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Formulation Development and *In Vitro* Evaluation of Metformin Hydrochloride Matrix Tablets Based on Hydroxypropyl Methyl Cellulose

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ABSTRACT

An attempt was to formulate the oral sustained release Metformin hydrochloride matrix tablets by using hydroxyl methyl cellulose polymer (HPMC) as rate controlling factor and to evaluate drug release parameters as per various release kinetic models. The tablets were prepared by direct compression method. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, drug content etc. and showed satisfactory results. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in vitro release studies. The in vitro dissolution study was carried out for 8 hours using United States Pharmacopoeia USP 22 (paddle-type dissolution apparatus) in phosphate buffer (pH 7.4) as dissolution media. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications. The release mechanisms were explored and explained with zero order, first order, Higuchi, Korsmeyer and Hixson-Crowell equations. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was only dependent on the type and amount of polymer used. The drug release followed both diffusion and erosion mechanism in all cases. Besides, this study explored both of the optimum concentration and the effect of polymer on drug release pattern from the tablet matrix for 8 hours period.

Key Words: Metformin HCl, Sustained release, Hydrophilic matrix, HPMC, Direct compression

INTRODUCTION

Metformin HCl is an antihyperglycemic agent which improves glucose tolerance in patients with type- 2 diabetes by lowering both basal and postprandial plasma glucose. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type- 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease. The low bioavailability and short half-life of metformin hydrochloride (MH) make the development of sustained-release forms desirable. However, drug absorption is limited to the upper gastrointestinal (GI) tract, thus requiring suitable delivery systems providing complete release during stomach-to-jejunum transit (Corti et al., 2008). This study was undertaken to develop a MH sustained-release formulation in compliance with these requirements.

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms (Amidon et al., 2000). Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and at constant rate for desired time period (Ford et al., 1985).

The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate (Reddy et al., 2003). A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers that primarily forming insoluble or skeleton matrices are considered as the first category of retarding

materials and are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials which are potentially erodable and the third group exhibits hydrophilic properties. There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Methocel K15M CR, used in this study is hydrophilic polymer that becomes hydrated, swollen and facilitates to diffuse the drug (Vazquez et al., 1992).

MTERIALS AND METHODS

Materials

Drug: Metformin HCl (Square Pharmaceuticals, Bangladesh); ***Polymer:*** Methocel K15M CR (Dow Chemical Company, Midland, MI, USA); ***Other excipients:*** Microcystalline Cellulose (Avicel-101) (Hanau Chemicals Ltd., Japan); Polyvinnyl pyrrolidone (Povidone K-30) (Hanau Chemicals Ltd., Japan); Colloidal anhydrous silica (Aerosil 200) (Hanau Chemicals Ltd., Japan); Magnesium stearate (Hanau Chemicals Ltd., Japan); ***Solvents and reagents:*** Potassium di hydrogen phosphate (Merck, Germany); Sodium hydroxide (Merck, Germany); ***Equipments:*** Single punch tablet press (Shanghai-Tianhe Pharmaceutical Machinery Company); UV Spectrophometer (Shimadzu, Japan); Digital pH meter (Hach Company, USA); Electronic Hardness tester (Ereweka, Germany); Tablet Dissolution Tester (Electrolab, India); Sartorius Electronic Balance.

Preparation of tablets

The tablets were prepared by simple blending of active ingredient with polymer, filler, binder, lubricant and flow promoter followed by direct compression (Table-1). 30 tablets were prepared for each proposed formulation. Properly weighed methocel K15M CR, Povidone K-30, avicel PH 101, magnesium stearate, aerosil and the active ingredient were then taken in a photo film container and blended in a laboratory designed small drum blender machine for 30 minutes to ensure thorough mixing and phase homogenization.

Evaluation of physical properties

The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity and drug content etc (Aulton et al.,1998). The prepared tablets were subjected to thickness, weight variation test, hardness, friability and drug content (Aulton et al., 1998 and Martin et al., 2001).

In vitro dissolution study

The release study was carried out for 8 hours using USP 22 paddle-type dissolution apparatus in buffer media (pH 7.4) at 100 rpm maintaining 37±0.5℃. A 10ml sample was collected from each vessel at 1, 2, 4, 6 and 8 hour and spectrophotometrically analyzed for metformin at 233 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer.

Table 1: Proposed formulations of Metformin HCl SR matrix tablets.

Formulation Code	F-1	F-2	F-3	F-4	F-5
Metformin HCl	500	500	500	500	500
Methocel K15M CR	50	100	150	200	250
Avicel PH 101	260	210	160	110	60
Kollidon 30	30	30	30	30	30
Mg-Stearate	5	5	5	5	5
Aerosil 200	5	5	5	5	5
Average tablet wt. (mg)	**850**	**850**	**850**	**850**	**850**
Polymer content (%)	**5**	**11**	**17**	**23**	**29**

RESULTS

The granules of proposed formulations (F-1 to F-5) were evaluated for LBD, TBD, compressibility index, total porosity, angle of repose and drug content (Table-2).

Table 2: Properties of granules of tablet matrix from Methocel K15M CR.

Tablet	Angle of Rrepose (°)	Loose Bulk Density (LBD) (g/mL)	Tapped Bulk Density (TBD) (g/mL)	Compressibilty Index (%)	Total Porosity (%)	Drug Content (%)
F-1	23.15±0.02	0.51±0.03	0.59±0.02	15.25±0.01	25.45±0.02	99.45±0.02
F-2	23.05±0.01	0.43±0.01	0.57±0.03	24.15±0.02	23.98±0.05	98.210.06
F-3	20.55±0.03	0.44±0.05	0.58±0.04	24.14±0.02	26.21±0.03	98.55±0.02
F-4	22.25±0.02	0.48±0.03	0.60±0.05	20.00±0.04	25.36±0.02	99.00±0.03
F-5	25.15±0.12	0.52±0.02	0.72±0.03	27.78±0.03	23.0 ±0.01	98.45±0.05

The results of LBD and TBD ranged from 0.45±0.05 to 0.55±0.02 and 0.57±0.03 to 0.72±0.05 respectively and the compressibility index (%) ranged from 15.25±0.01 to 27.78±0.03. The results of angle of repose ranged from 22.25 ±0.02 to 25.15±0.02 (°). The percentage porosity values of the granules ranged from 25.0±0.01 to 27.25±0.06 % indicating that the granules might range from close to loose packing. The drug content in all formulations (F-1 to F-5) ranged from 96.25±0.08 to 99.45±0.04%.

The thickness of the tablets ranged from 6.05±0.10 to 9.75±0.03 mm. the hardness and percentage friability ranged from 7.0±0.02 to 10.1±0.04 kg/cm^2 and 0.05±0.04 to 0.50±0.01% respectively (Table-3).

Table 3: Properties of Metformin HCl SR matrix tablets prepared from Methocel K15M.

Tablets	Thickness (mm)	Weight Variation (%)	Drug Content (%)	Hardness (Kg/cm^2)	Friability (%)
F-1	4.10±0.0.2	2.20±0.01	97.07±0.02	7.50±0.01	0.50±0.01
F-2	4.08±.003	2.25±0.02	96.03±0.05	6.02±0.03	0.50±0.01
F-3	4.75±0.03	4.20±0.03	98.07±0.05	6.50±0.03	0.25±0.01
F-4	4.50±0.02	2.75±0.01	99.07±0.05	5.00±0.02	0.33±0.01
F-5	4.05±0.10	1.25±0.05	98.07±0.03	7.00±0.05	0.49±0.01

In weight variation test, the limit of percentage deviation for all tablets was found ±0.5%. The percent drug release from Methocel K15M CR based matrix tablet of formulations, F-1, F-2, F-3, F-4,and F-5 were 10.32%, 99.25%, 93.65%, 90.56% and 77.25% respectively at the end of 8 hour. The proposed formulation F-3 and F-4 exhibited official drug release pattern for 8h period. This drug release pattern was compared with a commercial brand and found both were similar to each other (Fig.- 6) (Mutalik et al., 2007).

DISCUSSION

Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time. The short biological half-life and dosing frequency more than one per day make the drug an ideal candidate for sustained release (Corti et al., 2008). The tablets prepared in the present study by direct compression method have advantages over those prepared by wet granulation in terms of time and energy consumption, thus making it possible to formulate tablets at a lower cost. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled

drug delivery (Bettin et al., 1998). The granules of proposed formulations (F-1 to F-5) were evaluated for various physico-chemical properties (Table-2).

Table 4: Release rate constants and R^2 values for different release kinetics of metformin HCl SR tablet matrix

Formulation	Zero order		Higuchi		First order		Korsmeyer		Hixson- Crowell	
	K_0	R^2	K_h	R^2	K_1	R^2	n	R^2	K_{HC}	R^2
F-1	10.92	0.924	34.53	0.984	0.155	0.964	0.528	0.980	-0.116	0.45
F-2	10.68	0.930	33.60	0.981	0.136	0.969	0.530	0.970	-0.122	0.53
F-3	10.69	0.94	33.42	0.995	0.132	0.962	0.555	0.979	-0.125	0.56
F-4	10.56	0.943	32.91	0.992	0.126	0.950	0.563	0.976	-0.129	0.60
F-5	9.32	0.947	28.97	0.981	0.082	0.981	0.621	0.984	-0.130	0.62

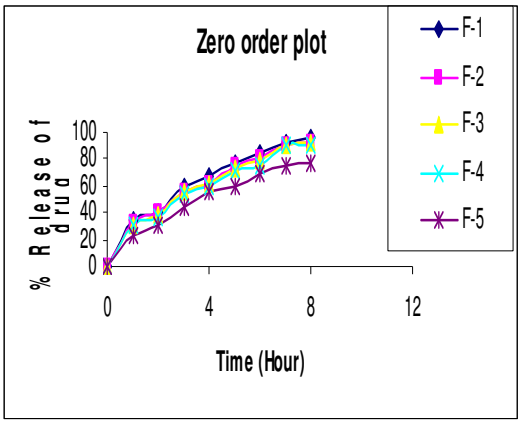

Figure 1: Zero order plot of release kinetics of proposed five formulations.

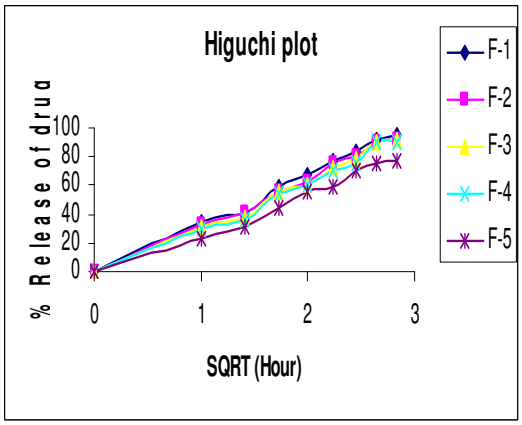

Figure 2: Higuchi plot of release kinetics of five proposed formulations.

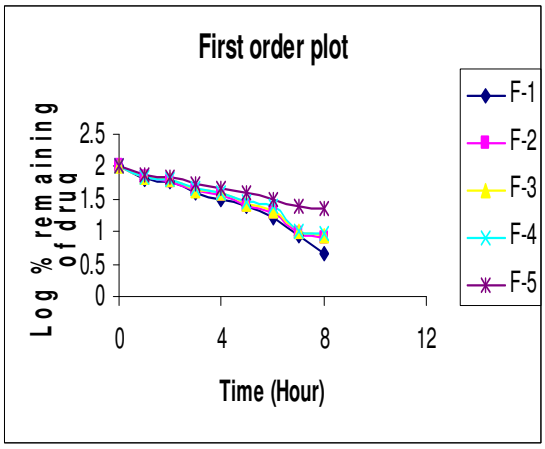

Figure 3: First order plot of release kinetics of five proposed formulations.

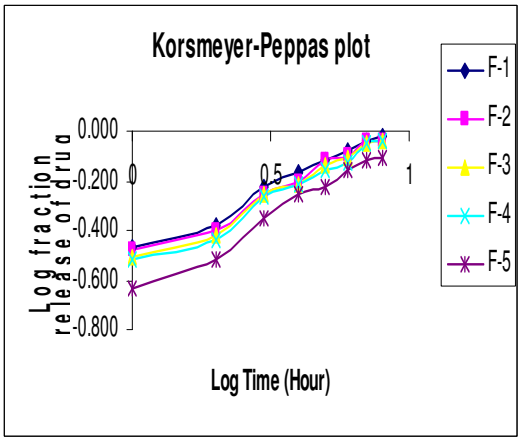

Figure 4: Korsmeyer plot of release kinetics of five proposed formulations.

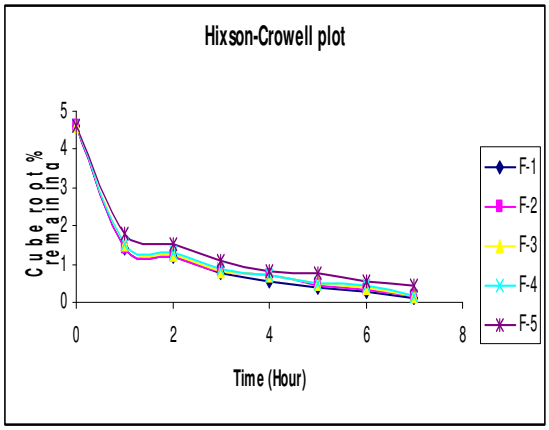

Figure 5: Hixson-Crowell plot of release kinetics of five proposed formulations.

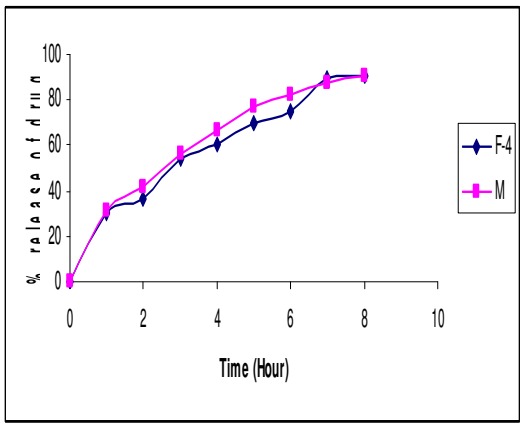

Figure 6: Comparison of release kinetics of F-4 and commercial brand (M).

The results of angle of repose (<30^0) indicated good flow properties of the granules which was further supported by lower compressibility index values. The percentage porosity values of the granules indicated that the packing of the granules might range from close to loose packing and also further confirming that the particles were not of greatly different sizes. Generally, a percentage porosity value below 26% shows that the particles in the powder are of greatly different sizes and a value greater than 48% shows that particles are in uniform of aggregates or flocculates. The drug content in a weighed amount of granules of all formulations indicated that the granules possessed satisfactory flow properties, compressibility and drug content (Liebermann et al., 1990). It was found that all the formulations showed uniform thickness and the average percentage deviation of all tablet formulations were found to be within the limit (Cooper et al., 1986). Uniformity in drug content was found among different batches of the tablets and the percentage of drug content was more than 96%. In this study the percentage friability for all the formulations was below 1% which was within the prescribed limits (Liebermann et al., 1990).

Among these formulations (F-1 to F-5), the rate and extent of drug release was decreased with increasing the amount of Methocel K15M CR. This polymer has been well known to retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate is related to its viscosity. Processing factors including particle size, hardness, porosity and compressibility index etc. also can affect the release rate of drug from tablets (Martin et al., 2001). The hydration rate of HPMC depends on the nature of the substituents like hydroxypropyl group content. Hence, Methocel K15M CR was used because it forms a strong viscous gel in contact with aqueous media which may be useful in controlled delivery of drug (Hogan et al., 1989). The drug release data obtained were extrapolated by Zero order, Higuchi, First order, Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations (Fig.1, 2, 3, 4&5). In this experiment, the *in vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (R^2: 0.98 to 0.99) (Higuchi *et al.,*1961). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation (Fig.- 4) (Korsmeyer et al., 1983). The formulations showed good linearity (R^2: 0.97 to 0.98) with slope (n) values ranging from 0.528 to 0.621 indicating that diffusion was the predominant mechanism of drug release from these formulations. When plotted according to Korsmeyer-Peppas equation, the formulations F-4 and F-5 showed high linearity (R2: 0.98) with a comparatively high slope (n) values of >0.5 which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion (Peppas et al., 1985). Hence, diffusion coupled with erosion might be the mechanism for the drug release from Methocel K15M CR based matrix tablet. The release profile of metformin from all these formulations displayed very poor fitting with Hixson-Crowell cube root model of drug release which were related with the method of manufacture followed (Fig.-5) (Hixson et al., 1931).

CONCLUSION

Hydrophilic polymer particles have unique quality to hold drug firmly through matrix formation while compressed into tablet. This matrix promote desired controlled drug release upon hydration, swelling and gel formation when interact with gastrointestinal fluid. Methocel K15M CR based

formulation F-3 and F-4 fulfilled the official release order and comparable with commercial brand. Thus, the proposed formulation F-3 and F-4 can be successfully used for the management of type-2 diabetes.

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