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Research Article

FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF METFORMIN HYDROCHLORIDE

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ABSTRACT

The present study was aimed to develop Metformin Hydrochloride Extended release tablets for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), particularly those with refractory obesity. Metformin Hcl extended release tablets reduces the dosage frequency, enhance patient compliance and maintain the therapeutic effect of the drug throughout the day. A total of 9 formulations were developed using varying proportions of Hydroxy propyl methyl cellulose K15M, Hydroxy propyl methyl cellulose K100M and Sodium carboxy methyl cellulose as release retardant polymers by wet granulation method. FT-IR studies revealed that there was no interaction between drug and polymer. Before compression, the granules were evaluated for precompression parameters 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, *in vitro* release studies and stability studies were performed. Out of 9 formulations, the drug release was found to be within the limit as per USP in formulation F_9. The stability study of formulation F_9 revealed there was no significant change in physical and chemical properties of drug stored at 40±2^{0}C/75±5% RH for 3 months. Hence it can be concluded that formulation F_9 containing HPMC K100M at a concentration of 24% and SCMC (H) at a concentration of 3.13% is suitable for development of extended release tablets of Metformin Hydrochloride.

Key words: Hydroxy propyl methyl cellulose, Metformin Hydrochloride.

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[1,2]. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency[3]. This factors as well as factors such as repetitive dosing and unpredictable absorption

lead to the concept of sustained or controlled drug delivery systems[4]. 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[5]. Metformin is used in patients with type 2 diabetes (non-insulin-dependent diabetes). Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems[6]. Proper control of diabetes may also lessen the risk of a heart attack or stroke[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[8, 9]. A total of 9 formulations were developed using varying proportions of Hydroxy propyl methyl cellulose K15M, Hydroxy propyl methyl cellulose K100M and Sodium carboxy methyl cellulose as release retardant polymers by wet granulation method.

MATERIALS AND METHODS

Materials

Metformin Hydrochloride was obtained from Aarti Trax, Gujarat. Microcrystalline Cellulose was procured from Vijlakpharma, Mumbai. Sodium Carboxy Methyl cellulose was obtained from Acolon, Hercules supplier, Chennai. HPMC K15M, HPMC K100M were obtained from Dow Chemicals, Hyderabad. Magnesium Stearate was procured from Amishi Drugs and Chemicals, Hyderabad. All other chemicals and reagents used were of analytical grade.

Methods

Formulation of Metformin Hydrochloride Extended Release Tablets:

Metformin Hydrochloride Extended release tablets were prepared by Wet granulation method. Accurately weighed Metformin Hcl, MCC, Sodium CMC (of required grade) 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^{o}C and Product temperature of 50^{o}C in FBD, until the required moisture content is obtained. (NMT 1- 2%). Then the granules are size reduced, using sieve#20.The granules were finally lubricated using magnesium stearate after sifting it through #60,for5minutes.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).

PRECOMPRESSION PARAMETERS

The granules were evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. The angle of repose was determined by fixed funnel method to assess the flow property of granules[10]. Bulk density is the ratio between a given mass of the powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of powder or granules after tapping. Bulk and tapped density were determined using digital bulk density apparatus. The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and tapped volume of powder (or) granules[11].

Hausner's Ratio = Tapped density/ Bulk density.

Carr's index (%) = [(TD-BD) / TD] ×100.

Where, TD = Tapped density, BD = Bulk density.

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 bromide and transformed into disk and scanned between 4000-400 cm^{-1} in a SHIMADZU FT-IR (IR Affinity-1) spectrophotometer[12].

POST COMPRESSION PARAMETERS

Thickness, Diameter and Hardness

Thickness and diameter of the tablets were determined using Vernier caliper. Hardness or tablet crushing strength was measured using Monsanto tablet hardness tester[13].

Weight variation test

Twenty tablets were selected at random and average weight was determined. The individual tablets were weighed and compared with average weight[14]. Not more than two of the individual weights deviate from the average weight of tablets by more than 5%.

Friability test

The friability of tablets was determined by "Roche" friabilator. Ten tablets were taken and weighed. The tablets were subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes, dropping the tablets from a distance of six inches with each revolution. After operation, the tablets were dedusted and reweighed[15]. The Percentage friability was determined using the formula:

Percentage Friability = [(Initial Weight – Final Weight) / Initial Weight] × 100

Drug content estimation[16]

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**

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 10 hours. The tablet was placed in dissolution jar and the samples were taken at 1h, 3h, and 10 hour intervals. The samples were diluted to suitable concentration and analyzed for Metformin Hcl content at 233nm by using Double beam UV–visible spectrophotometer. The *in vitro* release of marketed product was carried out in the similar manner and the results were compared[17].

Stability Studies

The best formulation of Metformin hydrochloride extended release tablets was subjected to stability studies by storing at $40^0C \pm 2^0C$ /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[18, 19, 20].

RESULTS AND DISCUSSION

The angle of repose was found in the range of $25.38^o \pm 0.34$ to $27.91^o \pm 0.15$ for all formulations. The bulk density and tapped density was found in the range 0.435±0.002 to 0.496±0.003g/cm^3 and 0.527±0.02 to 0.601±0.002g/cm^3 respectively. The compressibility index and Hausner's ratio lies in the range of 14.00±0.07 to17.60±0.11% and 1.15 to 1.18.It proved that the flow behaviors and compressibility of the granules are good. All the formulations showed excellent flowability as expressed in terms of micrometric parameters (Table 2).

The thickness of the tablets was found to be in the range of 5.63±0.05 to

6.15±0.02mm. The results showed that the thickness of all formulated tablets are found to be uniform. The hardness of all tablet formulations was found to be in the range of 6±0.28 to 8±0.25kg/cm^2. It indicates all the tablets have adequate mechanical strength. The accepted percentage deviation was ±5% for more than 250mg weight tablets. The result showed that weight variation was ranging from 795±0.04mg to 799±2.21mg.Hence the tablets complied within the IP limit in terms of uniformity of weight.In friability test the maximum weight loss should be not more than 1%.The results revealed that the tablets passed the friability test. Drug content in different formulations was estimated by UV spectrophotometric method. The drug content was found in the range of 95.8±0.96% to 101.3±1.62%.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).

The *in vitro* release of Metformin Hcl was slow and extended over longer period of time (Fig 1). In formulations F_1-F_8, the drug release was not found to be within the limit as per USP. But formulations F_9 showed drug release as per USP limit. The drug release at the end of 1hr, 3hr and 10 hour was found to be 29.4±1.53%, 56.8±0.17% and 91.0±0.39% respectively. The drug release was found to be within the limit as per USP at end of 1st h, 3rd h and 10th hour. The best formulation F_9 compared with marketed sustained release tablet showed similar release profiles (Fig 2).

Stability study data of formulation F_9 reveals that there was no significant change in appearance, percentage moisture content, drug content and percentage drug release, even after storing at 40±2^{0}C/75±5% RH for 3 months (Table 4).

CONCLUSION

From all the parameters studied, it can be concluded that formulation F_9 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, 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 K100M and SCMC (H) as rate controlling polymers (F_9) demonstrated slow release when compared with other formulations and could be used for effectively treating diabetes mellitus.

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Table 1: Formulation of Extended Release Tablets of Metformin Hydrochloride

Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)
Metformin Hcl	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose	100	75	50	100	100	125	100	75	75
Sodium CMC(L)	50	50	50	50	--	--	--	--	--
Sodium CMC(M)	--	--	--	--	50	--	--	--	--
Sodium CMC(H)	--	--	--	--	--	25	50	50	25
Hydroxy propyl methyl cellulose K15M	140	165	190	--	--	--	--	--	--
Hydroxy propyl methyl cellulose K100M	--	--	--	140	140	140	140	165	190
Magnesium stearate	10	10	10	10	10	10	10	10	10
Weight of each tablet is 800 mg									

Table 2: Evaluation of Metformin Hydrochloride granules

Formulation code	Angle of repose (θ)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio
F_1	27.36±0.61	0.445±0.005	0.529±0.03	16.00±0.03	1.17±0.23
F_2	27.12±0.35	0.448±0.002	0.530±0.02	15.60±0.18	1.18±0.004
F_3	26.72±0.20	0.490±0.006	0.575±0.002	14.80±0.02	1.18±0.002
F_4	26.17±0.19	0.470±0.004	0.550±0.01	14.60±0.13	1.17±0.02
F_5	27.91±0.15	0.496±0.003	0.601±0.002	17.60±0.11	1.16±0.01
F_6	25.94±0.20	0.456±0.007	0.539±0.002	15.40±0.04	1.18±0.02
F_7	25.38±0.34	0.462±0.003	0.537±0.003	14.00±0.07	1.16±0.02
F_8	27.54±0.31	0.442±0.006	0.527±0.02	16.20±0.06	1.18±0.04
F_9	26.34±0.18	0.435±0.002	0.562±0.003	14.58±0.011	1.15±0.06

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

Table 3: Evaluation of Metformin Hydrochloride Extended Release Tablets

Formulation code	Thickness (mm)	Hardness (Kg/cm²)	Weight variation (mg)	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	96.0±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	796±1.50	0.04±0.05	99.3±0.43

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

Table 4: Stability study datas of Formulation F_9 stored at 40±2°C/75±5%RH for 3 months

Test Parameters	Specification	Initial period	After 1 Month	After 2 Month	After 3 Month
Description	White to Off-white caplet shaped uncoated tablet with breakline on one side	White to Off-white caplet shaped uncoated tablet with break line on one side	white caplet shaped uncoated tablet with break line on one side	white caplet shaped uncoated tablet with break line on one side	white caplet shaped uncoated tablet with break line on one side
Moisture Content (%)	NMT 5.0	1.64	1.98	2.02	2.61
Drug content (%)	95-105	100.58	100.27	99.89	99.81
Dissolution Study - Percentage drug release (%)					
1 Hr	20-40	33.62	32.23	33.65	34.78
3 Hr	45-65	61.55	62.17	63.55	63.08
10 Hr	NLT 85	97.45	98.69	96.38	96.31

***In vitro* release profiles of Metformin Hydrochloride ER tablets**

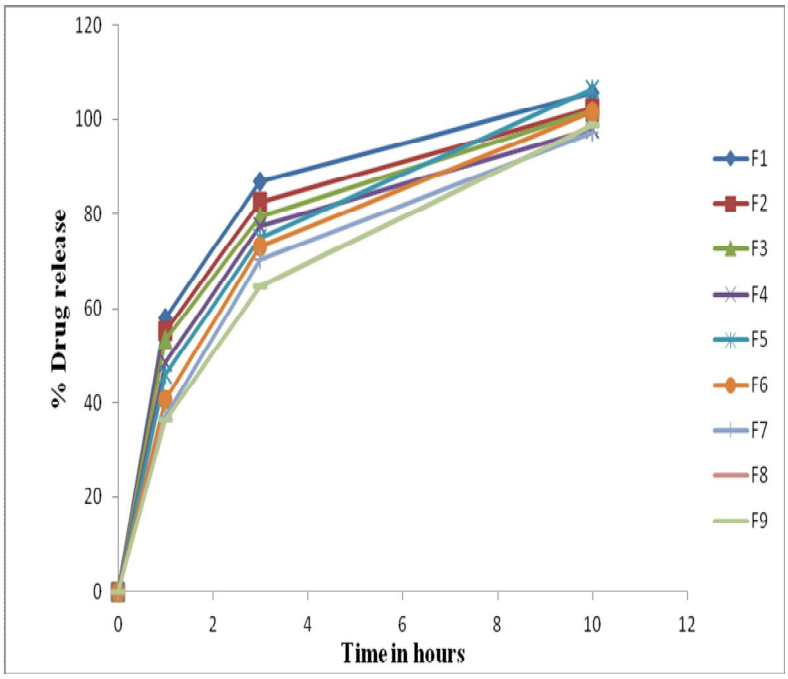

Fig. 1: Comparative *in vitro* release profiles of Formulations F_9 and innovator

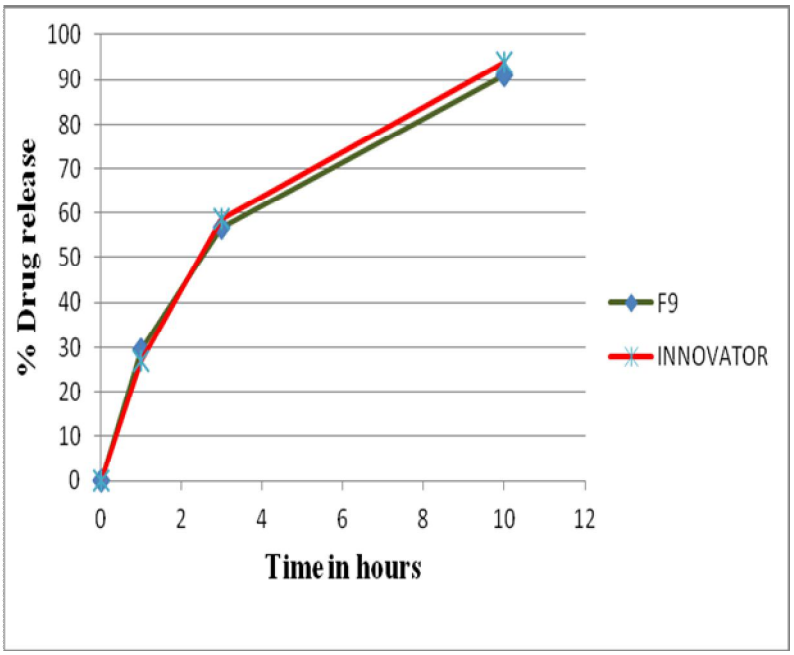

Fig. 2:

REFERENCES

1. Remington G and Edward Rudnic. The Pharmaceutical Sciences; Mack Publishing Company, 2005; 18th Ed: 1633.
2. Remington G. The Science and Practice of Pharmacy; B. I. Publication Pvt. Ltd; Vol. I, 2005; 21st Ed.: 903-913
3. Brahmankar DM and Jaiswal SB.Biopharmaceutics and Pharmacokinetics; "A Treatise" Vallabh Prakashan, 1995; 1st Ed.: 347-352.
4. Lee VH and Robinson JR. Sustained and Controlled Release Drug Delivery System, Marcel Dekker; New York, 1996; 5th Ed.: 71-121.
5. Jayanti.B, Madhusudan PK, Mohanta GP and Manavalan R. Pre oral extended release products-an overview. Journal of Applied Pharmaceutical Science. 2011;1(1):50-55.
6. Prescribing Information for Metformin Hcl. Available from: http://www.R_X list.com.
7. Prescribing Information for Metformin Hcl. Available from: http://www. Drugs.com.
8. Sathoskar RS, Bhandarkar SD and Nirmala N. Pharmacology and pharmacotherapeutics,. Popular Prakashan; Mumbai, 2009; Re Revised 21st Ed: 895.
9. Tripathi KD .Medical Pharmacology. Jaypee brother's medical publishers; New Delhi, 2008; 6th Ed: 266-269.
10. Manavalan R and Ramasamy C. Physical pharmaceutics.Vignesh Publishers; Chennai, 2004; 2nd Ed: 325.
11. Herbert A, Liberman, Leon Lachman, Joseph B. Schwartz. Pharmaceutical Dosage Forms, Tablets. New York Marcel Dekker Inc, 1989; 2nd Ed. Vol-I: 195-197, 285-286.
12. Mutalik S, Naha A, Usha AN, Anju P, Ranjith AK, Musmade P, Manoj K and Prasanna. Preparation, in vitro, preclinical and clinical evaluation of once daily sustained release tablets of aceclofenac. Arch Pharm Res. 2007;30:222-234.
13. Sharma, Shukla, Indoria Manish and Jha sajal. Design, Development and Evaluation of Aceclofenac Sustained release matrix tablets. International Journal of Drug Development & Research.2011;3(1):303-313.
14. Sandeep Divate, Kunchu Kavitha, Ganesh Nanjan Sockan. Fast Disintegrating Tablets – An Emerging Trend. International Journal of Pharmaceutical Sciences Review and Research. 2011;6(2):18-22.
15. Rama krishnan PN and Palanichamy S. Pharmaceutics-I. Jai Publishers; Madurai, 2007; 11th Ed: 147.
16. British Pharmacopoeia. British Pharmacopoeial Commission, London, 2000; Vol-2: 209,299.
17. The United State of Pharmacopoeia 24/NF26. The official compendia of United States of pharmacopoeial Convection Inc. Rockville, 1995; Asian Ed.:1015-1016.
18. Stability Testing of Active Substances and Pharmaceutical Products. World Health organization.1211 Geneva, Switzerland, 2006: 1-33.
19. Prescribing Information for Stability studies Available from: http://www.fda.com.
20. Prescribing Information for Stability studies Available from: http://www.microtestlabs.com/ aseptic-processing/stability/index-html.