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Research Article

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Formulation, Development and Evaluation of Metformin Hydrochloride Extended Release Tablets

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Abstract The drug chosen for the present investigation, Metformin hydrochloride, is an orally active antidiabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) Type II. It is more appropriately referred to as antihyperglycemic agent and found to be well-tolerated and safe even on chronic use. The objective of this study was to design and evaluate oral sustained drug delivery system for metformin hydrochloride using hydrophilic polymers such as HPMC K4M and HPMC K100M. Four batches were prepared by using HPMC K4M in drug: polymer ratio of 5:1, 6:1, 7:1, 8:1 and four batches using HPMC K100M in ratios of 5:1, 6:1, 7:1, 8:1. Further formulations were modified by varying the ratios of diluents i.e. F9, F10, F11, F12 to check the effect of diluents on drug release. Matrix tablets were prepared by wet granulation method and were evaluated for weight variation, drug content, friability, hardness, thickness, and *in-vitro* dissolution. Among the formulations studied, formulation F6 containing HPMC K100M (6:1) showed sustained release of drug for 24 hrs with cumulative percent drug release of 98.11%, similar to that of the research listed drug. The kinetic treatment showed that the optimized formulation follow first-order kinetic with release exponent (n) 0.711 and having good stability as per ICH guidelines. The matrix formulation F6 showed sustained release of metformin hydrochloride by the diffusion mechanism.

Keywords Metformin hydrochloride, Sustained drug delivery system, Hydrophilic polymers, HPMC K4M, HPMC K100M.

Introduction

The oral route is considered to be one of the most acceptable routes used for the drug administration. Tablets are mostly preferred formulations by patients for the treatment of diseases particularly when the long term therapy is required, conventional tablet formulations are administered in several doses and therefore resulted in different disadvantages. Controlled release tablet formulations are more preferred for the management for such therapy due to its excellent compliance, retain drug levels, decrease side effects and dose and enhanced the safe use of high potency compounds [1].

Controlled release drug delivery methods facilitate the rate of drug release over an extended period of time after drug administration. These systems control the drug release rate with little effect from the intrinsic features of the active ingredient. Extended release formulations have the similar dose as that of immediate release formulation, but considered to be more preferred since the drug administration can be minimized. Extended release formulations maintained the drug therapeutic levels with reduced fluctuations. From a controlled release dosage form the rate of drug release will be significantly depend on the manufacturing technique, which may resulted in various drug release kinetics and varied therapeutic and pharmacokinetic response. Different polymers have been used in the controlled release drug delivery systems, like methyl cellulose, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose. Extended release technology can be categorized either as

matrix or membrane system, depending on the formulation technique and release mechanisms. Membrane systems control the release rate by using osmotic pumping or solution diffusion mechanism and the matrix systems can be attained by swelling and erosion control, by altering geometry/area, and/or inconsistent distribution [2].

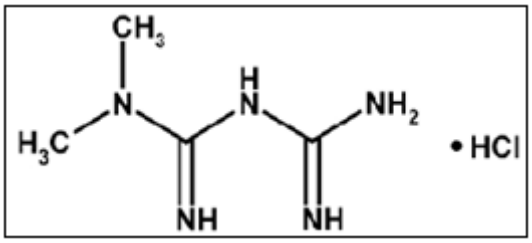

Figure 1: *Structure of Metformin hydrochloride*

Metformin Hydrochloride is an antihyperglycemic compound that has been used for the management of type 2 diabetes mellitus. Metformin can be categorized as BCS Class III drug due to its high water solubility and less permeability to cell membranes [3]. The membrane permeability of Metformin hydrochloride is the rate-limiting process in its absorption rather than drug release process. Absorption of metformin in GI tract is dose dependent but the rate and extent of drug absorption can be reduced by food slightly. The objective of this study was to design and evaluate oral sustained drug delivery system for metformin hydrochloride using hydrophilic polymers such as HPMC K4M and HPMC K100M [4].

Materials

Metformin HCl was donated by Wanbury Ltd, Maharashtra, India. Microcrystalline Cellulose 200, Hydroxy propyl methyl Cellulose E5, Hydroxy propyl methyl Cellulose K4M, Hydroxy propyl methyl Cellulose K100M, Colloidal silicon dioxide, Magnessium stearate, Opadry white were donated by Colorcon Asia Pvt Ltd, Verna, Goa, India.

Methods

Preparation of hydrophilic tablets:

Twelve different hydrophilic formulations were prepared by wet granulation procedure having Metformin HCl 1004.52 mg, Hydroxy propyl methyl Cellulose K4M or Hydroxy propyl methyl Cellulose K100M (12-16%) were accurately weighed. The dry components were mixed together which were then wet massed with Hydroxy propyl methyl Cellulose E5 (1%), the granules were dried in an oven which were mixed with Microcrystalline Cellulose 200 (3%) then lubricated with Aerosil (0.6%) and Magnesium stearate (0.4%). At the end, tablets were compressed by using multiple punch tablet machine. The formulations were coat with Opadry white (2%) as shown in Table 1 (a) and 1 (b) respectively.

Table 1 (a): Composition of Hydrophilic Formulations (Batch F1-F6)

S. No.	Ingredients	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)	F5 (mg/tab)	F6 (mg/tab)
1.	Metformin hydrochloride	1004.52	1004.52	1004.52	1004.52	1004.52	1004.52
2.	HPMC K4M	200.90	167.32	143.50	125.56	---	---
3.	HPMC K100M	---	---	---	---	200.90	167.32
4.	HPMC 5 cps	12	12	12	12	12	12
5.	MCC 200	5.68	39.26	63.08	81.02	5.68	39.26
6.	Aerosil	5	5	5	5	5	5
7.	Mag. stearate	8	8	8	8	8	8
8.	Opadry white	23.90	23.90	23.90	23.90	23.90	23.90
Total Weight		1260	1260	1260	1260	1260	1260

Table 1 (b): Composition of Hydrophilic Formulations (Batch F7-F12)

S. No.	Ingredients	F7 (mg/tab)	F8 (mg/tab)	F9 (mg/tab)	F10 (mg/tab)	F11 (mg/tab)	F12 (mg/tab)
1.	Metformin hydrochloride	1004.52	1004.52	1004.52	1004.52	1004.52	1004.52
2.	HPMC K4M	---	---	---	---	---	---
3.	HPMC K100M	143.50	125.56	167.32	167.32	167.32	167.32
4.	HPMC 5 cps	12	12	17	22	7	2
5.	MCC 200	63.08	81.02	34.26	29.26	44.26	49.26
6.	Aerosil	5	5	5	5	5	5
7.	Mag. stearate	8	8	8	8	8	8
8.	Opadry white	23.90	23.90	23.90	23.90	23.90	23.90
Total Weight		1260	1260	1260	1260	1260	1260

Evaluation of granules and powder blends:

Carr's Index and Haussner's ratio

In order to assess the flow characteristics of powder blends, ratio of tapped and bulk density can be explained in the two ways as followed:

$$\text{Haussner's ratio} = \text{Tapped Density}/\text{Bulk Density} \quad \ldots (1)$$

$$\text{CI \%} = (\text{Tapped Density} - \text{Bulk Density}) * 100 / \text{Bulk Density} \quad \ldots (2)$$

Where,

$$\text{Bulk density} = \text{Weight of the powder} / \text{Bulk volume} \quad \ldots (3)$$

$$\text{Tapped density} = \text{Weight of the powder} / \text{Tapped volume} \quad \ldots (4)$$

Bulk and tapped densities were analyzed by pouring 50 gm of powder into the 100 mL cylinder and assessing bulk volume and then the final volume after 100 times tapping [5].

Angle of repose

The angle of repose was estimated by fixed base technique. By assessing the powder heap and its radius, angle of repose was estimated as follows:

$$\theta = \tan^{-1} h/r \quad \ldots (5)$$

Evaluation of trial batches:

All the formulations were evaluated by various physical parameters such as diameter and thickness (by vernier caliper), weight variation analysis was done by using electronic balance, hardness was determined by hardness tester and friability assessment was done by friability tester [6].

Evaluation of content uniformity test:

Finely powder 10 tablets. Transfer powder, equivalent to the average tablet weight, to a homogenization vessel, and add 500 mL of 10% acetonitrile solution. Alternately, homogenized and allowed to soak until the sample is fully homogenized [7].

Calculate the percentage of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the portion of tablets taken:

$$\textbf{Result} = (r_U/r_S) \times (C_S/C_U) \times 100 \quad \ldots (6)$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Metformin Hydrochloride RS in the Standard solution (mg/mL)

C_U = nominal concentration of metformin hydrochloride in the Sample solution

Dissolution test:

Dissolution test of all the formulations were carried out using dissolution apparatus USP-I (Basket) at 100 rpm, 900 mL of phosphate buffer pH 6.8 was taken as a medium, at 37 ± 0.5^0C. The cumulative % drug release was

estimated by UV-visible spectrophotometer (UV-1800 Shimadzu) at 233nm [8].

Analysis of Data:

Model-dependent Methods

Data obtained from drug release were built-in into four kinetic models which were: Zero-Order (Eq.7), First-Order (Eq.8), Higuchi model (Eq.9) and Korsmeyer-peppas model (Eq.10).

$$\mathbf{F = K.t} \quad \ldots (7)$$

Where K is the zero-order rate constant expressed in units of concentration/time, t is the time in hours and F is the concentration of drug release in time t.

$$\mathbf{log\ C = log\ C_o - (K.t / 2.303)} \quad \ldots (8)$$

Where C_0 is the original amount of drug, K is the first order rate constant and t is the time.

$$\mathbf{F = K.t^{1/2}} \quad \ldots (9)$$

Where K is the Higuchi release rate constant and t is the time (hr).

$$\mathbf{M_t/M_\infty = K.t} \quad \ldots (10)$$

Where M_t is the absolute cumulative concentration of drug release at time t and M_∞ is the absolute cumulative concentration of drug release at infinite time, K is the kinetic constant property of the compound/polymer system and *n* was measured through the slope of the straight line which explains the drug release mechanism [9]. Kinetic models explained above were estimated by DD-Solver an ad in program for Microsoft Excel TM 2007 (Microsoft Corporation, USA).

Model-independent Methods

This model can be estimated by f_1 (difference factor) and f_2 (similarity factor) which were explained by various scientists [10]. For the evaluation of f_2, Microsoft Excel TM 2007 (Microsoft Corporation, USA) was used.

$$f_2 = 50 \bullet \log \{[1+(1/n)\textstyle\sum_{i=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\} \quad \ldots (11)$$

Where, R_t is the % release of reference product and T_t is the % release of test product at specific time points and n is the nom. of sampling time.

Stability Studies:

The optimized formulation was subjected for 2 months stability study according to ICH guidelines**.** The selected formulations were packed in HDPE bottles closed tightly. They were then stored at 40ºC ± 2ºC / 75% RH ± 5% RH for 2 months and then evaluated for their drug release study [11].

Results and Discussion

One of the basic objectives of dosage form design is to maintain the release rate in *in-vivo* environment. Sustained release formulations are designed to attain extended therapeutic response over an extended period of time after the administration of the single dose. Thus, at a specific site maximum drug concentration will be ensured without much difficulty, which is often seen in conventional dosage form [12].

Evaluation of reference formulation:

In the present study the physical attributes of the reference formulation were assessed by different physico-chemical tests and the results were found within the adequate limits as presented in Table 2.

Table 2: Parameters of Reference Formulation

Parameters	**Reference Formulation**
Diameter (mm)	13.00 ±0.10
Thickness (mm)	9.00 ±0.10
Hardness (kg/cm^2)	12.00 ±0.29
Weight (mg)	1210.00 ±1.30
Friability (%)	0.06

Content Uniformity (%)	100.10

The *in-vitro* drug release profile was performed using phosphate buffer pH 6.8. The amount of drug release at 2, 8, 16 and 24 hrs were found to be 17.50%, 68.50%, 93.50% and 98.50% respectively as shown in Figure 2 and Table 4.

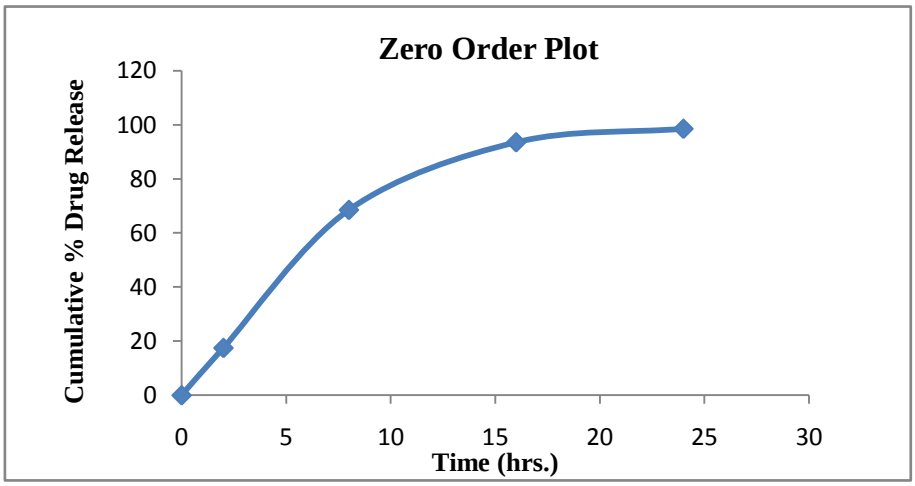

Figure 2: *Cumulative % Drug release of reference formulation*

Evaluation of powder blend and tablets:

As preformulation assessment, the flow features of powders were estimated by various flow parameters such as carr's index, haussner's ratio and angle of repose. Results indicated that powders showed satisfactory flow properties and compressibility during tablet manufacturing. Powder flow establishes tablet weight, hardness and content uniformity. It is important to evaluate the flow properties of powders prior to tablet compression [13].

Table 3: Preformulation studies of powder blends

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Compressibility Index %	Angle of Repose (^{0})
F1	0.423±0.003	0.632±0.005	1.49	33.90	32.3±0.30
F2	0.412±0.003	0.646±0.005	1.56	32.70	35.8±0.95
F3	0.462±0.004	0.648±0.002	1.40	34.70	34.2±0.34
F4	0.423±0.006	0.623±0.002	1.47	33.80	32.6±0.50
F5	0.453±0.003	0.655±0.001	1.44	29.40	32.5±0.50
F6	0.421±0.001	0.652±0.004	1.50	33.40	35.9±0.45
F7	0.441±0.002	0.648±0.003	1.46	21.40	36.8±0.52
F8	0.430±0.036	0.663±0.003	1.54	35.60	31.6±0.50
F9	0.423±0.006	0.623±0.002	1.47	33.80	32.6±0.50
F10	0.421±0.001	0.652±0.004	1.54	33.40	35.9±0.45
F11	0.437±0.002	0.638±0.003	1.45	32.10	33.1±0.62
F12	0.437±0.002	0.638±0.003	1.45	32.10	33.1±0.62

In order to assess the *in-vitro* drug release profile, dissolution test was performed, It was found that the *in-vitro* dissolution profile of metformin hydrochloride from Batch F6 containing HPMC K100M (6:1) is almost similar with that of RLD (Figure No. 3 and Table No. 4). Hence, Formulation F6 was selected as a best formulation.

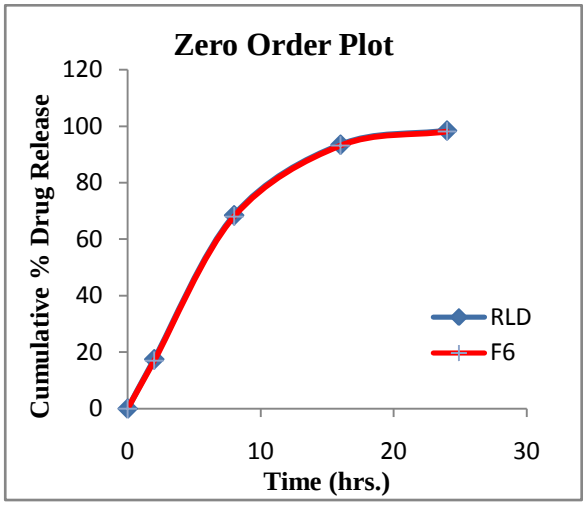

Figure 3: Comparison of drug release profiles

Table 4: Comparison of drug release profiles

Time (hrs.)	Cumulative % Drug Release	
	RLD	F6
0	0	0
2	17.50	17.01
8	68.50	68.02
16	93.50	93.12
24	98.50	98.11

Drug release kinetics:

The *in-vitro* drug release profiles of Batch F6 and reference formulation expressed cumulative % drug release at time point 2 hr, 8 hr, 16 hr and 24 hr.

Dissolution profiles were then analyzed by model-independent and model-dependent method. In the present study the drug release kinetics were described by various kinetic models and equations (Table No. 5) i.e., Zero-order, First-order, Higuchi and Korsmeyer-peppas were applied to reference formulation and Batch F6.

Table 5: Mathematical Modeling and Drug Release kinetics

Formulation	Drug Release Kinetics (R^2)				Release exponential (n)
	Zero-order	First-order	Higuchi	Korsmeyer	
RLD	0.865	0.996	0.960	0.935	0.700
F6	0.866	0.997	0.960	0.939	0.711

In this experiment, the *in-vitro* release profiles of the drug from these formulations can be best expressed by Higuchi's equation as the plots showed the highest linearity (R^2 0.950 to 0.990). To confirm the diffusion mechanism of metformin hydrochloride from matrix tablets, the dissolution data were subjected to the Korsmeyer-peppas diffusion model. The 'n' values for all formulations ranged from 0.60 to 0.80, indicating that the release mechanism was non-fickian or anomalous release ($0.45 < n < 0.89$). It can be inferred that the release was dependent on both drug diffusion and polymer relaxation.

Model-independent method was used in order to evaluate the similarity of drug release among tablet dosage forms. Similarity factor (f_2) of Batch F6 was determined and found to be 98. So it concluded that developed product is similar to that of Reference product.

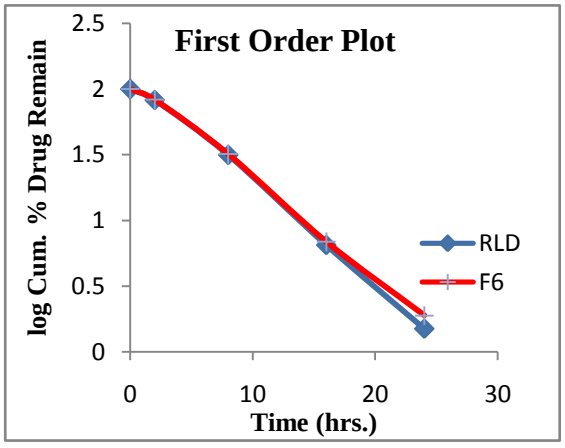

Figure 4: *First order plot of Batch F6 and RLD*

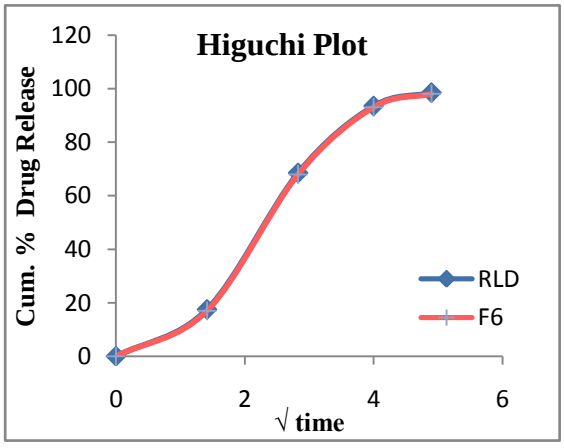

Figure 5: *Higuchi plot of Batch F6 and RLD*

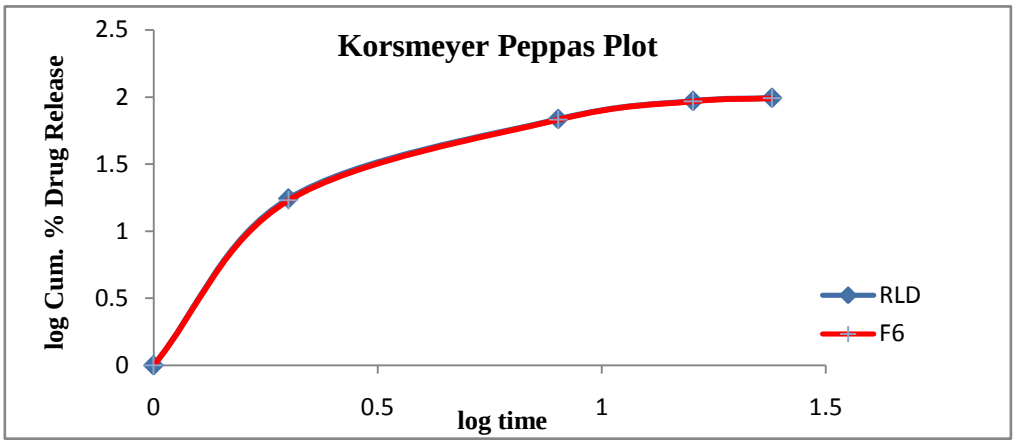

Figure 6: *Korsmeyer-peppas plot of Batch F6 and RLD*

Stability Studies:

The formulation subjected for stability studies was found to have no change in the physical appearance and drug content (Table No. 6).

Table 6: Stability profile of RLD and Batch F6

Time period	Description	Assay of RLD (%)	Assay of F6 (%)
Initial	No change	100.10	100.02
1st Month	No change	99.90	99.90
2nd Month	No change	99.80	99.80

Conclusion

In the present study, metformin hydrochloride extended release tablet were formulated and evaluated. These formulations showed excellent drug release profiles. Results showed that First-order kinetics was fitted to all formulations.

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