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Formulation and evaluation of Metformin HCl extended release tablets

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ABSTRACT

Metformin HCl is an oral anti-diabetic medicine which keeps the blood sugar level under control. It's extensively used in Type 2 (non-Insulin dependent) diabetes. The present study undertaken aims at the formulation development and evaluation of extended release tablets of metformin HCl, which releases the drug in a sustained manner over a period of 12 hours. Two different grades of Hydroxy Propyl Methyl Cellulose (HPMC) namely K_{15M} and K_{100M} were used for the preparation of tablets. The tablets were prepared by wet granulation method and evaluated for thickness, weight variation; hardness, friability, disintegration time, and percentage drug content, invitro drug release and Fourier transform infrared (FT-IR) spectroscopy. During the study it was found that the formulation F_{11} can be considered as an ideal or optimised formulation for extended release tablet of metformin HCl. The optimised formulation showed sufficiently sustained drug release for more than 12 hours. As the concentration of HPMC increased the drug release pattern declined.

Key words: Metformin HCl, Extended release, Hydroxy Propyl Methyl Cellulose (HPMC), Wet granulation, Release kinetics.

INTRODUCTION

Conventional drug products like tablets and capsules are formulated to release the active drug immediately to obtain rapid and complete systemic absorption of the drug. The conventional dosage form maintains the constant plasma drug concentration for the long period of time by administering in a particular dose and at particular frequency[1].

Increased complications and expense involved in discovery of new drug entities has greater attention on development of sustained release or controlled release drug delivery system. Among various dosage forms, matrix tablets are widely accepted for oral controlled release as they are simple to formulate. This system prolongs or controls release of drug that is dissolved or dispersed in the matrix. Polymers and release retarding materials are used as matrix forming materials. They play a vital role in controlling the drug release from the matrix materials [2]. Sustained-release products have become important for the oral administration of many drugs because they give more consistent blood levels [3].

Metformin HCl, an effective antidiabetic that requires controlled release owing to its short biological half-life of 3.4 ± 0.7 hours[4]. Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of and the type -II diabetes, is a common disease that combines defects of both insulin secretion and insulin action[5].It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability is reported to be of 50% - 60%[6].An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occurs during the initially period of treatment. The compound has relatively short plasma half life of 1.5-4.5 hours and the low absolute bioavailability of 50%-60% [7]. Side effects, short half lives, low bioavailability and the need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release formulation that would maintain plasma level for 8-12 hrs might be

sufficient for daily dosing for metformin sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances.

The present study undertaken aims at the formulation development and evaluation of extended release tablets of metformin HCl, which releases the drug in a sustained manner over a period of 12 hours. Two different grades of Hydroxy Propyl Methyl Cellulose (HPMC) namely K_{15M} and K_{100M} were used for the preparation of tablets.

MATERIALS AND METHODS

Materials

Metformin HCl was obtained from universal medicament, Nagpur, India. Microcrystalline cellulose (MCC P^{H}_{102}), Sodium Carboxy Methyl Cellulose, Aerosil, povidone where purchased from S.D Fine Chem. Labs (Mumbai, India). HPMC (K_{15M} and K_{100M}) was obtained as gift sample from Apex Pharmaceuticals, Chennai, India. All other ingredients used throughout the study were of analytical grades and were used as received.

Estimation of Metformin HCl

The analysis for the drug was carried out using UV/VIS spectrophotometer (Shimadzu 1700, Kyoto, Japan) at the y max of the drug which is 233 nm, using a quartz curette cell and against an appropriate blank .All samples were appropriately diluted before reading the absorbance. The absorbance readings were converted to concentration in µg/mL by using an appropriate

Preparation of the tablets

Metformin hydrochloride extended release tablets were prepared by wet granulation method. A rotary tabletting machine (Rimek Minipress I Ahmadabad, India), equipped with 14-mm flat faced circular punches was employed to prepare tablets at a constant compression force. All the ingredients were weighed accurately. Metformin hydrochloride was passed through sieve no.30.Methocel K 100MCR, Microcrystalline cellulose PH102, sodium CMC, povidone k30 and Colloidal silicon dioxide were passed through sieve. No 40.Magnesium stearate was passed through sieve. No 60.metformin, MCC PH102, Sodium CMC, Methocel were mixed and blended. To this povidone in water mixture was added. Colloidal silicone dioxide was also added and sieved to get granules. These granules were dried in a tray dryer at 60^0c. Finally lubricant was added and compressed (Table 1).

Table 1: Composition of various trial Formulations for the Metformin HCl Extended release tablet

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
01.	Metformin HCl	500	500	500	500	500	500	500	500	500	500	500
02.	MCC PH102	220	160	125	100	75	200	150	125	85	60	55
03.	HPMC K100M	0	0	0	0	0	200	250	275	300	320	330
04.	HPMC K15M	200	250	275	300	325	0	0	0	0	0	0
05.	Sodium CMC	10	20	30	30	30	30	30	30	45	45	45
06.	Povidone	30	30	30	30	30	30	30	30	30	30	30
07.	Aerosil	5	5	5	5	5	5	5	5	5	5	5
08.	Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5
09.	Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Total weight	990	990	990	990	990	990	990	990	990	990	990

Evaluation of Granules [8,9]

Angle of repose is a relatively simple technique for estimation of the flow property of a powder. Powders with low angle of repose are free flowing and those with a high angle of repose are poorly flowing powders.10 gm of granules were passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:-

Angle of repose (θ) = tan-1

The Carr's compressibility index was calculated by calculating the tapped and bulk density using the 100 ml measuring cylinder. Compressibility is calculated by the formula,

$$C = 100 \times \left(1 - \frac{\rho B}{\rho T}\right)$$

Where ρB is the freely settled bulk density of the powder, and ρT Hausner's Ratio is the tapped bulk density of the powder. A Carr's index greater than 25 is considered to be an indication and poor flowability, and below 15, of good flow ability.

Hausner's ratio was related to interparticle friction and could be used to predict powder flow properties. Hausner's values of the prepared granules ranged from 1.12 to 1.25 were thought to indicate good flow properties.

Evaluation of Tablets [10]

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tabmachine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method.

***In-vitro* Drug release studies [11]**

Drug release studies were conducted using USP dissolution apparatus I, basket type (Electrolab, Mumbai, India) at a rotational speed of 100 rpm at 37±0.5 ºC. The dissolution media used were 900 mL of 1.2 pH for first 2 hours followed by pH 6.8 phosphate buffer solutions for 12 hrs. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of prewarmed (37±0.5 ºC) fresh dissolution medium was replaced to maintain the volume constant.

FT-IR Studies

The infrared spectra of metformin HCl pure drug, physical mixture of optimized formulation were recorded between 400-4000 cm^{-1} on FT-IR spectroscopy.

Table 2: Physicochemical evaluation of the formulations

Trial	Bulk Density	Tapped Density	Compressibility Index (%)	Hausner's Ratio (%)	Angle Of Repose(^{0})
F1	0.5	0.63	16.21	1.0	25
F2	0.490	0.67	17.45	1.01	27
F3	0.6	0.72	16.10	1.05	25
F4	0.5	0.69	16.1	1.0	24
F5	0.59	0.72	16.8	1.3	24
F6	0.52	0.65	15.8	1.27	25
F7	0.5	0.73	14.69	1.29	23
F8	0.58	0.69	15.4	1.19	24
F9	0.58	0.68	14.98	1.11	25
F10	0.56	0.68	13.9	1.21	23
F11	0.57	0.65	13.2	1.1	23

Table 3: Evaluation of tabletting parameters of Metformin HCl

Formulation Code	Thickness (mm)	Weight variation (mg)	Friability (%)	Hardness (Kg/cm^2)	Disintigration Time(min)	%drug content
F1	5.6±0.2	990±0.5	0.4	7	13	93.2
F2	5.7±0.2	985±0.8	0.38	7	15	94.19
F3	5.5±0.1	980±0.4	0.4	8	14	94.02
F4	5.9±0.3	980±0.08	0.09	9	13	95.6
F5	6.9±0.3	990±0.05	0.2	9	15	97.01
F6	6.8±0.2	985±0.5	0.35	10	14	99.27
F7	6.9±0.2	980±2	0.2	9	14	98.00
F8	6.7±0.3	980±0.05	0.3	8.7	15	97.16
F9	6.9±0.4	985±0.8	0.4	9.2	14	96.04
F10	6.8±0.3	980±0.5	0.3	9.2	15	98.21
F11	6.8±0.2	985±0.7	0.2	9.2	14	99.09

RESULTS AND DISCUSSION

The UV scanning of metformin HCL showed a maximum absorbance at 233 nm. There was no sifting in λ max for the drug at various pH values. The calibration curves of metformin HCL was linear in different dissolution media at various pH values. The correlation coefficient (r^2) was higher than 0.993. The powder blend of nine formulations (F_1 to F_{11}) was evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio showed that the pre-compressed blends has good flow property (Table 2).Permissible limits: hardness of tablet was fixed at 10kg/cm^2.The tablets were subjected for weight variation, thickness, hardness, friability, disintegration and drug content. These parameters were found to be within standard limits and satisfactory (Table 3).

In-vitro drug release studies were performed with all formulations. The results are accordingly tabulated in (Table 4, 5 Fig 1, 2). The percentage drug release for the formulation $F_{11}$was found 96% respectively at the end of 12 hours. Formulation F5 prepared was found to be the optimised formulation.

Table 4: Drug release profile of formulae containing HPMC K15M

Time(hr)	**% drug release**					
	innovator	F1	F2	F3	F4	F5
0	0	0	0	0	0	0
1	30.8	49.2	48.5	45.3	43	40
3	54.6	66.7	65	57.6	58	58.9
6	70.4	90.6	85	88.3	83.8	80.8
9	81.3	100.2	98	98.1	96.7	92.6
12	92.1	100.1	100	100	100	100

Table 5: Dissolution profile of formulae containing HPMC K100 MCR

Time(hr)	**% Drug Release**						
	Innovator	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0
1	30.8	49	45.6	44.1	43	40.8	38.8
3	54.6	61.9	61	59.8	58	58.9	59
6	70.4	85	88.9	88.3	81.8	77.9	76.5
9	81.3	98	99	98.1	96.7	88.5	87.9
12	92.1	100	100.1	100	100	95.6	96

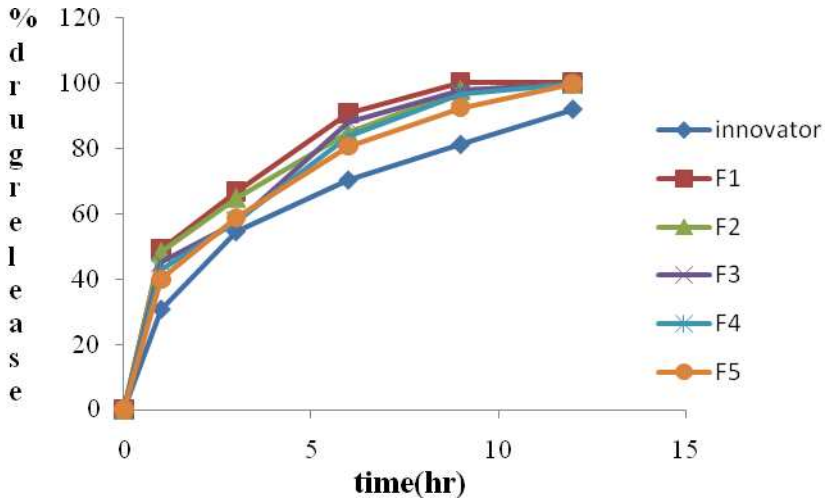

Figure.1: Dissolution profile of HPMC K15M

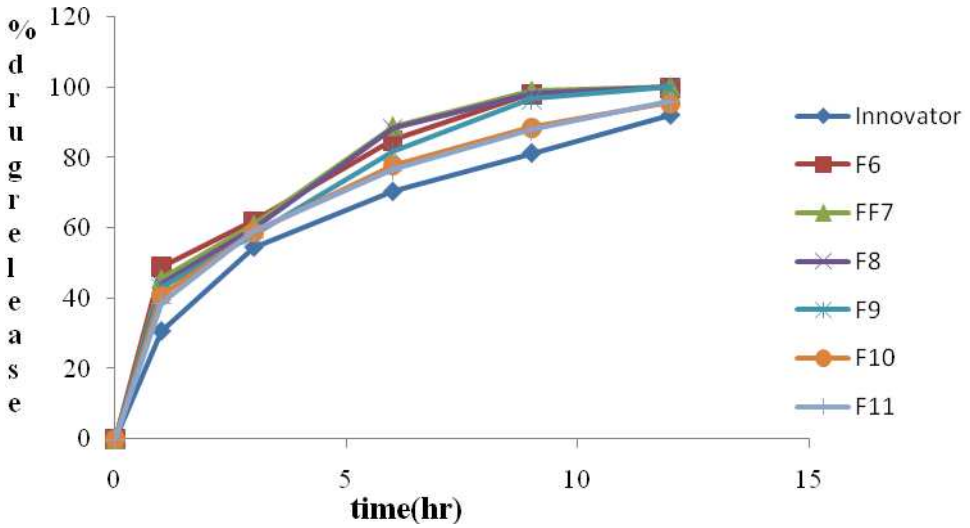

Figure.2: Dissolution profile of HPMC K100M

The drug release pattern of formulation F_{11} was best fitted to Korsmeyer – peppas model and first order kinetics (Table 6). Drug excipient interaction of formulation F_{11} was carried out by using FT-IR spectroscopy which indicated absence of any interaction (Fig. 3, 4). Hence it was concluded that formulation F_{11} can be taken as an ideal or optimised formulation for extended release tablets for 12 hours, as it fulfils all the criteria for an extended release tablets.

Table *6: In vitro* release kinetics of Metformin HCl

S.No	Formulation	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
1	F_{11}	0.830	0.8573	0.99	0.509

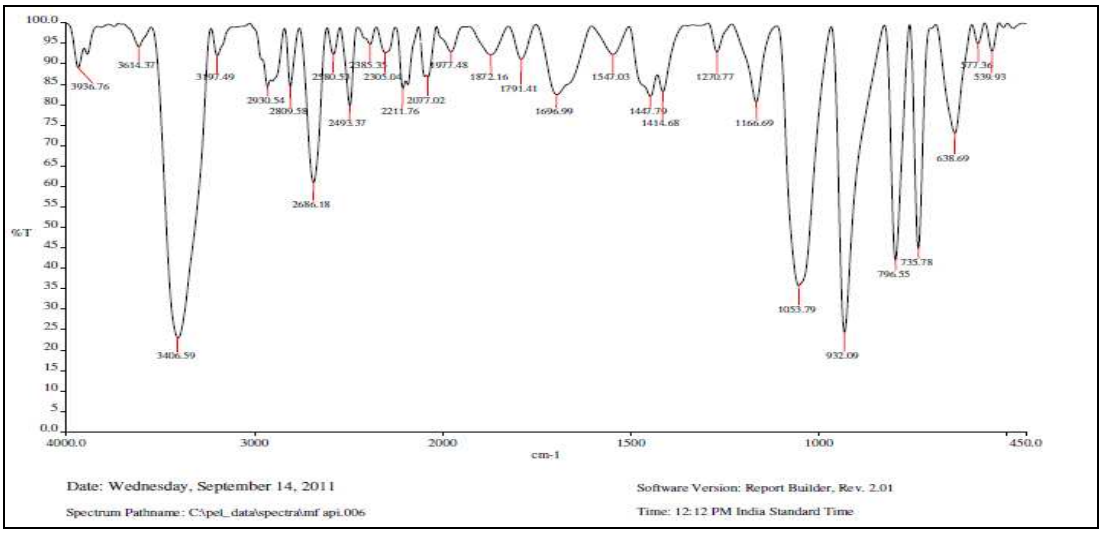

Fig. 3: FTIR spectra of the pure drug

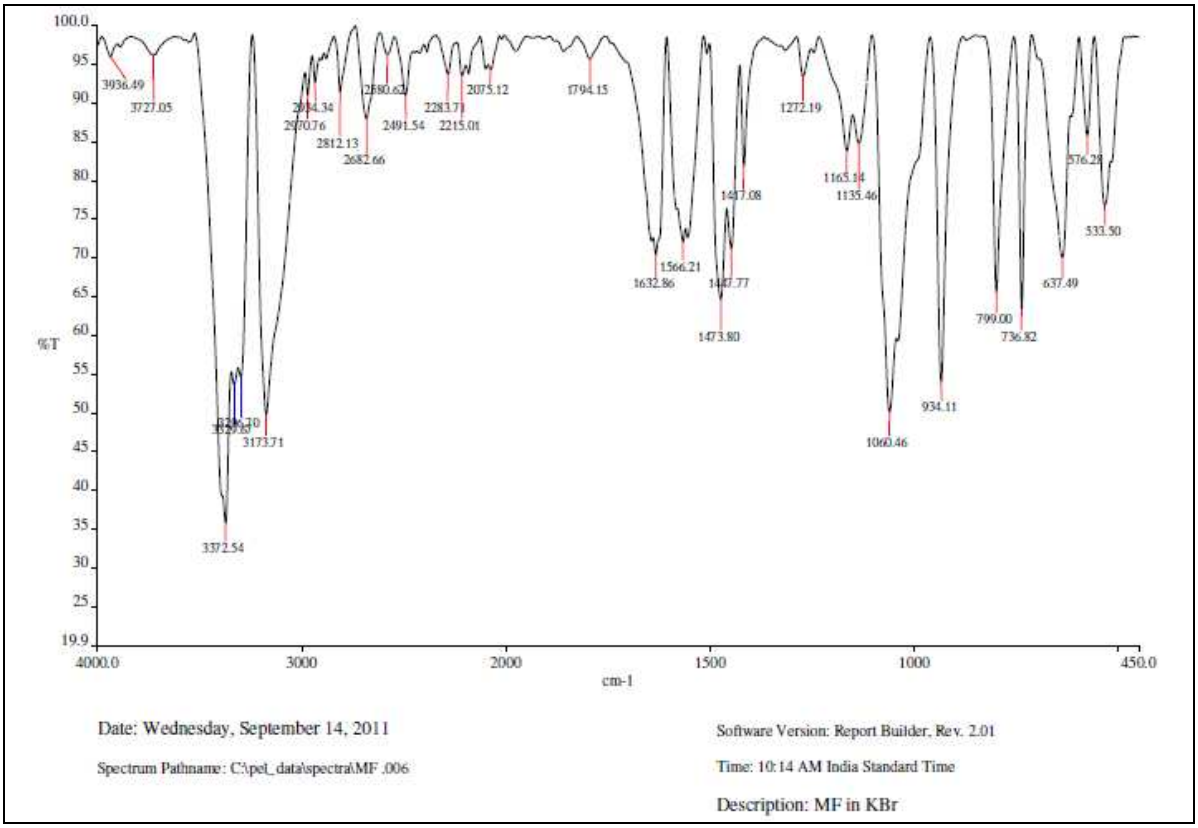

Fig. 4: FTIR spectra of the optimized formula

CONCLUSION

The prime objective of the study was to develop metformin HCl, extended release tablet by using commonly available excipients and conventional technology. From the above study it was concluded that by employing commonly available excipients such as, hydrophilic excipients and proper filler an extended release tablet of metformin HCl can be developed which can be commercialized.

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