WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 7, 499-506. Research Article ISSN 2277 – 7105

DESIGN, FABRICATION AND EVALUATION OF DRUG RELEASE KINETICS FROM METFORMIN HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS BY USING NATURAL GUMS

***Raju.Manda, Bonagiri Sreedevi, Virajaji Kaya, Bandla Navya and Dr.R.Suthakaran**

Teegala Ram Reddy College of Pharmacy, Meerpet Hyderabad– 500097,
Telangana (State). India.

Article Received on
13 July 2014,

Revised on 07 July 2014,
Accepted on 31 August 2014

***Correspondence for Author**
Raju. Manda
Teegala Ram Reddy College of Pharmacy, Meerpet Hyderabad– 500097, Telangana (State). India

ABSTRACT

Sustained release formulation of Metformin hydrochloride presents significant challenges due to its poor inherent compressibility, high dose and high water solubility. Sustained release matrix tablets of Metformin hydrochloride were formulated using different concentration of Guar gum, Xanthan gum, and Chitosan polymers, Drug: Polymer ratio of (3X3+1) 5:1, 5:2, 5:3 and 5:4 by direct compression method. The formulated powder blends were evaluated for angle of repose, bulk density, true density, compressibility index and total % porosity. The tablets were subjected to hardness, friability, % weight variation and % drug content. *In vitro* release studies were carried out at pH 1.2 and pH 7.2 using the dissolution test apparatus IP/BP/USP. The formulated powder blends and tablets showed satisfactory results from selected formulation. Tablet thus formulated provided Sustained release of Metformin hydrochloride over a period of 10 hrs.

KEY WORDS: Metformin hydrochloride, Guar gum, Xanthangum, and Chitosan, Sustained release Direct compression method.

INTRODUCTION

Metformin hydrochloride, an anti-diabetic drug lowers both basal and postprandial-elevated blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM or type-II diabetes) whose hyperglycemia cannot be satisfactorily managed by diet alone. Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea and diarrhea, many occur during the treatment. Administration of a extended release, once-a-day

Metformin hydrochloride dosage form could reduce the dosing frequency and improve patient compliance. In spite of its favorable clinical response and lack of significant draw backs, chronic therapy with Metformin hydrochloride suffers from certain problems of which the most prominent is the high dose (1.5 – 2.0 g/day) low bio-availability (60%) and high incidence of gastrointestinal tract (GIT) side effect (30%) case). Therefore, there were continued efforts to improve the pharmaceutical formulation of Metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on extended release of drug including the sophisticated gastro retentive system.

Numerous studies have been reported in literature investigating the HPMC matrices to control the release of variety of drug from matrices .Several authors have reported the use of ethyl cellulose matrices to control the release a variety of drugs. Therefore, in this study, the hydrophobic (EC) and hydrophilic polymer (HPMC) alone/ in combination have been used as matrix material in order to get the required release profile of Metformin hydrochloride.

MATERIALS AND METHODS

Materials

Metformin hydrochloride – USP was a gift sample from wockhard pharmaceuticals (Mumbai, India), hydroxyl propyl methyl cellulose (K100M) USP was obtained from shin-etsu, Chemicals Co.Ltd., (Tokyo, Japan). Ethyl cellulose (18 centipoises) was procured from SD fine chemicals Ltd, (Mumbai, India). Microcrystalline cellulose powder I.P. was obtained from sigha ehichiro chemicals Pvt Ltd., (India), sodium chloride injection I.P. mound mettur pharmaceutical Ltd., (Tamilnadu, India). Alloxan, loba chemie (Bombay, India). All other chemicals and reagents used were of high analytical grade. Double distilled water was used for evaluation studies.

Machineries

Machineries and equipment used was tablet compression machine, (cadmech machinery Co. Pvt Ltd.,). UV-visible spectrophotometer, (Shimadzu 1700), six stage dissolution rate test apparatus IP/BP/USP, (tab machines), Monsanto hardness test apparatus, (Rollex pvt Ltd) India, B.S.Sieves, (Jaynant scientific) and tray dryer (Mumbai engineering works). Differential scanning colorimeter (perkin elemer DSC-7 model).

METHODS

Preparation of Metformin Hydrochloride Sustained Release Matrix Tablets

Different tablet formulations (F_1 to F_{10}) were prepared by direct compression technique. Ingredients required per tablet are given in Table no: 1 and tabulated as follows.

Table No: 1 – Composition Of Tablet Formulations F_1 To F_{10}

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metformin hydrochloride	500	500	500	500	500	500	500	500	500	500
Guar gum	30	60	90	-	-	-	-	-	-	-
Xanthan gum	-	-	-	30	60	90	-	-	-	-
Chitosan	-	-	-	-	-	-	30	60	90	-
F1+F2+F3(1:1:1)	-	-	-	-	-	-	-	-	-	90
Lactose	84	54	24	84	54	24	84	54	24	84
Polyvinylpyrolidone	14	14	14	14	14	14	14	14	14	14
Methyl paraben	6	6	6	6	6	6	6	6	6	6
Talc	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6
Total weight	650	650	650	650	650	650	650	650	650	650

The Metformin hydrochloride, Guar gum, Xanthangum, and Chitosan and Lactose, Polyvinylpyrolidone and Talc were separately passed through mesh No.44. The powders were uniformly mixed in a double cone blender for 5 mins. Then the dried powders were lubricated with magnesium stearate by mixing in a rapid mixer at slow speed for 5 mins, separately and compressed using 16/32 inch flat punches in cadmach tablet compression machine to get tablets.

Evaluation of Powder Blends

The formulated powder blends were evaluated for compatibility, angle of repose, bulk density, true density, percentage compressibility index and total percentage porosity.

Evaluation Of Tablets

The compressed tablets (formulations F_1 to F_3) and reference standard (F_4M) were tested for hardness, percentage friability, percentage weight variations and the percentage drug content.

In-Vitro Release Studies

In-vitro dissolution studies were carried out using six stage dissolution rate test apparatus IP/BP/USP at 50 rpm. The dissolution medium consisted of simulated gastric fluid (pH 1.2 - acid buffer) (for first 2 h) and followed by in simulated intestinal fluid (pH 7.2 - Phosphate

buffer) from 2 to 12 hours (900 ml), maintained at 37°±0.5°C. Samples were withdrawn at predetermined time intervals and drug content was analyzed by UV visible spectrophotometer at 227.5 and 230 nm respectively compared with blank. The same procedure was followed to study the *in-vitro* release of Metformin hydrochloride sustained release tablet. All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviations less than 3 indicating the reproducibility of the results. Statistical calculation of ANOVA and t-test were used to find out best formulation.

RESULTS AND DISCUSSION

Metformin hydrochloride is a highly water soluble drug. Its poor inherent compressibility coupled with high dose (500mg) posses a significance challenge for developing an extended release dosage form. For developing extended release matrix tablet with desirable drug release profile, cost effectiveness and broader regulatory acceptance combination of HPMC (K100M) and EC (18 CPS) was chosen as release controlling polymers.

Compatibility Study of Metformin Hydrochloride By DSC

DSC thermograms of pure Metformin hydrochloride, blend of polymer/polymers mixture with drug were determined (Figure: 1).

The different in the peak areas in the thermograms of blends of drug in the polymer from that of pure drug is due to less quantum of drug in the blend. Absence of any new endothermic peak are disappearance of no shift of endothermic peak confirms that peak in thermo grams of pure drug and the blends of drug in the polymer confirms that there is no any interaction and hence the polymers are compatible with drug.

Evaluation of Physical and Chemical Parameters of Formulated Powder Blends

Physical parameters such as specific surface area, shape, hardness, surface characteristics and size can be significantly affect the rate of dissolution of drugs contained in a complex system. The formulated powder blends of different formulations (F1 to F3) were evaluated for angle of repose, true density, bulk density, compressibility index and total percentage porosity (Table No: 2).

Table No: 2 Physical and chemical parameters of formulated Metformin hydrochloride powder blends (F_1 to F_{10}) an

Table 2: Flow Properties of Powder

Formulation Code	Angle of repose (θ)*	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Hausner ratio (HR)*	Carr's index (IC)*
F1	21.30±0.19	0.690±0.006	0.779±0.008	1.12±0.011	11.41±0.94
F2	20.99±0.28	0.693±0.010	0.786±0.011	1.13±0.02	11.99±2.07
F3	20.3±0.49	0.697±0.0005	0.788±0.008	1.12±0.011	11.95±1.60
F4	22.37±0.30	0.695±0.01	0.779±0.002	1.12±0.015	10.85±0.94
F5	22.11±0.24	0.684±0.009	0.786±0.01	1.14±0.001	12.92±0.88
F6	21.07±0.29	0.692±0.004	0.777±0.011	1.11±0.02	12.02±1.75
F7	20.88±0.60	0.682±0.004	0.773±0.01	1.13±0.02	11.78±1.65
F8	20.84±0.72	0.672±0.009	0.790±0.06	1.15±0.011	12.87±0.84
F9	21.15±1.00	0.683±0.005	0.789±0.05	1.15±0.02	13.44±1.71
F10	20.32±0.76	0.682±0.004	0.764±0.06	1.14±0.03	13.56±1.64

*All the values are expressed as mean± SE, n=3.

*All values are mean ±S.D for n=3

The results of angle of repose (<30) indicated good flow properties of all the formulated powder blends except one formulation (F_1). The compressibility index value were recorded <15%, result in good to excellent flow properties in one formulation (F_3) supporting the angle of repose indicating good flow, which in rest of the formulations it can >15%. Formulated powder blends density; porosity and hardness are often interrelated properties and are likely to influence compressibility, porosity, dissolution profile and properties of tablets made from it. The percentage porosity value ranged from 24.31 to 31.25 indicating that the packaging of the powder blend may range from close to lose packaging and also confirming that the particle are not of greatly different sizes. Generally a percentage porosity value below 25% shows that the particles in the powders are of greatly different sizes and values greater than 48 % shows that particle in the powder are in the form aggregates of flocculates. All these results indicate that the formulated powder blends processed satisfactory flow properties and compressibility.

Evaluation of Formulated Tablets

Code	Thickness (mm)*	Weight variation test (%)	Hardness (kg/cm^2)*	Friability (%)*	Drug content (%)*
F1	3.2±0.14	±2.30	5.83±0.25	0.42±0.03	97.89±6.65
F2	3.2±0.10	±2.40	5.66±0.40	0.48±0.08	100.59±6.09
F3	3.3±0.07	±1.90	5.58±0.37	0.49±0.08	96.32±5.92
F4	3.2±0.07	±2.19	5.75±0.41	0.45±0.02	97.02±5.79
F5	3.2±0.05	±2.12	5.66±0.40	0.47±0.05	97.99±5.18

F6	3.3±0.054	±1.92	5.66±0.40	0.54±0.04	100.11±2.38
F7	3.3±0.089	±2.09	5.83±025	0.53±0.09	99.14±5.37
F8	3.3±0.075	±2.12	5.66±0.40	0.49±0.04	99.15±4.680
F9	3.2±0.075	±2.03	5.57±0.37	0.46±0.05	100.11±2.65
F10	3.1±0.074	±2.14	5.52±0.36	0.45±0.07	100.04±1.24

*All the values are expressed as mean± SE, n=3.

The tablets of different formulations (F_1 to F_{10})) were evaluated for various parameters viz., hardness, friability, percentage weight variation and percentage drug content. The results of these parameters are given in Table No: 2

***In-Vitro* Release Studies**

Table 4: In Vitro Release Of Optimized Formulation F9

Time(hours)	% Drug release (%)*	Cumulative % Drug release (%)*
0	0	0
0.5	2.93±0.48	2.93±0.48
1.0	5.07±0.14	5.07±0.14
1.5	8.32±0.36	8.32±0.36
2.0	11.03±0.68	11.03±0.68
2.5	8.58±0.35	19.63±0.35
3	22.83±1.06	33.91±0.97
4	34.50±0.13	45.57±0.13
5	43.34±1.26	54.57±1.26
6	56.79±0.73	67.60±1.50
7	61.77±0.48	72.30±0.48
8	70.25±0.93	81.28±0.93
9	76.40±1.41	86.32±1.32
10	82.38±0.91	91.79±0.91
11	84.55±1.20	95.54±1.19

*All the values are expressed as mean± SE, n=3.

Results of the *in-vitro* release studies of various formulations designed and manufactured along with reference standard formulations (a marketed sustained release product) are presented in Table No: 3. the graphical representation of the data presented in the figure: 2.

The plot of cumulative percentage *In-vitro* drug release profile of Metformin hydrochloride from 10 formulations F1 to F10 made with different concentration and combination Polymers It is found that the cumulative percentage drug release of the formulation

Table 5: Different Kinetic Models For Metformin Hydrochloride Sustained Release tablets (F1 to F10)

Code	Zero order		First order		Higuchi		Korsemeyer-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	n	
F1	0.9696	12.809	0.9127	0.2208	0.8774	26.433	0.9696	1.68	Zero order
F2	0.9684	10.971	0.956	0.1956	0.9142	26.044	0.9067	1.30	Zero order
F3	0.9778	8.256	0.920	0.1468	0.866	21.287	0.9911	1.45	Peppas
F4	0.9820	10.004	0.937	0.1709	0.8854	23.425	0.9898	1.39	Peppas
F5	0.9783	8.987	0.8966	0.1623	0.8624	22.042	0.9923	1.49	Peppas
F6	0.9585	9.053	0.8737	0.1693	0.8328	22.043	0.9736	1.90	Peppas
F7	0.9901	9.341	0.9488	0.1627	0.9614	23.248	0.9721	1.25	Zero order
F8	0.9857	9.010	0.9356	0.1719	0.8729	23.410	0.9481	1.44	Zero order
F9	0.9853	8.370	0.9579	0.1571	0.9093	22.866	0.9450	1.34	Zero order
F10	0.9678	10.981	0.954	0.1573	0.9023	26.144	0.9063	1.32	Zero order

Characteristic	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm2)*	5.57±0.37	5.33±0.76	5.16±0.422	5.00±0.00
Drug content (mg/tablet)*	101.11±2.65	98.07.04±0.79	96.96.±0.13	95.17±0.70
In vitro drug release at 11 hour*	95.58±1.11	94.62±1.11	93.35±0.32	91.26±1.61

*All the values are expressed as mean± SE, n=3.

Table 6: Stability Studies of Optimized Formulation (F10) of Sustained Release Metformin Hydrochloride Tablet

CONCLUSION

The aim of the study was to study the effect of various hydrophilic polymers on in vitro release rate from sustained release tablet of **Metformin hydrochloride** based on a low density polymer. The sustained release drug delivery was a promising approach to achieve a prolonged therapeutic action of drug. Different types of matrix forming polymers guar gum, Xanthan gum and chitosan were studied. Formulation F9 containing chitosan polymer showed sustained drug release for 11 hours. The Metformin hydrochloride sustained release tablets were stable at 40°C/75% RH up to 3 months.

REFERENCES

1. Hermann LS, Melender A. Biguanides: Basic aspects and Clinical use. New York, Wiley, 1992; 773-95.
2. Tucker GT, Casey C, Phillips PJ. Metformin kinetics in health subjects and in patients with diabetes mellitus. J Cli Pharmacology, 1981; 12(2): 235-46.

3. Stepensky D, Friedman M, Srour N, Hoffman AR. Preclinical evaluation of pharmacokinetic pharmacodynamic rational for oral controlled release Metformin formulation. J Contro Rel, 2001; 71:107-115.
4. Neol M. Kinetic study of normal and sustained release dosage forms of Metformin in normal subjects. J Int Biomed Data, 1980; 1:9-20.
5. Pentikainen P. Bioavailability of Metformin: Comparision of solution, rapidly dissolving tablet, and three sustained release product. Int J Clin Pharmacol Ther Toxicol, 1986; 24 (4): 213-220.
6. Yuen HH, Peh KK, Tan BL. Relating *In-vitro* / *In-vivo* data of two controlled released Metformin formulations. Drug Dev Ind Pharm1999; 25(5):613 - 618.
7. Fujioka K, Ledger G., Stevens J, Goyvaerts H, Stein P. Once daily dosing of Metformin extended release (Met-XR) formulations: effectson glycemic control in patients with type 2 diabetic currently treated with Metformin, In: American Association, 60th Scientific Sessions, San Antonia, Texas, 2000.
8. Raghuram Reddy K, Srinivas Mutalik, Srinivas Reddy. Once daily sustained Release matrix tablets of Nicorandril: Formulation and Invitro Evaluation. AAPS Pharm Sci Tech, 2003; 4(4): 1-9.
9. Savavanan S, Nataraj KS, Verampalayam K, Ganesh S. Hydroxy propyl methyl cellulose based cephalexin extended release tablet: influence of tablet formulation: Hardness and storage on Invitro release kinetics. Chem Pharm Bull, 2003; 51(8):978-983.
10. Nagoji KEV, Srinivas Rao S, Bhanoji Rao ME. Release studies of nimesulide from ethyl cellulose and hydroxyl propyl methyl cellulose matrices. Indian J Pharm Sci, 2000; 62(5): 482 - 484.
11. Rao KR, Senapti P, Das MK. Formulation and invivo evaluation of ethyl cellulose microspheres containing Zidovudine. J Micro encapsule, 2005; 22(8):863-876.
12. Ray S, Ghosh PK, Das B, Gosh LK, Gupta BK. Statistical optimization supported product development of antiasthamatic multiparticulate drug delivery system. Ind J Pharm Sci, 2000; 62(3):175-180.
13. Banker GS, Anderson LR. Theory and Practice of industrial Pharmacy, Mumbai, India, Varghese Publishing House, 1987;296 -29.
14. Skoog DA, Holler JF, Nieman T. A Principles of Instrumental analysis, United Kingdom: Thomson Brooks Cole, 2005;805-803.