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FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE EXTENDED RELEASE TABLETS

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ABSTRACT

The aim of the study is to formulate extended release tablets of Metformin HCL by employing different polymers like hydroxy propyl methyl cellulose K15M, hydroxy propyl methyl cellulose K100M and sodium carboxy methyl cellulose in different concentrations. A total of 12 formulations were prepared and studied for pre compression parameters like sieve analysis, bulk density, tapped density, angle of repose, compressibility index, Hausner's Ratio and post compression parameters like weight variation, thickness, hardness, friability, drug content, *in vitro* drug release, comparative *in vitro* drug release study with innovator product and stability studies. Drug content in different formulations was estimated by UV spectrophotometric method. The standard deviations among the three values were found to be small. That indicates the drug was distributed almost uniformly throughout in all the formulations. The *in vitro* release of metformin HCL was slow and extended over longer period of time. In formulations F_1-F_8, the drug release was not found to be within the limit as per USP. But formulations F_9-F_{12} showed drug release as per USP limit. Metformin HCL containing HPMC K100M and sodium CMC (H) as rate controlling polymer demonstrated slow release when compared with other formulations. The best formulation F_9 compared with marketed sustained release tablet (glucophage) showed similar release profiles.

Key words: Metformin HCL, extended release tablets, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose

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INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc. Usually conventional dosage form produce wide

ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery (1-5).The design of controlled-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a sustained release dosage form. Mainly physicochemical and biological properties of the drug are most important (6, 7).The biological half life of Metformin Hcl is 1.5-4.5hours. So conventional Metformin Hcl tablets should be administered 2-3 times a day to maintain the therapeutic effect of the drug throughout the day. Metformin Hcl extended release tablets reduces the dosage frequency and enhance the patient compliance. So Metformin Hcl extended release tablets are most convenient for patients than conventional dosage form. The aim of this project is to develop Metformin HCl Extended Release tablets to have dissolution profile similar to innovator product (Glucophage SR) and to comply with USP limits for product characteristics.

MATERIALS AND METHODS

Materials

Metformin HCL from Aarti Trax, Gujarat, Microcrystalline Cellulose from Acolon, Hercules supplier, Chennai, HPMC K15M, HPMC K100M from Dow Chemicals, Hyderabad, Magnesium Stereate from Amishi Drugs and Chemicals, Hyderabad, Potassium Dihydrogen Phosphate and Sodium Hydroxide from Merck chemicals, Mumbai.

Methods

Preformulation studies (8-12)

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined 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 maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Drug- Excipients interaction studies

To determine any interaction between drug and polymer, Fourier Transform Infra red (FT-IR) study was carried out. The drug and excipients must be compatible with one another to produce a stable, efficacious, easy to administer and safe product. FT-IR analysis of pure drug, individual polymers and combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium chloride and transformed into disk. Disk was applied to the centre of the sample holding device and scanned between 4000-400 cm^{-1} in a SHIMADZU FT-IR (IR Affinity -1) spectrophotometer.

Preparation of extended release tablets of Metformin Hydrochloride

Metformin Hydrochloride Extended release tablets were prepared by Wet granulation method. Accurately weigh specified quantity of raw materials - Metformin HCL, MCC, Sodium CMC (of required grade), in a weighing balance.Sift the above materials using # 60 and place in separate poly bags. Mix the sifted materials for 5 minand granulate with required quantity of water by kneading method (Hand granulation) or in FBP.Add required quantity of water to granulate .Once the binder spraying is completed, start drying at an inlet temperature 80^{o}C and Product temperature of 50^{o}Cin FBD, until the required moisture content is

obtained. After drying, check for Moisture content required in granules as per limit,(NMT 1- 2%). If the required amount of moisture is found out in granules, stop drying and the granules are size reduced, using sieve#20.Mix the above granules first with HPMC of required grade,sifted through #60 for 5 minutes, in a poly bag. Finally lubricate using specified quantity of Magnesium stearate after sifting it through #60, for 5 minutes. Compress the lubricated granules into tablet each containing 500mg Metformin hydrochloride and a total weight of 800mgusing 16.7 x 8.1 mm punches (Table-1).

Table-1 Formulation of extended release tablets of Metformin hydrochloride

Ingredients	B_1 (mg)	B_2 (mg)	B_3 (mg	B_4 (mg)	B_5 (mg)	B_6 (mg)	B_7 (mg)	B_8 (mg)	B_9 (mg)	B_{10} (mg)	B_{11} (mg)	B_{12} (mg)
Metformin HCl	500	500	500	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose	100	75	50	100	100	125	100	75	75	60	49	40
Sodium CMC(L)	50	50	50	50	--	--	--	--	--	--	--	--
Sodium CMC(M)	--	--	--	--	50	--	--	--	--	--	--	--
Sodium CMC(H)	--	--	--	--	--	25	50	50	25	40	50	50
Hydroxy propyl methyl cellulose K15M	140	165	190	--	--	--	--	--	--	--	--	--
Hydroxy propyl methyl cellulose K100M	--	--	--	140	140	140	140	165	190	190	191	200
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10
	Weight of each tablet is 800mg											

Evaluation of Tablets

The prepared Extended Release tablets were evaluated for the following parameters such as thickness and diameter, Hardness, Weight Variation, Friability, Assay and *In vitro* drug release.

Stability testing of pharmaceutical product

From the Twelve batches of Metformin hydrochloride extended release tablets, the best formulation F_9 was selected for stability studies. The formulation F_9 was stored at $40^0C \pm 2^0C$ /75±5% RH for 3months. At every month interval, the appearance, drug content and drug release of the formulation F_9 were determined by the method discussed previously

RESULTS AND DISCUSSION

The present study was undertaken to formulate extended release tablets of Metformin hydrochloride by wet granulation method using different rate controlling polymers with different concentration. A total of 12 formulations were prepared using different rate controlling polymers sodium carboxy methyl cellulose and HPMC with different concentration.

Before compression, the granules was undertaken for evaluation studies such as bulk density, tapped density, angle of repose, compressibility index and hausner's ratio. After compression, evaluation tests of tablets such as general appearance, hardness, thickness, weight variation, friability, content uniformity, IR spectral studies, *in vitro* release studies and stability studies were performed. The results are present in Table-2.

Table-2 Evaluation of Metformin hydrochloride extended release

Code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation (%)	Friability (%)	Drug content (%)
F_1	5.70±0.10	7±0.28	795±0.04	0.22±0.01	101.3±1.62
F_2	6.00±0.07	8±0.25	796±2.21	0.12±0.05	101.1±0.90
F_3	5.95±0.05	6±0.28	797±0.97	0.01±0.04	95.8±0.96
F_4	5.75±0.05	7±0.5	799±0.08	0.15±0.03	95.0±0.2
F_5	5.70±0.1	8±0.25	797±2.21	0.05±0.01	101.2±0.83
F_6	5.63±0.05	6±0.28	795±1.33	0.08±0.05	99.7±0.55
F_7	5.70±0.07	7±0.28	799±2.21	0.18±0.03	99.3±1.11
F_8	5.65±0.05	7±0.25	795±0.08	0.20±0.02	99.0±1.03
F_9	6.15±0.02	8±0.11	794±1.50	0.04±0.05	99.3±0.43
F_{10}	6.00±0.02	7±0.28	796±1.33	0.03±0.06	99.9±0.01
F_{11}	6.25±0.05	9±0.5	799±0.98	0.07±0.04	98.11±0.25
F_{12}	6.15±0.07	8±0.25	799±0.97	0.04±0.03	98.71±0.17

*All the values are expressed as mean ±Standard deviation; n=3

In vitro release studies were performed to evaluate the dissolution character of Metformin HCL extended release tablets using various polymers in different ratios and comparing the release datas with marketed sample (Glucophage). The result of the *in vitro* release profiles were presented graphically in Fig 1-4.

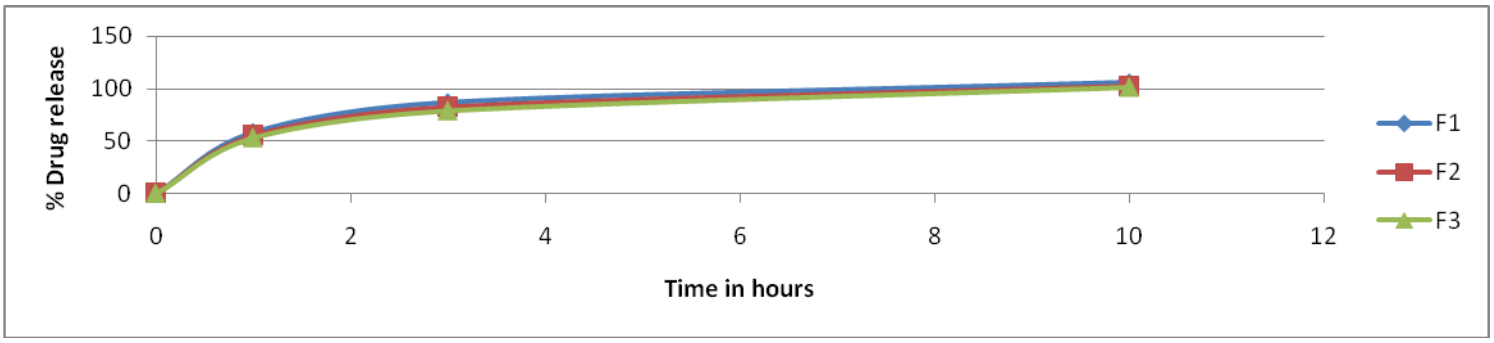

Fig-1 *In Vitro* release profile of Metformin Hydrochloride ER tablet formulations (F_1, F_2, F_3)

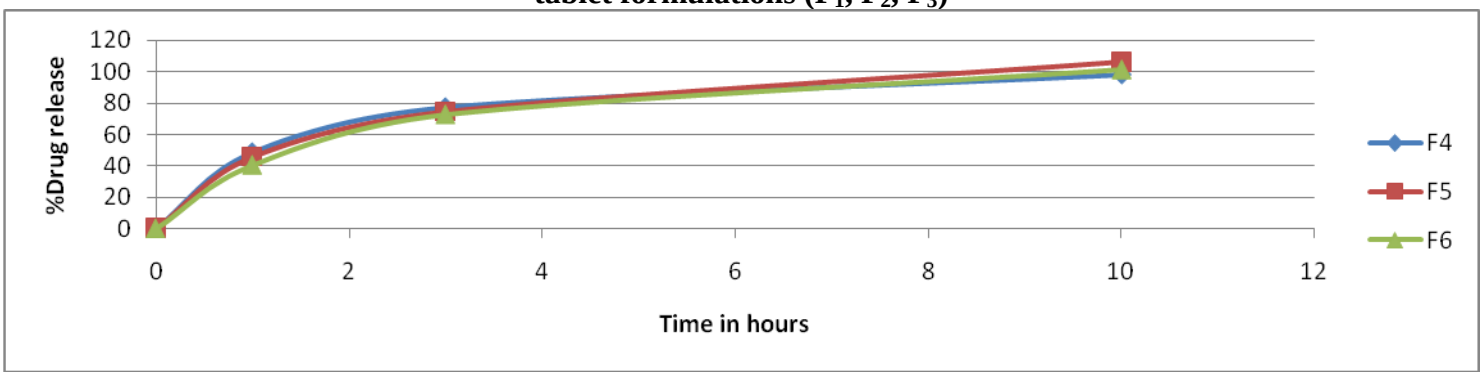

Fig-2 *In Vitro* release profile of Metformin Hydrochloride ER tablet formulations (F_4, F_5, F_6)

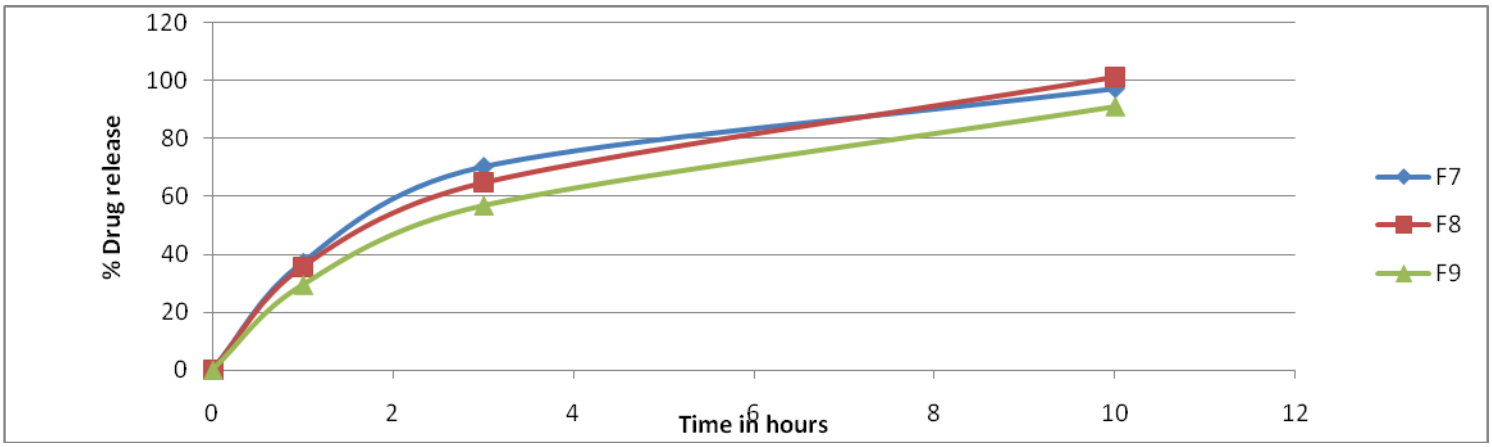

Fig-3 *In Vitro* release profile of Metformin hydrochloride ER tablet formulations (F_7, F_8, F_9)

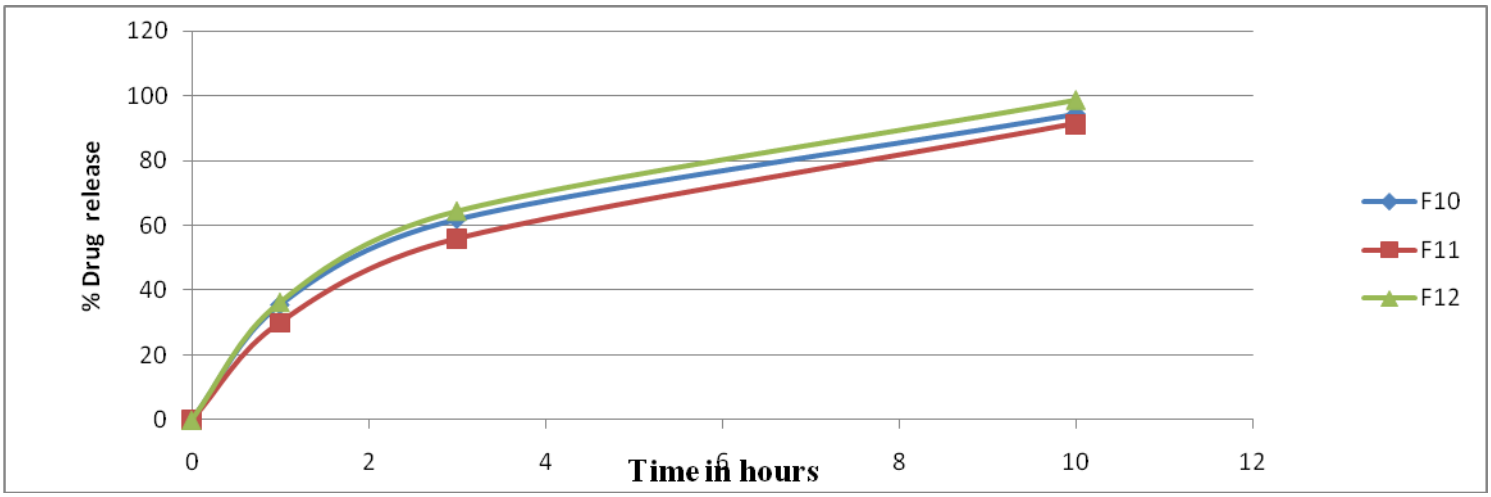

Fig-4 *In vitro* release profile of Metformin Hydrochloride ER tablet formulations (F_{10}, F_{11}, F_{12})

In vitro dissolution studies of Metformin HCL extended release tablets were performed as per the method and time intervals specified in USP. Twelve formulations of metformin HCL extended release tablets were prepared using various polymers such as HPMC K15M, HPMC K100M and SCMC in different concentration and dissolution studies were carried out. The percentage drug release was gradually increased with increase in time intervals. The standard limits of drug release in the prescribed time as per USP are first hour: 20-40%; 3rd hour: 45-65%, 10th hour NLT 85%. The results revealed that the drug released from marketed product is fairly matching with the drug release from Metformin HCL extended release tablet formulation F_9. Based on this, F_9 was selected as best formulation and subjected for stability studies.

Stability studies

The formulation F_9 was selected for the stability study and stored at $40\pm2^0C/75\pm5\%$ RH for a period of 3 months. At every month interval, the tablets were evaluated for appearance, moisture content, drug content and percentage drug release. The accelerated stability study was conducted for 3 months under $40\pm2^0C/75\pm5\%$ RH. The product was analyzed for appearance, moisture content, drug content and percentage drug release at every one month interval. The results were within the specified limits. There was no significant change in appearance, moisture content, drug content and percentage drug release after

3 months. The results revealed that the product was stable even after storing at 40±2^{0}C/75±5% RH for 3 months.

CONCLUSION

From all the parameters studied, it can be concluded that formulation F_9 was found to be best formulation regarding all the properties evaluated. The drug release was found to be within the limit as per USP at the end of 1st, 3rd and 10th hour. The formulation F_9 showed release profile close to that of marketed sample of Metformin HCL. The stability study indicated that the formulation F_9 was stable even after storing at 40±2^{0}C/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 and SCMC as rate controlling polymers for effectively treating diabeties mellitus.

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