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Research Article

Formulation and Design of Metformin Hydrochloride Extended Release Tablets

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ABSTRACT

Aim: The current paper was an attempt to design a extended release dosage form of Metformin hydrochloride using various grades of hydrophilic polymers, hydroxy propyl methyl cellulose (HPMC K4M, HPMC K15M, HPMC K100M and HPMC K200M) and MCC.

Materials and Methods: Laboratory scale batches of 4 tablet formulations were prepared by wet granulation technique. Precompression parameters of the granules were evaluated prior to compression. Tablets were characterized as crushing strength, friability, weight variation, thickness, drug content or assay and evaluated for in-vitro release pattern for 12 hr using Phosphate buffer of pH 6.8 at 37 ± 0.5°C.

Results and Discussion: The results obtained revealed that HPMC K100M in formulation (F3) was able to sustain the drug release for 12 h and followed the Higuchi pattern quasi-Fickian diffusion. and charged for stability testing, parameters were within the limit of acceptance. There was no chemical interaction found between the drug and excipients during Fourier Transform Infrared Spectroscopy (FTIR).

Conclusion: Hence it can be concluded that formulation F3 containing HPMC K100M is suitable for development of extended release tablets of Metformin Hydrochloride.

Keywords: Metformin, Extended Release Tablets, Diabetes

INTRODUCTION

Diabetes a global public health problem is a chronic disease and is now growing as an epidemic in both developed and developing countries. Around 150 million people suffer from diabetes in the world out of which above 35 million are Indians. Current drugs used for managing TYPE II Diabetes and its precursor syndromes, such as insulin resistance, fall within five classes of compound such as the biguanides, thiazolidinediones, the sulfonyl-ureas, benzoic acid derivatives and alpha glucosidase inhibitors. Metformin is an oral antidiabetic drug from the biguanide class[1].

Metformin is the most popular antidiabetic drug that requires controlled release owing to its short biological half life of 3.4 ± 0.7 hours[2]. 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. 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%[3].An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as

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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% . 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[4].

Extended release drug delivery system achieves a slow release of the drug over an extended period of time or the drug is absorbed over a longer period of time.[5] Extended release dosage form initially releases an adequate amount of drug to bring about the necessary blood concentration (loading dose, DL) for the desired therapeutic response and therefore, further amount of drug is released at a controlled rate (maintenance dose, DM) to maintain the said blood levels for some desirable period of time.[6] Extended release drug delivery system (ERDDS) have emerged as an effective mean of enhancing the bioavailability and controlled delivery of many drugs. ERDDS play an important role in reducing the dosing frequency as well as by enhancing the biological half life of specific certain drugs. In recent years, various efforts were made to reduce the dosing frequency of certain patent drugs by this approach.[4,7]

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 rime. different grades of Hydroxy Propyl Methyl Cellulose (HPMC) namely K4M,K200M, K15M, K100M and Micro crystalline cellulose were used for the preparation of tablets.

MATERIALS AND METHODS

Materials: Metformin HCl was obtained from universal medicament, Nagpur, India. Microcrystalline cellulose (MCC PH 102), HPMC (K4M,K200M, K15M, K100M) , Aerosil, povidone where purchased from S.D Fine Chem. Labs (Mumbai, India). HPMC (K15M and K100M) 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.

Methods

Calibration curve of metformin HCl: Calibration curve of metformin HCl was prepared in 0.1N HCl and phosphate buffer of pH 6.8 at using spectrophotometric method at absorbance 233 nm of UV region.

Formulation of Metformin Hydrochloride Extended Release Tablets: Metformin Hydrochloride Extended release tablets were prepared by Wet granulation method. Accurately weighed Metformin HCl, MCC and HPMC (of required grade) were sifted using # 60 and placed in separate poly bags. The sifted materials were mixed for 5 min and granulated with required quantity of binder by kneading method (Hand granulation) or in FBP.The granules were passed through sieve and dried at an inlet temperature of 80 ^{0}C and Product temperature of 50 ^{0}C in FBD, until the required moisture content is obtained. Then the granules are size reduced, using sieve#20.The granules were finally lubricated using magnesium stearate after sifting it through #60,for 5minutes.The lubricated granules were compressed into tablet each containing 500mg Metformin hydrochloride and a total weight of 800mg using 16.7 x 8.1 mm punches. The formulation of Metformin Hydrochloride extended release tablets are listed in (Table 1) [8]

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Table no-1 Formulation of Extended Release Tablets of Metformin Hydrochloride

S.No	INGREDIENTS	FORMULATION BATCH CODE			
		F 1	F 2	F 3	F 4
1	Metformin Hcl	500	500	500	500
2	HPMC K4M(mg)	200	-	-	-
3	HPMC K15M(mg)	-	200	-	-
4	HPMC K100M(mg)	-	-	200	-
5	HPMC K200M(mg)	-	-	-	200
6	Micro crystalline cellulose	80	80	80	80
7	Magnesium stearate	10	10	10	10
8	Aerosil	10	10	10	10
9	IPA	QS	QS	QS	QS
10	Water	QS	QS	QS	QS
	TOTAL WT	800	800	800	800

PRECOMPRESSION PARAMETERS

The granules were evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio.

Angle of repose[4,9]: 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 (tan θ) = h/r

Where, h and r are height and radius of the pile respectively.

Angle of repose as an indication of powder flow properties.

Bulk density[9,10]**:** The powder sample (blend) under test was screened through sieve #18 and the sample equivalent to 20g was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (V0) was noted. The bulk density was calculated in g/cm3 by the formula,

Bulk density (ρ0) =M/ V0

Where,

M = mass of powder taken

V0= apparent untapped volume.

Compressibility Index[9]**:** Percentage compressibility or Carr's index (CI) Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

$$\text{Carr's index (\%)} = \frac{\text{poured density-tapped density}}{\text{poured density}} \times 100$$

Hausner's ratio[11]**:** Hausner's ratio is called as index of flowability and is Calculated using the formula,

Hausner's ratio = V_1/V_2

Where V1 is the volume before taping and V2 is the volume after tapping.

POST COMPRESSION PARAMETERS

Thickness, Diameter and Hardness[8,12]**:** Thickness and diameter of the tablets were determined using Vernier caliper. Hardness or

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tablet crushing strength was measured using Monsanto tablet hardness tester.

Weight variation test[8,13]**:** Ten tablets were selected at random and average weight was determined. The individual tablets were weighed and compared with average weight. Not more than two of the individual weights deviate from the average weight of tablets by more than 5%.

Friability[9]**:** The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The friability was then calculated using the formula,

$$\text{Friability (\%)} = \frac{\text{Initial weight- final weight}}{\text{Initial weight}} \times 100$$

Content uniformity test: From the randomly selected 30 tablets of each formulation, 10 tablets were assayed individually. All of the tested tablets contained more than 99% of active Metformin Hydrochloride. In order to determine the drug content collectively, three tablets of each formulation were crushed. Powder equivalent to 100 mg of the drug was dissolved in phosphate buffer solution pH 6.8, and was analyzed spectrophotometrically at 233 nm after sufficient dilution with the respective solvent of phosphate buffer solution pH 6.8.

Drug content estimation [14]: Metformin Hydrochloride content in the extended release tablets was estimated by UV Spectrophotometric method based on measurement of absorbance of 10µg/ml solution at 233nm using phosphate buffer solution pH7.4.

***In vitro* drug release studies** [15,16,17]: The *in vitro* release of Metformin HCl tablets were performed using USP dissolution apparatus Type II (Paddle).The studies were carried out using 900ml of phosphate buffer solution pH 6.8 as dissolution medium. The studies were performed at a temperature of 37 ± 0.5° C and 100 rpm speed for 12 hours. The tablet was placed in dissolution jar and the samples were taken at 1hr, 6hrs, and 12 hours intervals. The samples were diluted to suitable concentration and analyzed for Metformin HCl content at 233nm by using UV–visible spectrophotometer. The *in vitro* release of marketed product was carried out in the similar manner and the results were compared.

Stability Studies [18,19,20]**:** The best formulation of Metformin hydrochloride extended release tablets was subjected to stability studies by Storing at 400C±20C /75±5% RH for 3 months. At every month interval, the tablets were visually examined for any physical change and evaluated for the drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

Evaluation of Tablets

All batches of prepared tablets were evaluated for various parameters like hardness, friability, thickness, weight Variation, content uniformity, in-vitro dissolution studies.

Angle of Repose : The angle of repose was found in the range of 25 to 27 for all formulations (Table 2).

Bulk density: The bulk density and tapped density was found in the range 0.5 to 0.52g/cm3 respectively (Table 2).

Compressibility Index and Hausner's Ratio: The compressibility index and Hausner's ratio lies in the range of 15.8 to16.21% and 1.0 to 1.28. It proved that the flow behaviours and compressibility of the granules are good. All the

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formulations showed excellent flowability as expressed in terms of micrometric parameters (Table2).

Table 2: evaluation of metformine hcl granules.

Formula code	Bulk density	Angle of repose	Compressibility Index (%)	Hausner's Ratio (%)
F1	0.51	26	15.9	1.1
F2	0.5	27	16.21	1.0
F3	0.52	26	15.8	1.27
F4	0.5	25	16.1	1.28

Thickness, Diameter and Hardness: The thickness of the tablets was found to be in the range of 5.8 to 5.92mm. The results showed that the thicknesses of all formulated tablets are found to be uniform. The hardness of all tablet formulations was found to be in the range of 7 to 7.1kg/cm2. It indicates all the tablets have adequate mechanical strength (Table 3).

Weight variation test: The result showed that weight variation was ranging from 797mg to 799mg. Hence the tablets complied within the IP limit in terms of uniformity of weight (Table 3).

Friability: In friability test the maximum weight loss should be not more than 1%.The results revealed that the tablets passed the friability test (Table 3).

Content uniformity test: Drug content in different formulations was estimated by UV spectrophotometric method. The drug content was found in the range of 98% to 101%.The standard deviations among the three values were found to be small. This indicates the drug was distributed almost uniformly throughout in all the formulations (Table 3).

Table no-3 Evaluation of Metformine HCl extended release tablets

Formulation code	Thickness (mm)	Weight variation (mg)	Friability (%)	Hardness (Kg/cm2)	%drug content
F1	5.8	798	0.31	7	101
F2	5.8	797	0.32	7.1	98
F3	5.9	799	0.30	7.1	100
F4	5.92	798	0.30	7	99

In vitro drug release studies: The *in vitro* release of Metformin HCl was slow and extended over longer period of time (Fig 1). Formulation F3 showed drug release as per USP limit. The drug release at the end of 1hr, 6hr and 12 hour was found to be 48%, 85.3% and 100.2% respectively. The drug release was found to be within the limit as per USP at end of 1st h, 6th h and 12th hour (Table 4).

Table 4: In Vitro Drug Release Studies of all formulations

TIME IN HRs	F1	F2	F3	F4
0	0	0	0	0
1	49.9	49.2	48	48.3
2	56.7	55.7	53.7	54.3

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4	70.3	71.2	69.2	70.9
6	89.2	90.2	85.3	87.3
8	97.2	95.7	93.2	95.2
10	100.5	100.2	98.4	98.9
12	100	100.1	100.2	99.6

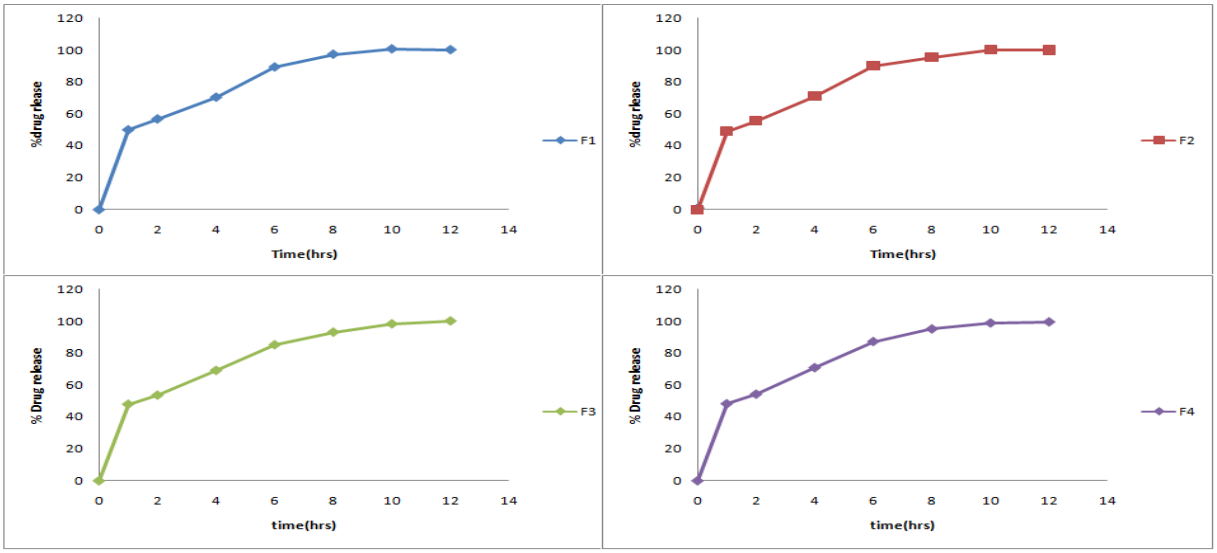

Figure no-1 Drug release profile of HPMC K4M, HPMC K15M, HPMC K100M, HPMC K15M.

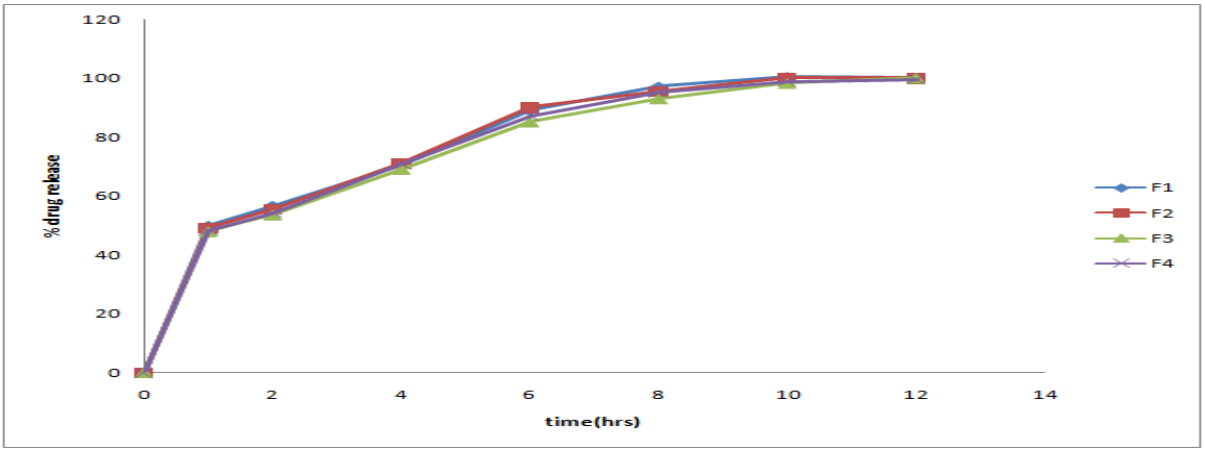

Figure no-2 Comparative drug release profile

Stability study: Stability study data of formulation F3 reveals that there was no significant change in appearance, percentage moisture content, drug content and percentage drug release, even after storing at 40±20C/75±5% RH for 3 months.

IR spectral analysis: FT-IR analysis of pure drug, individual polymer and combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium

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bromide and transformed into disk and scanned between 4000-400 cm-1 in a SHIMADZU FT-IR (IR Affinity-1) spectrophotometer [8].

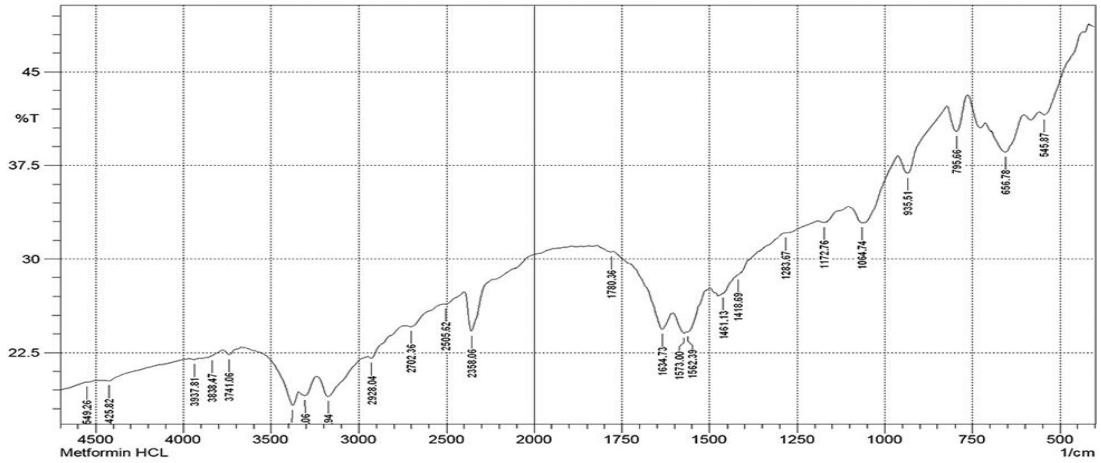

Figure 3: Infrared spectra of Metformin hydrochloride

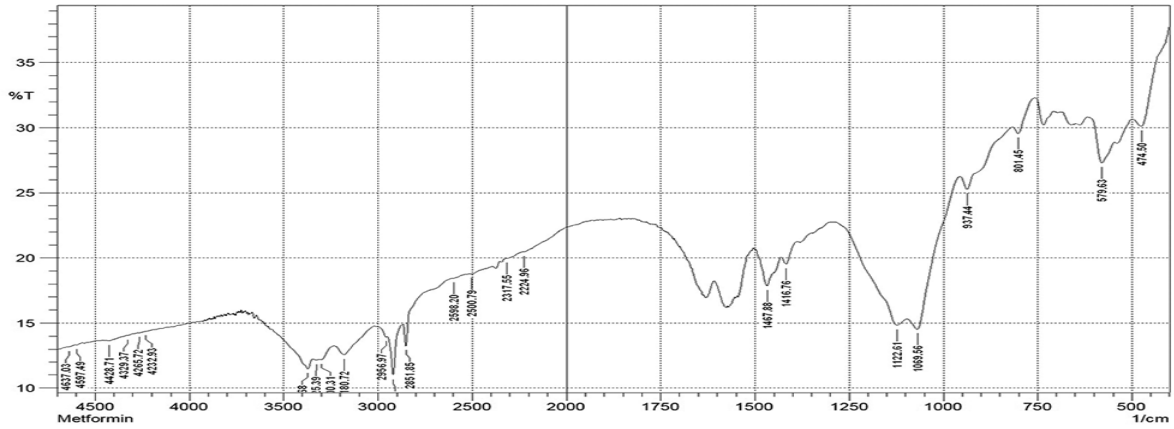

Figure 4: Infrared spectra of optimized batch F3

CONCLUSION

From all the parameters studied, it can be concluded that formulation F3 was found to be best regarding all the properties evaluated. The drug release was found to be within the limit as per USP at the end of 1st, 6TH and 12th hour. The stability study indicated that the formulation F3 was stable even after storing at 40±20C/75±5% RH for 3 months. Thus the results of the present study clearly indicated a promising potential of extended release Metformin HCl tablets containing HPMC K100M as rate controlling polymers (F3) demonstrated slow release when compared with other formulations and could be used for effectively treating diabetes mellitus.

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