Formulation and Evaluation of Sustained-Release Tablet of Metformin Hydrochloride

Saroj Kale[1], Trusha Shangrapawar[2], Ashok Bhosale[3]
[1, 2, 3]Shankarrao Ursal College of Pharmaceutical science and research centre, Kharadi, Pune, Maharashtra, India

Abstract-
Objective: *The aim of this investigation was to develop and optimize metformin hydrochloride tablets for sustained release application. The sustained release tablet of metformin hydrochloride was prepared by wet granulation technique.*

Material and Methods: *Extended release of metformin hydrochloride matrix tablets was prepared by wet granulation method. The influence of varying the polymer ratios was evaluated. The excipients used in this study did not alter physicochemical properties of the drug.*

Results: *All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity. The in vitro drug dissolution study was carried out using USP apparatus Type II, paddle method, and the release mechanisms were explored. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release is retarding efficiency of the polymer. This study revealed that as the concentration of matrix material increased, drug release from matrices decreased. This may be due to slower penetration of the dissolution medium into the matrices.*

Conclusion: *The F1 to F7 of sustained release tablet of Metformin Hydrochloride batches were dormulated.*

The batch F7 was found with disintegrating time 54 min and 98.398 %drug release of drug hence it was selected as best batch and then subjected to stability study.

The best formulations MF7 subjected to 3 months stability studies and results showed there was no significant change in the hardness, friability, drug content and invitro drug release. Thus it was found that prepared tablets were physico-chemically stable throughout stability period.

Keywords- Sustained release tablet, Metformin hydrochloride, Hydroxypropyl methyl cellulose, Xanthan gum, Chitosan.

I. INTRODUCTION

Metformin Hydrochloride is antihyperglycemic agent; Metformin is absorbed mainly from the small intestine. Diabetes is one of the major causes of death and disability in the world. Diabetes is a long-lasting health condition that affects how our body turns food into energy does not make enough insulin that cause serious health problems, like heart disease, vision loss and kidney disease. Diabetes mellitus are be classified into two main types. First is type I or juvenile diabetes which is also called as insulin dependent diabetes and second type is type I or non-insulin dependent diabetes mellitus, this Type II diabetes is most common type of diabetes. Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and parenteral routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Metformin Hydrochloride is the best drug of choice as a sustain release drug delivery system. 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 % Metformin HCl 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 %. Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Unlike other antidiabetic drugs metformin HCl does not induce hypoglycemia at any reasonable dose, and hence it is called as an antihyperglycemic rather than a hypoglycemic drug 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 % and there is need to formulate sustained release tablet of Metformin Hydrochloride induce hypoglycemic at any reasonable dose, and hence it is called as an antihyperglycemic rather than a hypoglycemic drug. The compound has a relatively short plasma half-life of 1.5–4.5 h with low bioavailability of 50–60% so need for the administration of 2–3 times a day when larger doses are required can decrease patient compliance [7]. The objective of the present study was to prepare oral sustained release matrix tablet of metformin hydrochloride by wet granulation using polymers such as chitosan, xanthan gum, and hydroxypropyl methylcellulose and to evaluate the effect of concentration of

polymers for the release of the drug. Such a sustained release formulation if achieved would be substantially more affordable to the patient.

II. MATERIAL AND METHODS

Materials

Metformin hydrochloride was the gift sample from Aurobindo Pharma Ltd., Hyderabad. All other ingredients used throughout the study were of an analytical grade such as chitoson, hydroxypropyl methylcellulose, and xanthan gum were received from Loba Chemicals, Mumbai. Isopropyl alcohol, talc, and magnesium stearate were procured from S.D. Fine Chemicals, Mumbai.

Nine different tablet formulations were prepared using wet granulation method. The composition of tablets was given in Table 1. Sustained-release matrix tablets of metformin hydrochloride were prepared using different polymer ratios. All ingredients were passed through a #80 sieve weighed on a digital balance (Shimadzu, Japan) and blended. Tablets weighing 750 mg were prepared containing 500 mg of metformin hydrochloride, hydroxypropyl methylcellulose, xanthan gum, and chitosan. Required quantities of drug, diluents, and polymers were mixed thoroughly by adding a sufficient quantity of binding agent like isopropyl alcohol slowly. After enough cohesiveness was obtained, the wet mass was sieved through #16 mesh. The sifted granules were dried at 50°C for 1 h in hot air oven (BTI, Bio Technics, Mumbai). The dried granules were mixed with talc as a diluent and magnesium stearate as a lubricant for 5 min [8]. Finally, tablets were compressed by 10 mm punches on 16 Station Rotary tablet machine (Saimach Ltd., India). All tablets were stored in airtight containers for further study. Before compression, the granules were evaluated for their flow and compressibility characteristics.

III. EVALUATION OF POWDER BLENDS OF MET FORM IN HYDROCHLORIDE

The powder blends of metformin hydrochloride formulations were evaluated before compression to assess the flow properties of the powder.

Bulk density

Required amount of powder m was transferred into the measuring cylinder, and apparent volume V_0 was measured, bulk density in g per ml is calculated by the formula.

Bulk density = m/V_0.

Where m-mass of powder, V_0 -apparent volume.

Tapped density

After determination of bulk density the measuring cylinder Va volume in ml was measured initially, later the same cylinder was set for 100 tappings on tapped density apparatus and measure the tapped volume finally Vb. Calculate tapped density in g per ml by the formula [9].

Tapped density = Va/Vb.

Where Va - initial volume, Vb - final tapped volume.

Carr's index

It is an indirect method of measuring powder flow from bulk densities to measure bridge strength and stability. Carr's index of each formulation was calculated according to the equation.

Carr's index = (Tapped density - bulk density)/tapped density *100.

HAUSNER RATIO

It is essential to determine the compressibility strength of powder. It was calculated according to equation [10].

Hausner ratio = Tapped density/bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of repose

Accurately weighed quantity of powder was transferred into a funnel which was adjusted to a height of 2 cm in such a way that the tip of funnel touches apex of a pile of powder heap [11]. Finally, the height and radius of powder cone were measured using the following equation.

$\tan \theta = h/r$.

Where θ = angle of repose, h = height of pile, r = radius of pile base.

IV. EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED-RELEASE MATRIX TABLETS

Weight variation

Ten tablets from each batch were selected randomly and weighed on a digital balance (Shimadzu, Japan) individual weights were compared with average weight. The percentage difference in the weight variation should be within the permissible limits [12].

Thickness

The thickness of all formulations was determined on screw gauge (Pharma Labs, Ahmedabad, India). Standard deviation values indicate all formulations were within the range [13].

Tablet hardness

Hardness of the tablets for shipping or breakage under conditions of storage, transportation, handling depends on hardness which was determined using Monsanto hardness tester [14] (E 30, Dwaraka Mai, Hyderabad).

Friability

The Friability of five tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and was subjected to 100 revolutions dedusted and reweighed [15]. The friability (F) is given by the formula:

$$F = (1-W_0/W)*100$$

Where, W0 is the weight of the tablets before the test. W is the weight of the tablet after the test.

Drug content

Five tablets were weighed accurately and powdered, powder equivalent to 10 mg of drug was dissolved in phosphate buffer pH 7.4, filtered using 0.2 um membrane filter [16]. The drug content was measured by ultraviolet (UV)-spectrophotometer (Shimadzu, Japan) at 233 nm.

In vitro drug release

In vitro, drug release studies for the prepared tablets were conducted using USP Type II paddle dissolution apparatus (Electrolab, Mumbai, India) at 100 rpm. One matrix tablet was placed in each flask of dissolution apparatus the study was conducted in 900 ml 0.1 N Hcl 37±0.5°C in first 2 h and later 900 ml of phosphate buffer pH 7.4 for remaining 12 h. 5 ml samples were withdrawn at regular intervals and same volume was replaced to maintain sink conditions [17]. The samples were analyzed after suitable dilutions with UV-spectrophotometer (Shimadzu, Japan) at 233 nm. All the experimental units were carried in triplicates.

Kinetic analysis of dissolution data

The in vitro drug release data were fitted into zero-order, first-order, and Higuchi by employing the method of least squares the mechanism of drug release was compared for all the formulations.

$$Mt/M\infty = Ktn$$
$$Mt/M\infty = b+k2t1/2$$
$$Mt/M\infty = a+k3t$$

In Peppas equation, $Mt/M\infty$ is the fraction of drug released up to time t, K kinetic constant and n is the release exponent indicative of the release mechanism. In Higuchi and zero-order release equations, k1, k2, and k3 are constants [18]. On the other hand, Higuchi equation expresses a diffuse release mechanism.

V. RESULTS AND DISCUSSION

In the present work, sustained-release tablets of metformin hydrochloride were prepared by wet granulation method as it was feasible and simple. Formulations were prepared by varying amount of polymers to see the effect of various polymer concentration on drug release rate. The prepared mixed powder was physically evaluated with some parameters and was suggested to be suitable for compression into tablets.

Evaluation of powder blends of metformin hydrochloride sustained-release tablets

The method employed for the preparation of metformin hydrochloride sustained-release tablets was wet granulation method, mixture of drug and excipients should possess good flow properties. The flow properties of powder blend metformin hydrochloride were checked by studying the angle of repose, compressibility index, and Hausner's ratio. The powder blends were found to be free flowing with good flow properties as shown in Table 2.

Bulk density was found to be in the range of 0.500–0.640 (g/ml) and tapped density between 0.623 and 0.647 (g/ml) for all the formulations. The % compressibility index was calculated using the density data. The obtained values 11.15–15.91% which were found to be good flow and Hausner's ratio values were in the range of 1.131–1.189 for all powder blends. This was further supported by the angle of repose values between 17.17 and 20.55°. As it was below 30° it indicated good flow properties of powder blend.

Preparation and evaluation of metformin hydrochloride sustained- release tablets

The studies were carried to find the effect of different concentrations ranges of polymers. Evaluation data of metformin hydrochloride sustained-release tablets were shown in Table 3.

All the tablets were having beveled edged flat surface in round shape with white color. Average weight of tablets was in the range of 740–769 mg and weight variation was according to the limits. Thickness of the tablets was in the range of 4.18–5.32 mm. The hardness of tablets was determined and found in the range of 6.10–7.41 Kg/cm2. As the aim of the study is to release the drug slowly, hardness was kept in the high range. The % of content uniformity in tablets was determined by UV spectrophotometer (Shimadzu, Japan). All formulations are subjected to content uniformity and were in the range of 98.4–101%. It was observed that all the formulations were as per I.P. specification limits (90.0–110.0%). The % drug release data and plot which were obtained for the metformin hydrochloride sustained-release tablets in 0.1N Hcl in first 2 h and phosphate buffer pH 7.4 up to 12 h at 233 nm was shown in Table 4 and Fig. 1, respectively.

From the drug release it was observed that at low concentrations of the polymers, the matrices of the tablets readily disintegrated during dissolution test. This was not, however, the case when the content of the matrix former was increased, thus indicating that a minimum level of the polymers is required to form a proper matrix that would not readily disintegrate. This study revealed that as the concentration of matrix material increased, drug release from matrices decreased. This may be due to slower penetration of the dissolution medium into the matrices. Formulations with chitosan drug release were 86% for MS1, xanthan gum was 89% for MS4, and finally MS7with hydroxypropyl methyl cellulose for 92% which exhibited highest drug release retardation with the lowest matrix concentration. Hence, a lower concentration of polymers is suitable to prepare metformin hydrochloride tablets compared to higher concentrations. The initial drug release may be attributed to "burst" release of the drug on the tablet surface. It has stated that the drug particles present on the surface of a matrix system

Table 1: Formula of metformin hydrochloride sustained-release tablets

Sr. No.	Ingredients	MF1	MF2	MF3	MF4	MF5	MF6	MF7
1	Metformin Hydrochloride	500	500	500	500	500	500	500
2	HPMCK100M	150	100	-	-	75	50	50
3	XanthanGum	-	-	150	100	75	100	100
4	PVPK-30	30	30	30	30	30	30	30
5	Microcrystalline cellulose(Avicel)	150	200	150	200	150	150	150
6	Magnesiumstearate	10	10	10	10	10	10	10
7	Talc	10	10	10	10	10	10	10
8	**Total(mg)**	850	850	850	850	850	850	850

Table 2: Evaluation of tablet blend of Sustained Release Tablet of Metformin Hydrochloride

Batch No.	Angle of Repose(º)	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index(%)	Hausner Ratio
MF1	21.32±0.28	0.2574±0.002	0.3201±0.002	10.17±0.004	1.09±0.33
MF2	22.54±0.5	0.2641±0.004	0.3279±0.005	10.31±0.01	1.07±0.37
MF3	21.52±0.28	0.2678±0.003	0.3245±0.002	9.96±0.01	1.08±0.4
MF4	28.37±1.96	0.2745±0.002	0.3360±0.003	10.12±0.02	1.07±1.02
MF5	27.31±0.8	0.2792±0.004	0.3374±0.003	14.78±0.01	1.12±0.37
MF6	24.87±0.14	0.2752±0.001	0.3340±0.004	12.79±0.04	1.14±0.37
MF7	26.87±0.14	0.2748±0.001	0.3350±0.006	13.89±0.06	1.16±0.48

Table 2: Evaluation of tablet blend of Sustained Release Tablet of Metformin Hydrochloride

Formulations	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)	Weight variations (mg)	Disintegration time (Min)
F1	4.12±0.2	8.07±0.02	0.23±0.036	98.37±0.45	851±1.52	52±3.28
F2	4.03±0.2	7.92±0.10	0.23±0.045	98.58±0.13	854±2.37	49±1.41
F3	4.22±0.1	8.14±0.10	0.33±0.044	99.12±0.22	850 ±1.44	51±1.41
F4	4.31±0.1	7.54±0.05	0.42±0.024	98.16±0.67	860±1.86	50±1.89
F5	4.07±0.1	7.92±0.04	0.41±0.022	98.23±0.04	852±2.56	49±1.41
F6	4.12±0.1	7.61±0.06	0.23±0.45	98.23±0.36	853±2.13	48±1.91
F7	4.06±0.2	7.92±0.03	0.23±0.036	98.67±0.37	852±2.56	47±1.89

Table no. 3: Dissolution profile

Time (hrs)	MF1	MF2	MF3	MF4	MF5	MF6	MF7
0	0	0	0	0	0	0	0
1	10 ± 3.38	12± 3.75	11 ± 3.38	10± 3.43	11 ± 3.97	12± 3.90	14 ± 3.25
2	19 ± 3.98	13 ± 3.27	14 ± 3.98	19 ± 3.54	19 ± 3.65	15± 3.68	19 ± 3.63
4	38 ± 3.99	45 ± 3.67	33 ± 3.99	32± 4.25	39 ± 3.23	34± 4.20	34 ± 4.25
6	59 ± 4.46	58 ± 3.78	55 ± 4.46	45± 3.88	56 ± 3.84	49± 3.06	49 ± 3.23
8	79 ± 3.45	77 ± 4.35	72 ± 3.45	69± 4.23	74 ± 3.5	62± 3.27	63 ± 4.21
10	99± 3.78	91 ± 3.88	82± 3.78	81± 3.65	89 ± 3.67	78± 3.74	83 ± 4.30
12						97± 3.98	98± 3.98

In cumulative percent drug release study F7 formulation gives higher percent drug release when compared to other formulations at the end of 12 hours and graphical representation is shown in Figure 10.10 Therefore it was concluded that F7 is the best batch because of its highest percentage drug release at the end of 12 hours among all the formulations.

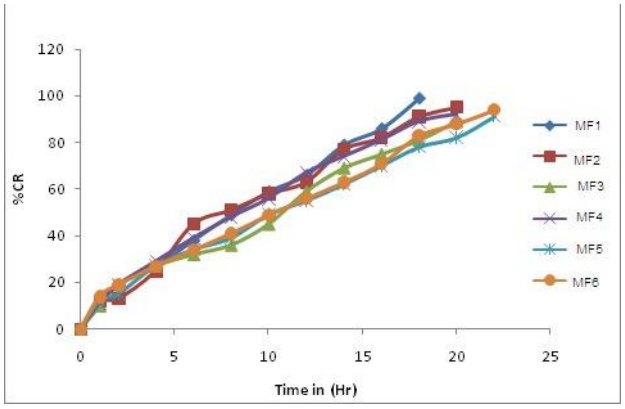

Figure No.10: Cumulative % Drug Release of F1-F7

VI. CONCLUSIONS

Metformin Hydrochloride is a biguanide antihyperglycemic agent; Metformin is absorbed mainly from the small intestine. The molecular weight of Metformin Hydrochloride is 129.1636g/mole half-life is 6-7 hours and its bioavailability 50-60%.

In this proposed research attempts are made to formulate sustained release tablet of Metformin Hydrochloride by using synthetic and natural rate controlling polymers like HPMC K100 and Xanthan Gum and versatile polymers like PVPK 30 which retards the drug release over a period of time. Metformin negligibly bounds to plasma proteins. It is excreted unchanged in the urine and does not undergo hepatic metabolism. It has a plasma elimination half-life of 3 hours.

The Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration 2-3 times. The use of polymers in sustaining the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. The sustained release can be achieved by using excipients PVP K30 as binding agent, MCC as a direct compressible agent, talc and magnesium stearate as a glidant and lubricating agent respectively. The drug was characterized according to different methods, into UV spectroscopy and drug excipient compatibility, organoleptic properties and other tests. In UV spectroscopy study, the maximum wavelength λmax of Metformin hydrochloride in 0.1 N HCl was found to be 233 nm. Standard calibration curve of metformin Hydrochloride in 0.1 N HCl developed absorbance against the concentration of drug in µg/ml which showed linearity with value 0.999.

The IR spectra did not show any significant differences from those obtained for their physical mixture. These obtained results indicates that there was no positive evidence for the interaction between Metformin Hydrochloride and other excipients. These results clearly indicates that the excipient can be used without any interaction of preparation of sustained release tablet.

The granulation were prepared for sustained release tablet of Metformin Hydrochloride.

The value of pre compression parameter evaluated, were within prescribed limits and indicated good free flowing properties.

The F1 to F7 of sustained release tablet of Metformin Hydrochloride batches were dormulated.

The batch F7 was found with disintegrating time 54 min and 98.398 %drug release of drug hence it was selected as best batch and then subjected to stability study.

The best formulations MF7 subjected to 3 months stability studies and results showed there was no significant change in the hardness, friability, drug content and invitro drug release. Thus it was found that prepared tablets were physico-chemically stable throughout stability period.

During stability study no change was observed in drug release profile, so prepared tablet of batch of sustained release tablet of Metformin Hydrochloride was concluded to be stable.

REFERENCES

[1] Hadi MA, Babu VL, Narottam P. Formulation and evaluation of sustained release matrix tablets of glimepiride based on combination of hydrophilic and hydrophobic polymers. J Appl Pharm Sci 2012;2:101-7.
[2] Patil J, Sarode SM, Sathe B, Jain PV. Formulation and evaluation of sustained release tablets of ritonavir. World J Pharm Pharm Sci 2014;3:857-69.
[3] Sanjit KR, Sweet N, Subhasis K, Ketousetuo K. Formulation and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Int J Pharm Pharm Sci 2015;7;264-9.
[4] Shanmugam S, Chakrahari R, Sundaramoorthy K, Vetrichelvan T. Formulation and evaluation of sustained release matrix tablets of losartan potassium. Int J Pharm Tech Res 2011;3:526-34.
[5] Bisht T, Rishiwer P, Kumar P. Review on matrix tablet. Indo Glob Pharm Sci 2016;6:38-42.
[6] Basavaraj K, Mhase SR, Manvi FV. Formulation of extended- release metformin hydrochloride matrix tablets. Trop J Pharm Res 2011;10:375-83.
[7] Dharmendra S, Kumar JS, Mahapatra S. Formulation and evaluation of sustained release metformin

hydrochloride matrix tablet using natural polysaccharide. Am J Pharm Tech Res 2014;4:492-503.
[8] Wadher KJ, Kakde RB, Umekar MJ. Study on sustained-release metformin hydrochloride from matrix tablet: Influence of hydrophilic polymers and in vitro evaluation. Int J of Pharm Inv 2011;1:157-63.
[9] Krishnarajan D, Reddy CM, Sasikanth K, Kumar NS, Purushothaman M. Formulation and evaluation of sustained release matrix tablets of levofloxacin using natural polymer pharmacophore. Int Res J 2013;4:146-57.
[10] Nagendrakumar D, Ganesh G, Ambarish GS. Sustained release matrix tablets of furosemide. J Pharm Sci 2015;5:105-14.
[11] Ch C, Kumar YG, Vishnu YV, Madhuri MM. Metoprolol succinate sustained release matrix tablets-Formulation development and in vitro evaluation. Int J Pharm Pharm Sci 2014;6:481-6.
[12] Jyothshna K, Pavan B, Venkateswara B, Pichika M. Formulation and development of multilayer and monolithic extended release matrix tablets of alfuzosin Hcl". Asian J Pharm Clin Res 2013;7:76-9.
[13] Patel J, Shah N. Formulation and evaluation of sustained release tablets containing atomoxetine hydrochloride. J Pharm Sci and Biosci Res 2014;4:196-200.
[14] Usman M, Ali I, Bibi H, Iqbal J. Preparation and evaluation of controlled release tablets containing mefenamic acid. Clin Exp Pharmacol 2012;2:1-3.
[15] Shanmugam S, Babu R, Satheeshkumar S, Shanmugasundaram P. Formulation and evaluation of sustained release matrix tablets of levosulpiride using natural polymer. Asian J Pharm Clin Res 2017;10:285-92.
[16] Kanti SM, Giriraj T, Suresh B. Development of sustained release bilayered tablets of diclofenac sodium using natural hydrogel as matrix material drug content. JchrDD 2013;4:53-64.
[17] Ajinkya, U., Sanjay, K., Mangesh, B. Design and optimization of sustained release matrix tablet of opipramol hcl by using quality by design approach. Asian J Pharm Clin Res 2014;7:227-34.
[18] Varma JN, Ch PK, Reddy AK, Raju PP. Evaluation of Moringa oleifera gum as a sustained release polymer in diclofenac sodium tablet formulation. Int J Res Pharm Chem 2014;4:687-93.