity were found to be within the limits (98 to 99.78%). It shows that the drug was uniformly distributed throughout the tablets.

Stability Studies

The optimized F_{10} formulation was subjected to accelerated stability conditions for 3 months at 4°C, 40°C / 60% relative humidity and 60°C/ 75% relative humidity. At the interval of 1 month tablets were withdrawn and evaluated for various parameters like thickness, diameter, weight variation, hardness, content uniformity and dissolution. The tablets did not show any variation in the tested parameters and the results were within the limits.

TG\DTA studies

The TG/DTA pattern for pure Metformin HCL. In DTA analysis weight loss occurs at 234.3°C and 365.1°C. In TG analysis weight loss occurs at 325ºC, 405ºC. The TG/DTA pattern for sample. In DTA analysis endothermic peak at 224.4°C, 342.2°C. When compared to pure sample (FC-1) it shows slight displacement, broadening of peak and less area of the peak. This is due to the presence of excipients. This confirms, the molecular integrity of Metformin HCL is still maintained.In TG analysis weight loss occurs at 300ºC, 425ºC. The sample (F-2) requires high range of temperature for degradation which is due to the presence of excipients. This denotes that there is no interaction occurs between drug and excipients.

Phenomenon of Drug Release

The formulations was subjected to graphical treatments to assess the kinetics of drug release.Release was approaching Zero order.

Zero order Equation

The results data was fitted into the Zero order equation.

$Q = K_0 t$

Q = The amount of drug released at time t

K_0 = Release rate

First order Equation

The results data was fitted into the first order equation.

$$\text{Log } C = \text{Log } C_0 - kt/2.303$$

C_0 – is the initial concentration of drug

K – is the first order constant

t - is the time.

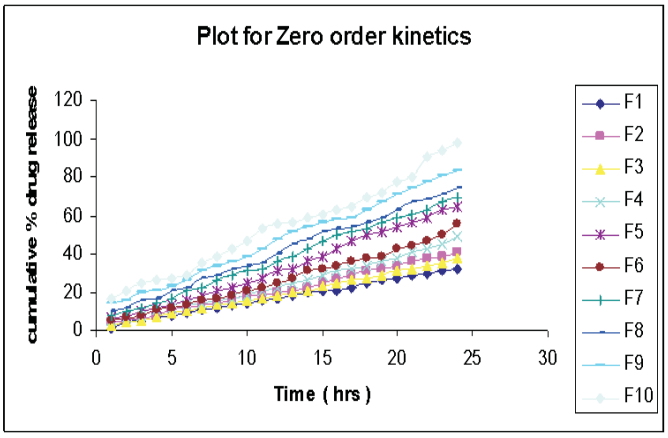

Fig. 1 : Zero order kinetics Treatment of formulations F1 to F10

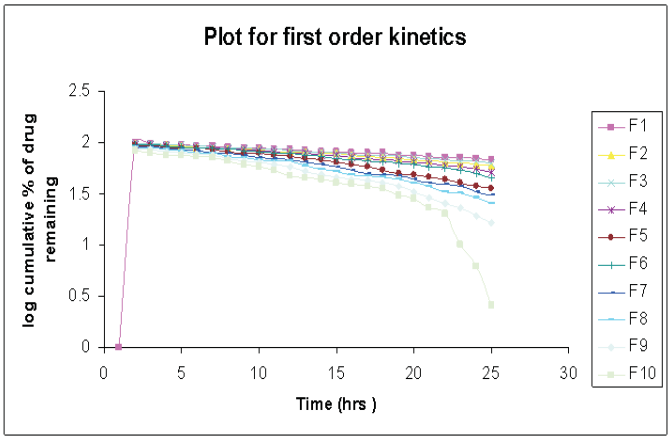

Fig. 2 : First order kinetics Treatment for formulations F1 to F10

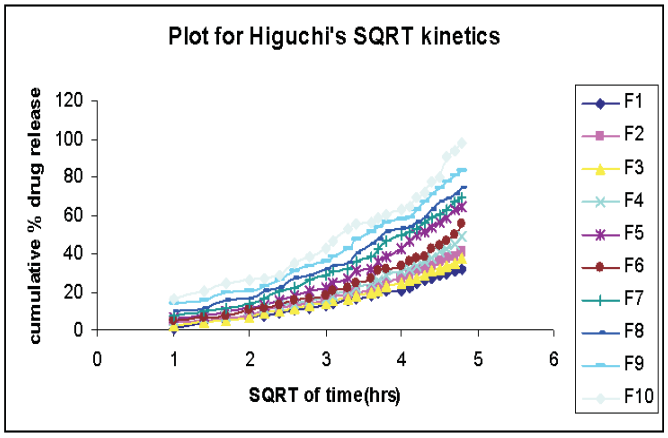

Fig. 3 : Higuchi's plot of formulations F1 TO F10

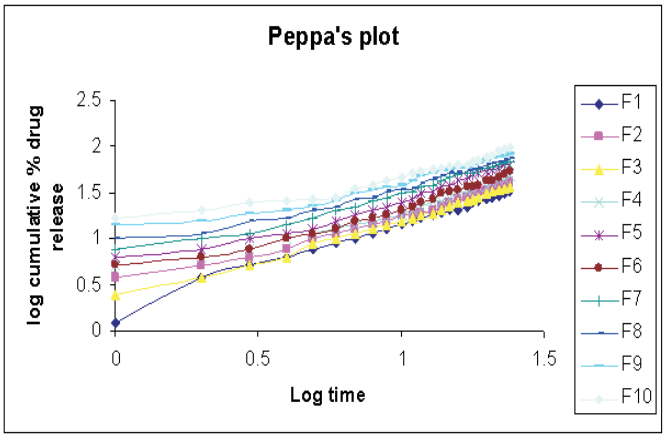

Fig. 4 : Peppa's plot of formulations F1 TO F10

Higuchi Plot

The graph was plotted between cumulative % release and square root of time. The regression value of F10 was 0.9692. This indicates, that diffusion is one of the mechanism of drug release.

Peppas Plot

The graph was plotted between log cumulative % of release and log time. The slope (n) value of F10 was 0.9736. This indicates, swelling mediated diffusion is the mechanism of drug release.

CONCLUSION

The Bilayer tablets of Metformin HCL were prepared by direct compression method. F_{10} is considered to be the optimized formulation with the desired drug release. The polymers which have been used in the best formulation (F10) are HPMC K_4M and SCMC, Starch, Croscarmelose sodium, Crospovidone. The granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, hausner's ratio and moisture content. The tablets were subjected to weight variation, thickness, hardness, friability, drug content and invitro release studies. The results of FTIR analysis of pure drug, drug – excipients mixtures and tablet formulations showed that there was no physical and chemical interaction of drug with the other excipients. The stability studies of optimized formulation did not show any variation in the tested parameters and release also. The TG/DTA analysis reveals that there is a weak intermolecular interaction between drug and excipients. The phenomenon of drug release shown that the release of optimized formulation F10 is controlled by swelling mediated diffusion

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