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Formulation and evaluation of metformin hydrochloride extended release tablets

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ABSTRACT

Metformin hydrochloride has relatively short plasma half-life, low absolute bioavailability. 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 h might be sufficient for daily dosing of metformin. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. The overall objective of this study was to develop an oral sustained release metformin hydrochloride tablet by using polymers like Methocel K100M CR, Polyox WSR 303, Ethocel 100 cps as rate controlling factor. The tablets were prepared by wet granulation method. The precompression blend was tested for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The tablets were evaluated for weight variation, hardness, friability, dissolution rate, content uniformity, and were found to be within standard limit. The *invitro* dissolution study was carried out using USP II apparatus method and the data was analysed using zero order, first order, Higuchi, Korsmeyer and Hixson-Crowell equations. The drug release study revealed that F5 shows sustain the drug release for more than 12 h. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport.

Keywords: Methocel K100M CR, Polyox WSR 303, Ethocel 100 cps, Matrix tablets.

INTRODUCTION

Sustained release dosage form is defined as "Any drug or dosage form modification that prolongs the therapeutic activity of the drug for an extended period of time." This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration to and below the minimum toxic level for the extended period of time. Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect

by continuously releasing medication over the extended period of time after administration of a single dose [1].

Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of type-II diabetes, a common disease that combines defects of both insulin secretion and insulin action Unlike other antidiabetic drugs metformin HCl does not induce hypoglycemia at any reasonable dose, and hence it is called as an antihyperglycaemic rather than a hypoglycemic drug . 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 % [2]. 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 initial period of treatment. The compound has relatively short plasma half-life of 1.5-4.5 h 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 products are needed for metformin to prolong its duration of action and to improve patient compliances. Matrix systems are widely used in oral controlled drug delivery because of their flexibility, cost effectiveness, low influence of the physiological variables on its release behavior and broad regulatory acceptance [2]

MATERIALS AND METHODS

Materials

Metformin HCl, Methocel K100M CR, Polyox WSR 303, Ethocel 100 cps were obtained from Yarrow chemicals, Vadodara and all other chemicals/ solvents used were of analytical grade.

Preparation of Metformin hydrochloride matrix tablets

Matrix tablets, each containing 500 mg metformin HCl were prepared by a conventional non-aqueous wet granulation technique. The composition of various formulations of the tablets with their codes is listed in Table 1. The composition with respect to polymer combination was selected on the basis of trial preparation of tablets. In each formulation, the amount of the active ingredient is 500 mg and the total weight of a tablet is 700 mg. A batch of 30 tablets was prepared with each formula. The ingredients were passed through a 60-mesh sieve. A blend of all ingredients except glidant and lubricant was mixed, a particular attention had been given to ensure thorough mixing and phase homogenization. Granulation was done manually with a solution of isopropyl alcohol. The wet masses were passed through a 12 mesh sieve and the wet granules produced were first air dried for 10 min and finally at 45-50º in a tray drier for 2 h. The dried granules were sized by a 16-mesh sieve and after lubrication with magnesium stearate.

Compression was carried out using 14 mm flat faced circular punches into tablets on an eight station rotary press tablet compression machine (Rimek Minipress I Ahmadabad, India) at a constant compression force. Just before compression, the surfaces of the die and punches were lubricated with magnesium stearate. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics [3, 4]

Table1: Formulation of extended release tablets of Metformin Hcl:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCl	500	500	500	500	500	500	500	500
Methocel K100M CR	85	100	120	60	40	60	40	40
Polyox WSR 303	_	_	_	60	80	_	_	40
Ethocel 100 cps	_	_	_	_	_	60	80	40
Avicel 101	75	50	30	30	30	30	30	30

K 90	40	40	40	40	40	40	40	40
Aerosil 200	3	3	3	3	3	3	3	3
Mg.Stearate	7	7	7	7	7	7	7	7
Total	700	700	700	700	700	700	700	700

Evaluation of Tablets

The formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time, content uniformity, assay and *in vitro* dissolution study [5].

Tablet Hardness

Hardness is the crushing strength of tablet which determines the ease of handling and rigors of the transportation. For each formulation, 3 tablets were used for the study. The hardness of the tablet was determined and expressed in Kp [6].

Weight Variation Test

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The data presented in **Table 2** clearly show the weight variation tolerance for uncoated tablets [7].

Thickness

The thickness of the tablets was measured using Digital Vernier Caliper, and expressed in mm.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Preweighed sample of tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dedusted and reweighed [8].

The percent friability was measured using the formula:

$\% F = \{(W - W_0)/W_0\}*100$

Where, %F = Friability in percent,

W = Initial weight of tablet.

W_0 = Weight of tablet after test.

Disintegration Time

One tablet was placed in each of six tubes of disintegration test apparatus. Disintegration test was carried out at 37 ± 2 ^{0}C according to USP XXII., Disintegration test apparatus without disc, time required for complete passage of tablet fragments through the sieve (#10) was considered as a disintegration time of a tablet [9].

Assay

For this, 30 tablets were randomly selected from all formulations. Out of 30 tablets 10 tablets were crushed into fine powder. The powder taken equivalent to label claim was weighed accurately, dissolved in their respective media and assayed individually at respective λ max against the reagent blank. The drug content should be within 90% to 110% of the labeled claim [10].

Uniformity of content

One tablet was powdered, shaken with 1 ml of dilute HCl and 40 ml of water for 15 min, and added sufficient water to produce 100 ml and mixed well. Centrifuged about 15 ml and to 10 ml of the clear, supernatant liquid 2 ml of 1M HCl and sufficient water were added to produce a solution containing about 0.005 % w/w concentrated HCl. The absorbance of the resulting solution was measured at the λmax. of 233 nm. Then the content corresponding to atenolol in the tablet was calculated [11].

In vitro Dissolution studies

The *in vitro* dissolution study was carried out in USP dissolution test apparatus Type 2 (paddle). Samples were withdrawn at 1, 3 and 10 hrs time intervals by replacing with same dissolution medium and the dissolution of the drug was expressed as percentage drug dissolved by using following formula [12].

RESULTS & DISCUSSIONS

Table 2: Physicochemical Properties of Metformin Hcl

Formulation Code	Weight Variation	Thickness (Mm)	Hardness (Kg/Cm^2)	Friability (%)	Drug Content (%)
F1	703	5.82	14	0.11	96.5
F2	704	5.83	15	0.08	98.7
F3	700	5.82	17	0.06	99.4
F4	702	5.83	16	0.04	98.5
F5	703	5.82	15	0.05	99.1
F6	702	5.84	15	0.11	97.4
F7	701	5.85	16	0.05	98.4
F8	700	5.85	17	0.04	97.8

Studies on Metformin HCl matrix tablets

The quality control tests adopted for the tablets were depicted in the **table 2.** The Hardness of the matrix tablets ranged between 14 to 17 kg/cm^2. The Thickness of the tablets ranged between 5.82 to 5.85 mm. The percentage Friability of the prepared tablets was well within the limits (<1%). There was no significant weight variation observed between average weight and individual weight.

Further results suggested that the drug release from the polymer was swelling followed by diffusion mechanism that correlates with results of release kinetics. The drug content in all the formulations was within the range of 96.5 to 99.4% ensuring uniformity of drug content in the formulations [13-16].

In-vitro dissolution studies

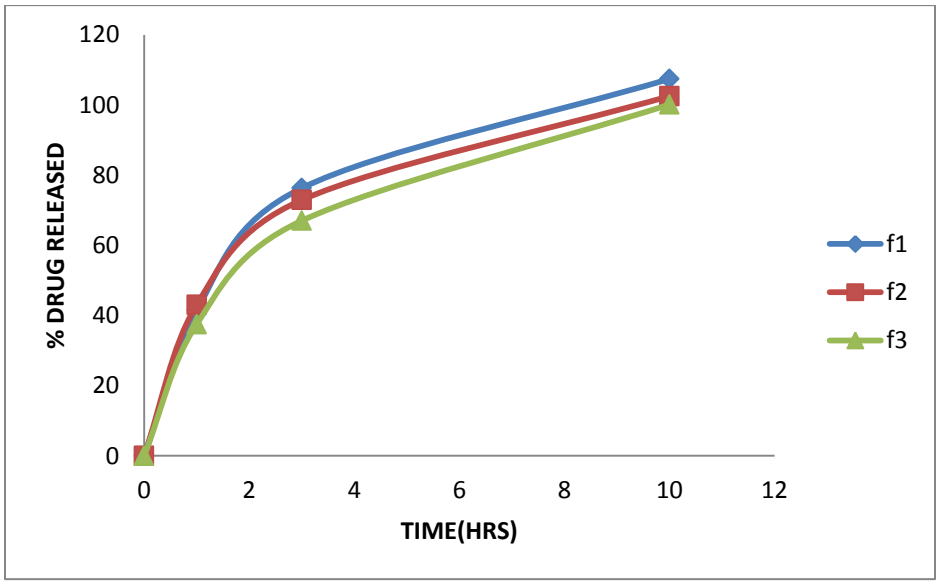

Fig.1. Comparison of zero order plots for F1, F2 and F3 formulations

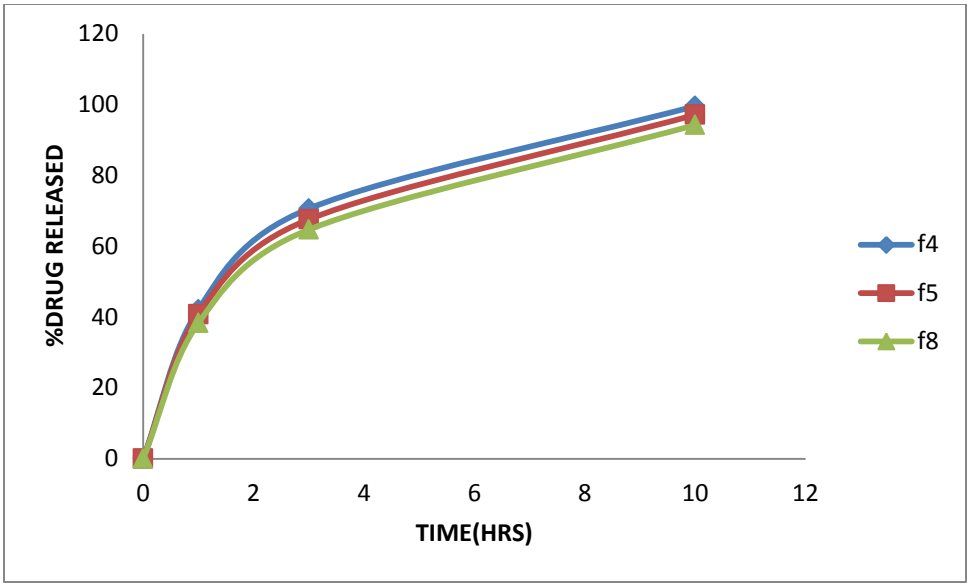

Fig.2. Comparison of zero order plots for F4, F5 and F6 formulations

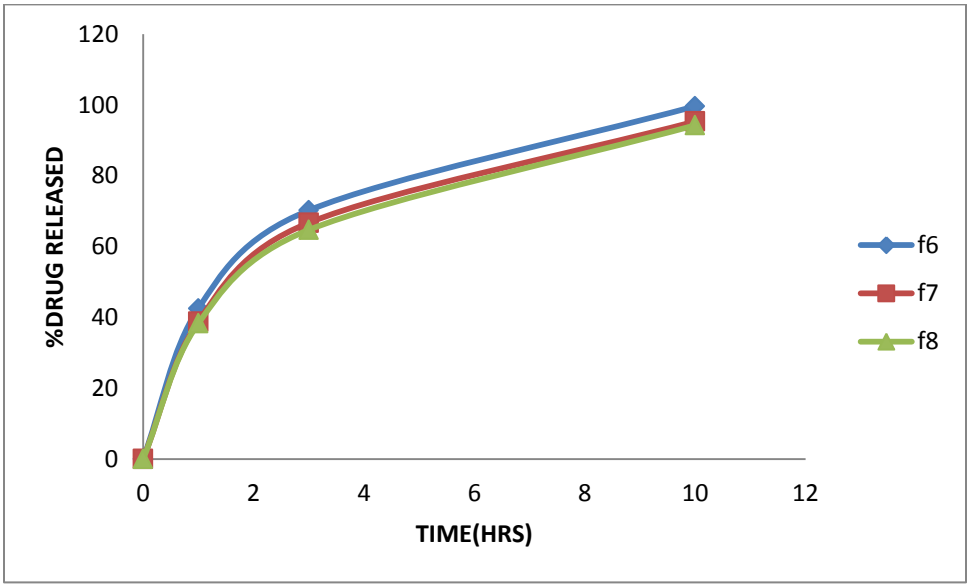

Fig.3. Comparison of zero order plots for F6, F7 and F8 formulations

Influence of different concentrations of polymers on release rate of Metformin HCl

In the present study methocel k100m cr, polyox wsr303 and ethocel 100 cps are used as drug release retarding polymers in matrix tablets. In formulations F1,F2 and F3 methocel k100m cr concentration was increased gradually(12%,14%,17%),and drug retardation was increased proportionally. in F4 & F5 formulations both methocel k 100m cr & polyox wsr303 are used as retarding polymers (1 : 1 & 1 : 2 ratio).compared to F3 formulation in F4 & F5 formulations more drug release retardation was observed because of combined polymers.in F6 & F7 formulations methocel k 100m cr & ethocel 100 cps are used in (1 : 1 & 1 : 2 ratio) more retardation was observed in F7 formulation because of increased ethocel 100 cps concentration.

The *In-vitro* dissolution profiles of F5 were found to be equivalent percentage of drug release with that of innovator product and the similarity

factor, more percentage of F2 indicating that the dissolution profile of formulation F5 was super imposable with the dissolution profile of the marketed product and concluded that F5 is better formulation and similar to innovator product. Therefore, it may be concluded that the Controlled release formulations are suitable delivery system for Metformin HCl and may be used for effective management in severe hyperglycemia.

CONCLUSION

Metformin HCl Controlled release matrix tablets were formulated by wet granulation method by using Magnesium stearate and HPMC as hydrophilic swellable and rate controlling polymers. The drug and excipient compatibility studies were performed by using IR Spectroscopy and found that they were compatible.

All formulations were analyzed for the pre-formulation parameters such as bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and the results were found to be within the limits.

All formulations were compressed into tablets and were analyzed for the parameters such as average weight, percentage of drug content, friability, thickness and hardness .The results were found to be within the limits.

In-vitro dissolution studies for all formulations were carried out in simulated gastric fluid for 1hr (without enzyme) and in simulated intestinal fluid (without enzyme) for 7 hrs and the percentage of drug release was calculated. It was found that all the formulations met the standard limits (not less than 85% drug release in 8 hr).

The order of drug release for all the formulations followed zero order kinetics and the mechanism of drug release governed by Higuchi. The diffusion coefficient value 'n' was found to be <0.5 indicates it follows diffusion mechanism.

The stability studies were conducted for optimized formulation (F5) as per ICH guidelines at 25^0C±2/60±5% RH and 40^0C±2/75±5% RH for 3 months and no changes were observed.

The present investigation focused on the improvement of the absorption and bioavailability of Metformin HCl along with sustained action. To meet the above criteria Controlled release tablets of Metformin HCl were formulated with hydrophilic swellable rate controlling polymers such as Sodium alginate and HPMC as key excipients.

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