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Preparation of Metformin Hydrochloride Extended Release Matrix Tablets by Direct Compression Method and Its *In vitro* Evaluation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors contributed equally. Author MSIP supervised the overall work. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Metformin Hydrochloride, a biguanide, is an orally active antihyperglycemic agent, used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It has relatively short plasma half life, low absolute bioavailability. Extended release formulation of Metformin Hydrochloride by direct compression method has significant challenges due to its poor inherent compressibility and high dose. The aim of this study was to develop extended release tablets of Metformin Hydrochloride by direct compression method and *In vitro* evaluation.

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Study Design: Nine different formulations were made by varying drug-polymer ratio and were subjected to different physical property tests of the powder blend as well as prepared tablets, followed by dissolution test.
Place and Duration of Study: Department of Pharmacy, State University of Bangladesh, Dhaka, Bangladesh, between January 2013 and July 2013.
Methodology: Nine formulations of Metformin Hydrochloride matrix tablets - F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8 and F-9 - were prepared by direct compression method using release retarding materials, Methocel K100 MCR Premium (derivative of hydroxypropyl methylcellulose - HPMC) and Xanthan gum. The drug and polymer ratio were 1:0.41, 1:0.45, 1:0.49, 1:0.59, 1:0.63, 1:0.67, 1:0.77, 1:0.81 & 1:0.85 respectively. The micromeritic behavior of the powder blends were evaluated for bulk density, angle of repose, compressibility index along with post compressional attributes of the tablets such as thickness, hardness, friability, weight variation and content of Metformin Hydrochloride in the tablets. The in-vitro drug release study was carried out in 1000 mL phosphate buffer medium (pH 6.8) at 37±0.5℃ at 100 rpm for 10 hours using USP Apparatus Type-II (paddle) method.
Results: FT-IR study showed drug-excipient compatibility and DSC analysis showed no solid state interaction between components. The physical properties of the powder blend and the tablets were within the acceptable limits. Maximum and minimum drug release were found in formulation F-1 and F-9 respectively which indicate that release rate is inversely proportional to the concentration of Methocel K100 MCR Premium and Xanthan gum in combination. Dissolution study also showed that, formulations F-7, F-8 & F-9 do not comply with drug release specification of USP and among the rest six formulations F-3, F-4 & F-5 comply better with drug release specification of USP. After fitting the data to Korsmeyer-Peppas equation we found that diffusion along with erosion could be the mechanism of drug release.Considering the micromeritic behaviour of the powder blend, physical attributes of the compressed tablets, and dissolution, formulation F-4 seemed most suitable.
Conclusion: Extended release Metformin Hydrochloride tablets can be produced to overcome frequent dosing related problems. However, Further study on formulation optimization and scale up, stability and bioequivalence is needed to confirm the appropriateness of these formulated extended release tablets.

Keywords: Extended release, matrix tablet, release retardant polymer, powder blend & Metformin Hydrochloride.

1. INTRODUCTION

Diabetes mellitus is a worldwide public health challenge due to its high morbidity & mortality rate. As of 2010, Metformin Hydrochloride is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines [1]. Metformin HCl, the only available biguanide, is the first-line drug of choice for the treatment of type 2 diabetes especially in overweight and obese patients. It mainly acts by decreasing hepatic glucose production through inhibiting gluconeogenesis and glycogenolysis and in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization. The maximum recommended daily dose of Metformin Hydrochloride immediate release tablet is 2550 mg in adults and 2000 mg in pediatric patients (10-16 years of age); the maximum recommended daily dose of Metformin Hydrochloride extended release tablet in adults is 2000 mg. It is a highly water soluble drug (BCS class-III), having the absolute bioavailability of 50-60% and relatively

short biological half-life of 1.5 – 4.5 h [2,3]. Because of its shorter biological half-life it should be repeatedly administered to maintain plasma drug concentration within therapeutic window [4]. The extended release tablets of Metformin Hydrochloride are needed to avoid repeated administration of immediate release products, to prolong its duration of action and to improve patient compliance [3].

Matrix devices (monolithic devices) are possibly the most common of the devices for controlling the release of drugs. They are relatively easy to fabricate, compared to reservoir devices, and there is no danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. Incorporation of drug in the matrix of hydrophilic and hydrophobic polymers have been successfully employed in the development of sustained release delivery systems to provide the desired release profile [5].

Hydroxypropyl methylcellulose (HPMC) is a semi synthetic derivative of cellulose, a hydrophilic polymer which is very suitable to use as a release retardant in sustained release matrix tablets due to its rapid hydration, excellent compressibility and gelling characteristics, ease of use & availability and less toxicity. It controls the release of drug by controlling swelling & cross linking [6]. Xanthan gum is also used as a release retardant sustained release carrier and considered as a nontoxic and non-irritant material [7]. In this study Methocel K100 MCR Premium (derivative of HPMC & trademark of The Dow Chemical Company) & Xanthan gum were used in different (w/w) combinations, to prepare extended release tablet.

Oral extended release dosage forms by direct compression method is a simple approach of drug delivery that proved to be rational in the pharmaceutical arena for its ease of manufacturing, quality control, faster production, less stability problem during processing of dosage forms [8]. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. Because, it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

Due to its poor compressibility the manufacturing of Metformin Hydrochloride tablets by direct compression is a big challenge for manufacturer. Therefore, the main objective of the present work was to prepare extended release matrix tablets of Metformin Hydrochloride by direct compression method to assure prolonged acting and well reproducible drug release profiles. In order to elucidate release kinetics it is essential to fit drug release data into a suitable kinetic model. The commonly adopted models for understanding the release of drugs from matrices are zero-order equation, first-order equation, Higuchi equation [9], Korsmeyer-Peppas equation [10] & Hixson- Crowell Model [11].

2. MATERIALS AND METHODS

2.1 Materials

Metformin Hydrochloride was obtained as a gift sample from Active Fine Chemicals Ltd, Bangladesh. Methocel K100 MCR premium, Xanthan gum, Microcrystalline Cellulose, Colloidal Silicon Dioxide and Magnesium Stearate were obtained as a gift sample from ACI Ltd. All other ingredients used throughout the study were of analytical grades and were used as received.

2.2 Drug-excipients Compatibility Study

FT-IR spectrophotometer (IR-Prestige 21, Shimadzu, Japan) was used to obtain the spectra of the pure Metformin Hydrochloride and the formulation F-9 (maximum release retardant polymer concentration) by KBr disc method. The spectra were obtained for pure Metformin Hydrochloride and the formulation F-9 which were compared to check compatibility of drug with polymers. Polystyrene disc was used as scanning reference before measurement of samples by FT-IR spectrophotometer in the range of wave number 4000 and 400 cm^{-1}. The samples were prepared in a smooth agate mortar and compressed into a disc of 13 mm diameter using hydraulic press.

DSC measurements were carried out on a differential scanning calorimeter (DSC60, Shimadzu, Japan) in order to evaluate the drug-excipient compatibility and to verify the absence of solid-state interactions. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10℃/min over a temperature range of 30–300℃.

2.3 Preparation of Metformin Hydrochloride Matrix Tablets

The active pharmaceutical ingredients and all other excipients were accurately weighed & passed through 60 mesh sieve for 100 gram batch size according to the formulations (Table 1). Metformin Hydrochloride, Methocel K100 MCR premium, Xanthan gum & Microcrystalline cellulose were added into poly bag and mixed for 30 minutes. Magnesium stearate and Colloidal silicon dioxide were finally added for lubrication & mixed for 10 minutes. Finally powder blend compressed into tablets using single punch tablet compression machine. Before compression of each batch, the surfaces of the die and punch were lubricated using Magnesium stearate as lubricant. All the batches were stored in airtight containers with proper label at room temperature for further study.

Table 1. Composition of different formulations of Metformin Hydrochloride matrix tablet (in mg)

Ingredients	Formulation/batch code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500
Methocel K100 MCR premium	80	100	120	140	160	180	200	220	240
Xanthan gum	125	125	125	155	155	155	185	185	185
Ratio (Drug:Polymer)	1:0.41	1:0.45	1:0.49	1:0.59	1:0.63	1:0.67	1:0.77	1:0.81	1:0.85
Microcrystalline cellulose	285	265	245	195	175	155	105	105	65
Colloidal silicon dioxide	7	7	7	7	7	7	7	7	7
Magnesium stearate	3	3	3	3	3	3	3	3	3
Total weight (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000

2.4 Evalution of Powder Blends

The powder blends of different formulations (F-1 to F-9) were evaluated for Bulk density (Untapped & Tapped), Compressibility index, Hausner ratio, Angle of repose & Loss on drying.

2.5 Evalution of Matrix Tablets

The prepared matrix tablets were characterized immediately after preparation for hardness, weight variation, thickness, friability and drug content. The weight variation of the tablets was evaluated (n=10) using an electronic balance (Shimadzu ATY 224, Japan). The hardness of the tablets (n=6) was tested using a Veego hardness tester (Veego, India). Friability (n=10) was determined in a Veego friabilator (Veego, India) for 4 minutes at a speed of 25 rpm. The thickness of the tablets (n=10) was measured by slide calipers. Drug content was analyzed by measuring the absorbance of standard and samples at λ_{max} = 232 nm using UV-Vis spectrophotometer (Shimadzu UV 1700, Japan).

2.6 *In-vitro* Drug Release Studies

Drug release studies were conducted using USP Apparatus Type II (Paddle) method (Shimadzu UV 1700, Japan) at a rotational speed of 100 rpm at 37±0.5℃. The dissolution media used were 1000 mL of pH 6.8 phosphate buffer solution. It was run for 10 hours. Samples (10 mL) were withdrawn at regular intervals (each hour) and the same volume of preheated (37±0.5℃) fresh buffer medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a Double Ring filter paper and the drug content in each sample was analyzed after suitable dilution (1mL into 50 mL) with a UV-Vis spectrophotometer (Shimadzu UV 1700, Japan) at λmax = 232 nm by using phosphate buffer solution as blank. The absorbance of each sample was taken three times. The percent release of Metformin Hydrochloride in dissolution medium after every hour was calculated, using the following equation. Drug dissolved at specified time periods was plotted as cumulative percent release versus time curve.

$$\% \text{ release of Metformin Hydrochloride} = \frac{\text{Absorbance of sample} \times \text{Weight of Standard (mg)} \times Y}{\text{Absorbance of Standard} \times 20}$$

Here, Y = Potency of working Standard.

2.7 Release Kinetics

The *in vitro* release data obtained from various formulations of Metformin Hydrochloride extended release tablet were fitted to various kinetic models such as Zero order, First Order, Higuchi model, Korsmeyer-Peppas model & Hixson- Crowell Model. In case of zero order ($Q_t = Q_0 + K_0t$) the graph was plotted as cumulative percent drug release vs time, and in first order release kinetics ($\ln Q = \ln Q_0 - K_1t$) the graph was plotted in log cumulative percent of drug remaining vs time. For Higuchi model Kinetics ($Q_t = K_2 t^{½}$) the graph was plotted in cumulative percent of drug released vs square root of time and for Korsmeyer-Peppas Model ($Q/Q_0 = Kt^n$) the graph was plotted in log cumulative percent of drug release vs log time. For Hixson- Crowell Model ($Q_t^{1/3} = Q_0^{1/3} - kt$) the graph was plotted Cubic root cumulative percent of drug remaining vs time.

3. RESULTS AND DISCUSSION

3.1 Drug-excipient Compatibility Study

FT-IR studies revealed that Metformin Hydrochloride showed two typical bands at 3369 and 3296 cm^{-1} due to N-H primary stretching vibration and a band at 3170 cm^{-1} due to N-H secondary stretching and characteristics bands at 1626 and 1567 cm^{-1} assigned to C=N stretching. No significant shifts of reduction in intensity of the FT-IR bands of pure Metformin Hydrochloride & the formulation F-9 were observed as shown in (Figs. 1 and 2.) respectively. It indicated instead of excipient-drug were compatibility.

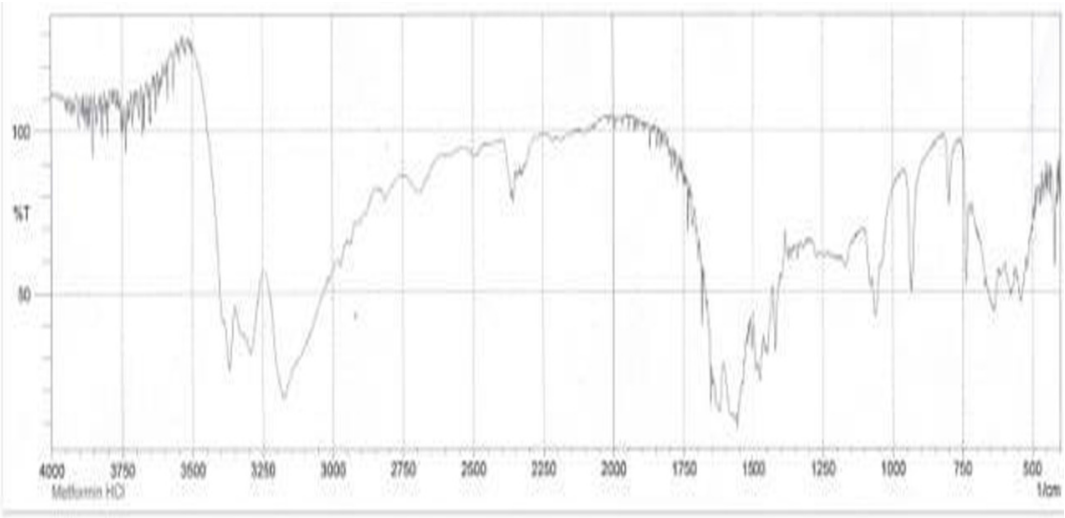

Fig. 1. FT-IR spectra of pure Metformin Hydrochloride

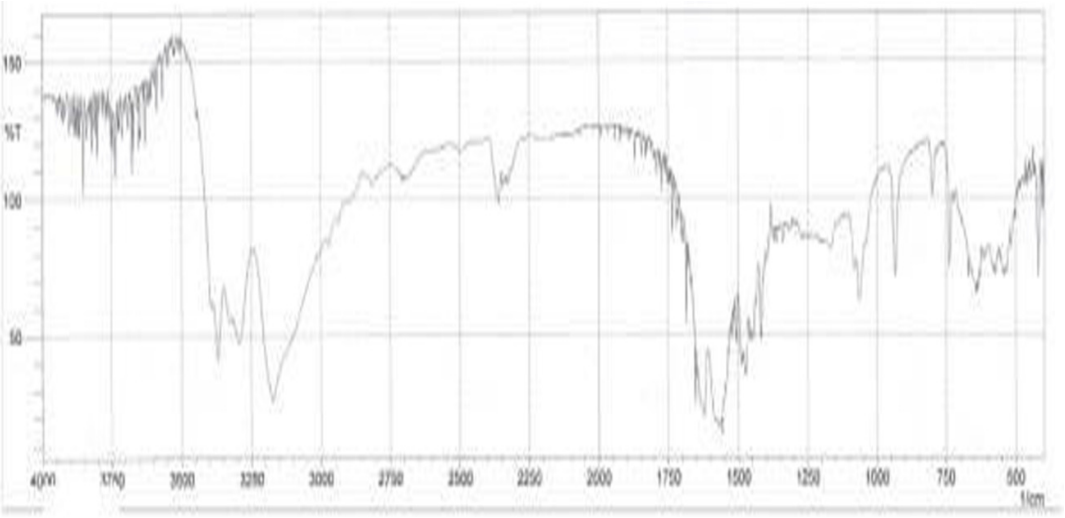

Fig. 2. FTIR spectra of formulation F-9

DSC analysis was performed in order to evaluate possible solid state interaction between the components to assess the actual drug-excipient compatibility. The thermal curves of pure Metformin Hydrochloride and formulation F-9 were performed which are shown in (Figs. 3 and 4). The DSC thermogram of pure Metformin Hydrochloride exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237℃. DSC curves of formulation F-9 exhibited a flat thermal profile. The thermal curves of formulation F-9 (Fig. 4), obtained by simple blending corresponded to the superimposition of the single component (Fig. 3), indicating the absence of solid-state interactions and allowing assessment of drug–excipient compatibility in the examined formulation.

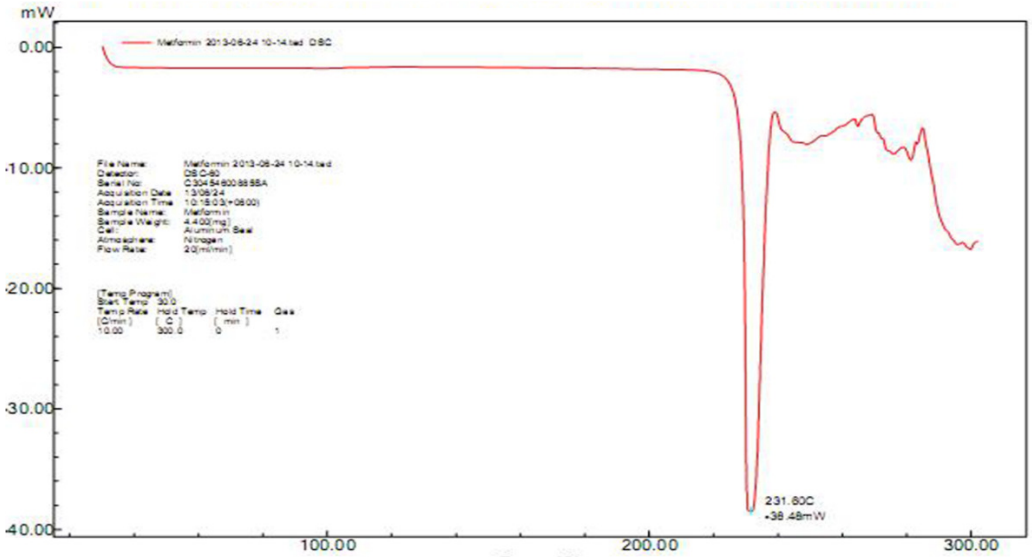

Fig. 3. DSC Thermogram of pure Metformin Hydrochloride

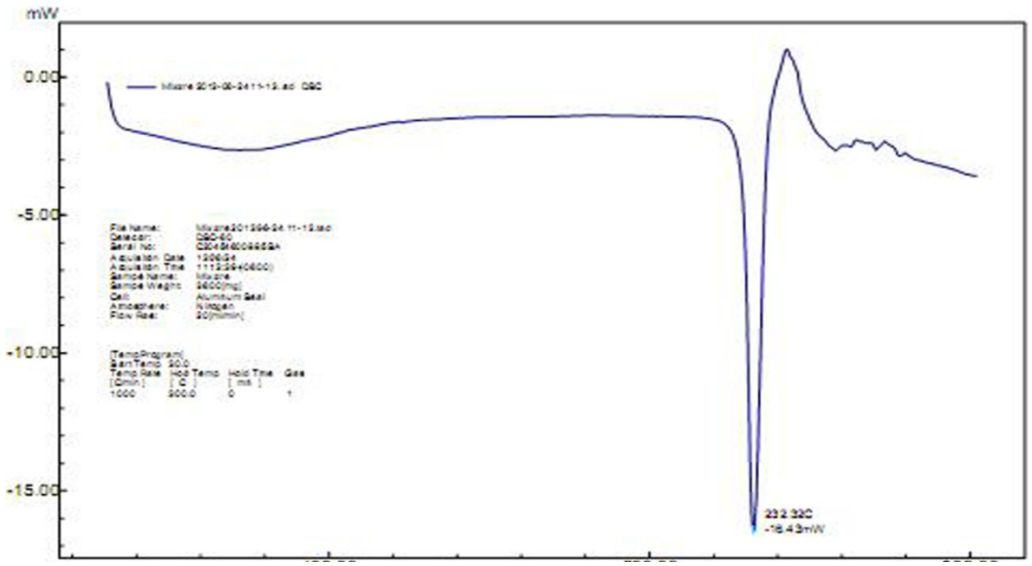

Fig. 4. DSC Thermogramof formulation F-9

3.2 Evalution of Powder Blend

The results are shown in (Table 2). The bulk density, untapped and tapped, of all the batches, varied from 0.53 to 0.59 gm/cm^3 and 0.63 to 0.69 gm/cm^3 respectively. Maximum bulk density (tapped) was found in formulation F-9 (0.70 gm/cm^3) which may be due to highest concentration of dissolution retarding polymer. The results of Carr's index or compressibility index of all the batches ranged from 14.49% to 20.5% which reveals that flow property of all the batches is good to fair; F-4 is excellent [12]. Hausner ratio of the formulations ranged from 1.169 to 1.259, which is indicative of good flow property, F-4 has the best value of all [13]. The values of angle of repose were found to be in the range of 25.78° to 29.25° which revealed excellent inherent flow property of the powder blend [13]. Lowest angle of repose was found in formulation F-5 (25.78°) and highest angle of repose found in formulation F-1 (29.25°). Loss on Drying of all the batches ranged from 2.96% to 3.49%. The residual moisture content found to be appropriate for good tableting properties and for good stability of compressed tablets.

Table 2. Physical properties of Metformin Hydrochloride powder blend (F-1 to F-9)

Formulation	Bulk density		Compressibility (%)	Hausner ratio	Angle of repose (º)	Loss on drying (%)
	Untapped	Tapped				
F-1	0.54	0.66	18.18	1.222	29.25	3.24
F-2	0.54	0.65	16.9	1.203	26.17	3.13
F-3	0.56	0.69	18.8	1.232	27.02	3.49
F-4	0.59	0.69	14.49	1.169	26.58	3.04
F-5	0.58	0.69	15.9	1.189	25.78	3.41
F-6	0.55	0.67	17.9	1.218	27.59	2.96
F-7	0.57	0.68	16.1	1.192	27.98	3.09
F-8	0.53	0.63	15.8	1.188	26.50	2.97
F-9	0.55	0.70	20.5	1.259	27.32	2.98

3.3 Evaluation of Matrix Tablets

The tablets were evaluated for diameter, thickness, weight variation, hardness, friability & drug content and the results are shown in (Table 3).

3.3.1 Uniformity of weight (Weight variation test)

All the tablets passed the uniformity of weight test, i.e., percentage weight variation was found within the official test limits of ±5%. (Table 3)

3.3.2 Hardness

Hardness or crushing strength of the tablets of all the batches was found to be ranging from 7.9 to 11.8 kg/cm^2 (Table 3). The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness. Maximum and minimum hardness were found 11.8 kg/cm^2 and 7.9 kg/cm^2 in formulation F-1 and F-9 respectively which reveals that hardness is directly proportional to the content of microcrystalline cellulose in the formulation.

Table 3. Physical properties of Metformin Hydrochloride extended release matrix tablet (F-1 to F-9)

Formulation code	Thickness (mm) ± SD (n=10)	Hardness (kg/cm^2) ± SD (n=6)	Friability (%) (n=10)	Weight variation (mg) ± SD (n=10)	Assay of Metformin Hydrochloride (%)
F-1	6.21±0.04	11.8±0.25	0.68	1001±5.02	98.51
F-2	6.25±0.03	11.4±0.36	0.69	1001±5.02	97.96
F-3	6.24±0.06	10.5±0.58	0.69	1001±5.02	98.79
F-4	6.25±0.04	9.2±0.36	0.70	1001±5.02	97.10
F-5	6.27±0.03	8.5±0.78	0.79	1001±4.10	97.90
F-6	6.27±0.04	8.2±0.56	0.80	1000±3.50	98.14
F-7	6.26±0.05	8.1±0.74	0.82	1002±4.05	98.89
F-8	6.25±0.06	8.1±0.59	0.83	1001±4.01	98.70
F-9	6.26±0.04	7.9±0.46	0.85	1002±3.05	98.37

3.3.3 Friability

Friability values of all the batches were in the range of 0.68% to 0.85% (Table 3). The obtained results were found to be well within the approved range (<1%) in all the designed formulations. That indicated tablets possess good mechanical strength. Maximum (0.85%) and minimum (0.68%) friability were found in formulation F-9 & F-1 respectively which represented that the tablet hardness has good role in friability.

3.3.4 Drug content

The assay of Metformin Hydrochloride matrix tablet was carried out by UV-Vis spectroscopy method. Metformin Hydrochloride content of all the batches was found to be between 97.10% to 98.89% (Table 3) indicating high degree of drug uniformity.

3.4 *In vitro* Drug Release Study

The *in vitro* dissolution studies were carried out for the prepared tablets using USP apparatus type II (paddle) method. Impact of polymers on drug release from different combinations of hydrophilic matrices was characterized by variation of drug release. The release profile of formulation (F-1 to F-9) of Metformin Hydrochloride extended release tablets are shown in (Figs. 5 and 6), which also represents zero order kinetic graph. At higher polymer concentration, gel matrix viscosity is increased that results a decrease in the effective diffusion coefficient of the drug [14] consequently drug diffusion and erosion. The release rate decreased as the concentration of Methocel K100 MCR Premium and Xanthan gum increased. It indicates that drug-polymer ratio is crucial factor affecting the rate of drug release from polymeric matrices. Initially 20.5% w/w combined polymer concentration was selected to keep the amount of the polymer matrix to a minimum. Formulation F-1, F-2, F-3, F-4 and F-5 containing drug polymer ratio of 1:0.41, 1:0.45, 1:0.49, 1:0.59, 1:0.63 showed drug release 41.71%, 41.3%, 38.61%, 35.93%, 34.57% respectively after 1st hour, meeting the desired specification [15]. And, 98.37%, 97.19%, 95.53%, 91.54% & 88.94% respectively after 10 hours, meeting desired rate [16] (Fig. 5). Among these five batches the drug release rate was slightly retarded as polymer concentration increased gradually.

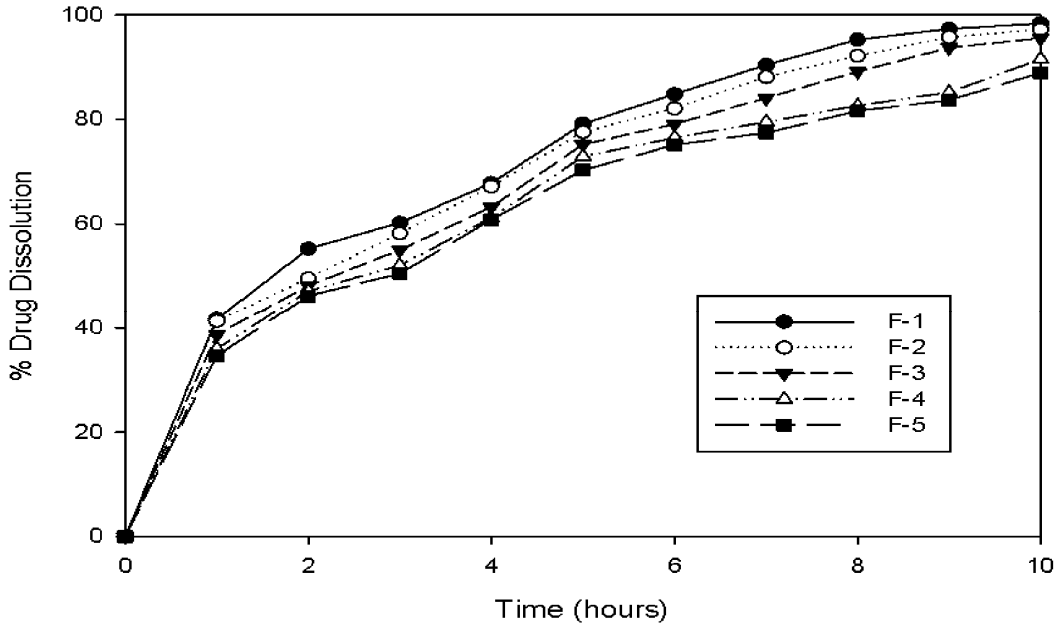

Fig. 5. *In vitro* cumulative release of Metformin Hydrochloride from batches F-1 to F-5

Formulation F-6, F-7, F-8 and F-9 containing drug polymer ratio of 1:0.67, 1:0.77, 1:0.81, 1:0.85 showed drug release 33.65%, 30.89%, 28.69%, 27.89% respectively after 1st hour and 6.91%, 83.98%, 80.92% & 79.85% respectively after 10 hours which is shown in (Fig. 6).

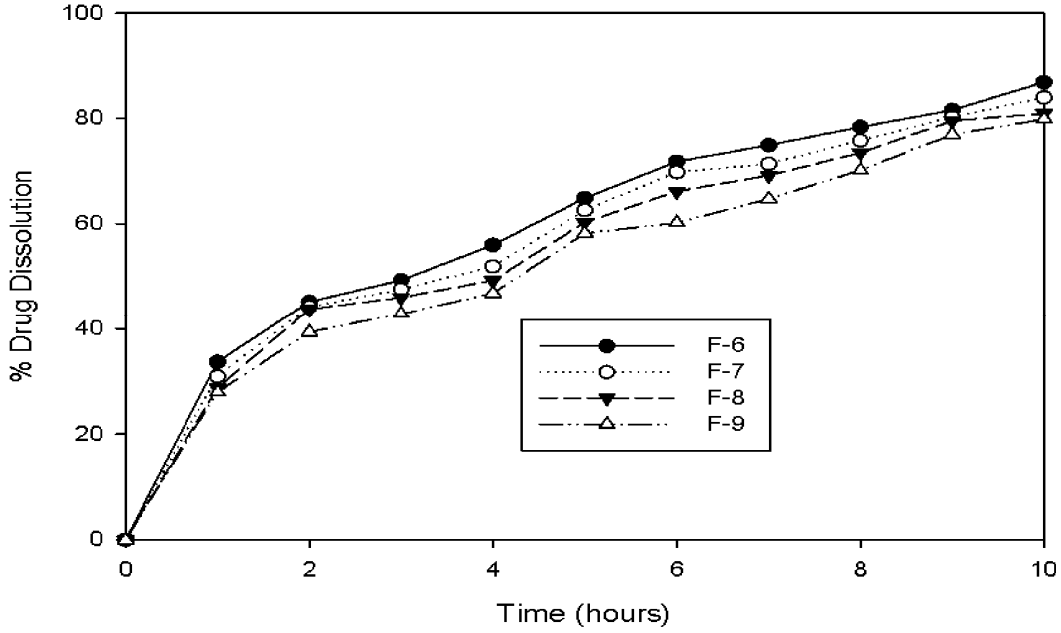

Fig. 6. *In vitro* cumulative release of Metformin Hydrochloride from batches F-6 to F-9

It is quite evident from above discussion that the release rate gradually decreased with gradual increase of the concentration of Methocel K100 MCR Premium and Xanthan gum. Among all the formulations F-7, F-8 & F-9 do not comply with drug release specification of USP and among the rest six formulations F-3, F-4 & F-5 comply better with drug release specification of USP. Considering the micromeritic behavior of the powder blend and the physico-chemical attributes of the compressed tablets, formulation F-4 is most suitable.

3.5 Interpretation of r^2 Values for Different Release Kinetics

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations, shown in (Table 4).

The dissolution curves of the First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell release model of metformin HCl are shown in (Figs. 7, 8, 9 and 10), respectively.

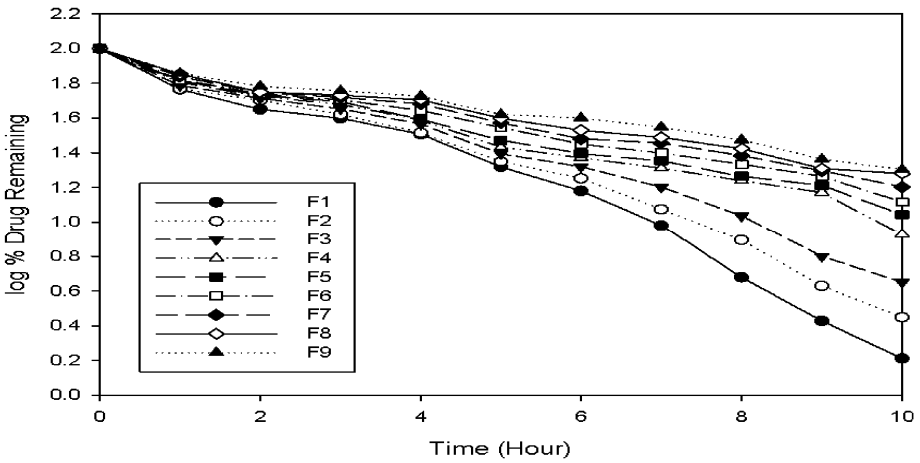

Fig. 7. First order release model of Metformin Hydrochloride extended release formulation

Table 4. r^2 values for different release kinetics of formulations of Metformin Hydrochloride extended release matrix tablets

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell	Best fitted
	r^2	r^2	r^2	r^2	r^2	
F-1	0.846	0.964	0.846	0.901	0.986	Hixson-Crowell
F-2	0.86	0.974	0.86	0.914	0.988	Hixson-Crowell
F-3	0.876	0.976	0.876	0.922	0.985	Hixson-Crowell
F-4	0.859	0.977	0.859	0.895	0.964	First order
F-5	0.86	0.984	0.86	0.891	0.964	First order
F-6	0.875	0.984	0.875	0.920	0.968	First order
F-7	0.883	0.983	0.883	0.910	0.966	First order
F-8	0.888	0.980	0.888	0.900	0.964	First order
F-9	0.909	0.978	0.909	0.935	0.97	First order

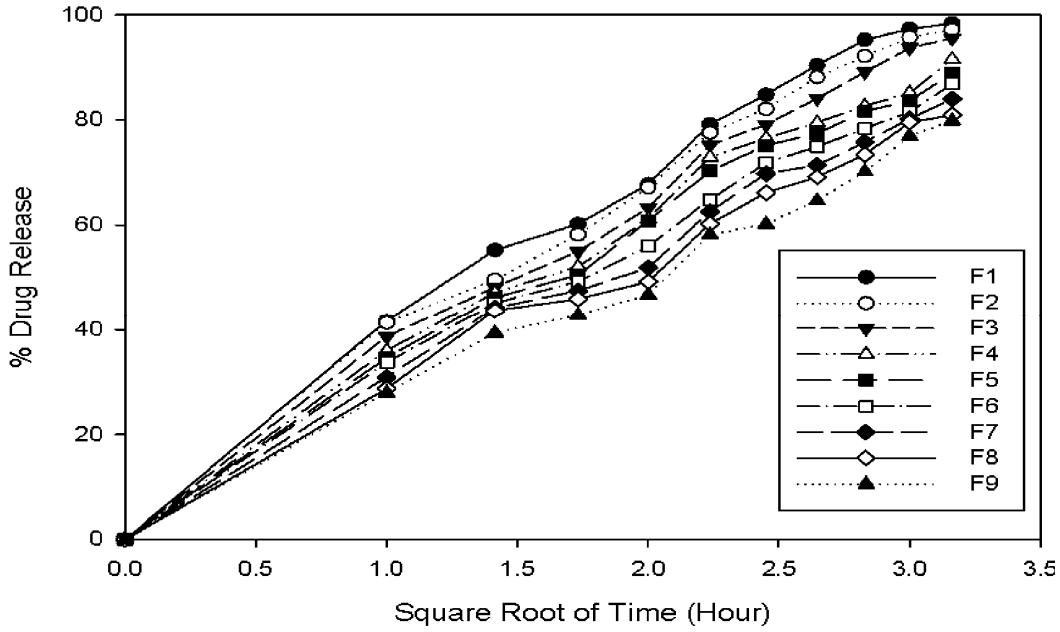

Fig. 8. Higuchi release model of Metformin Hydrochloride extended release formulation

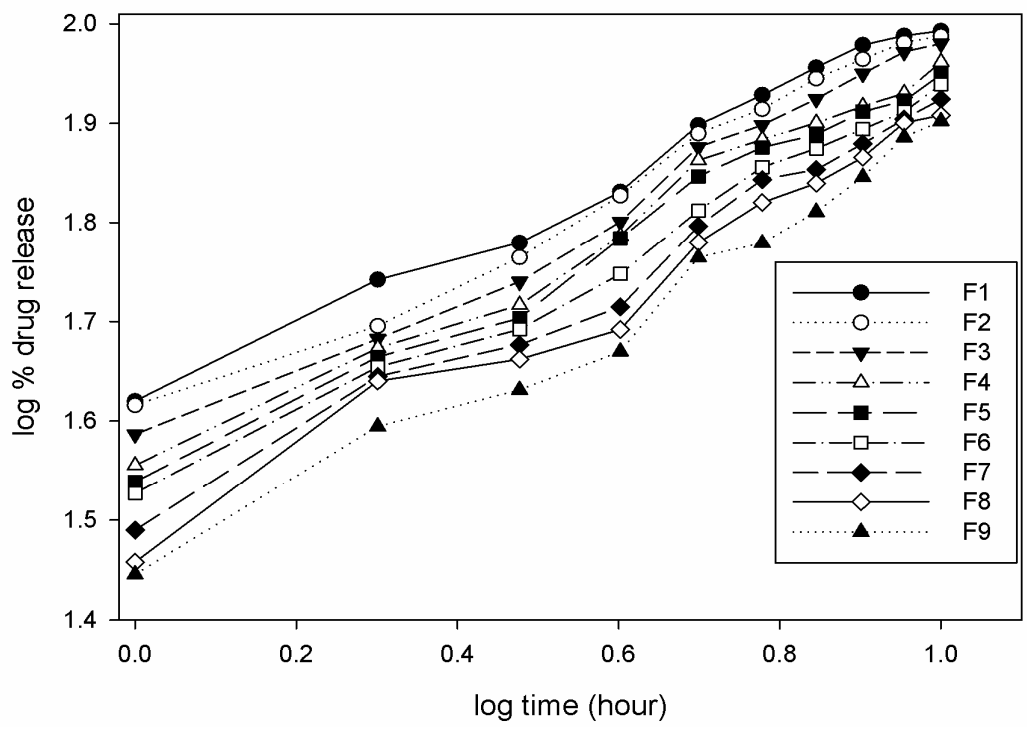

Fig. 9. Korsmeyer-Peppas release model of Metformin Hydrochloride extended release formulation

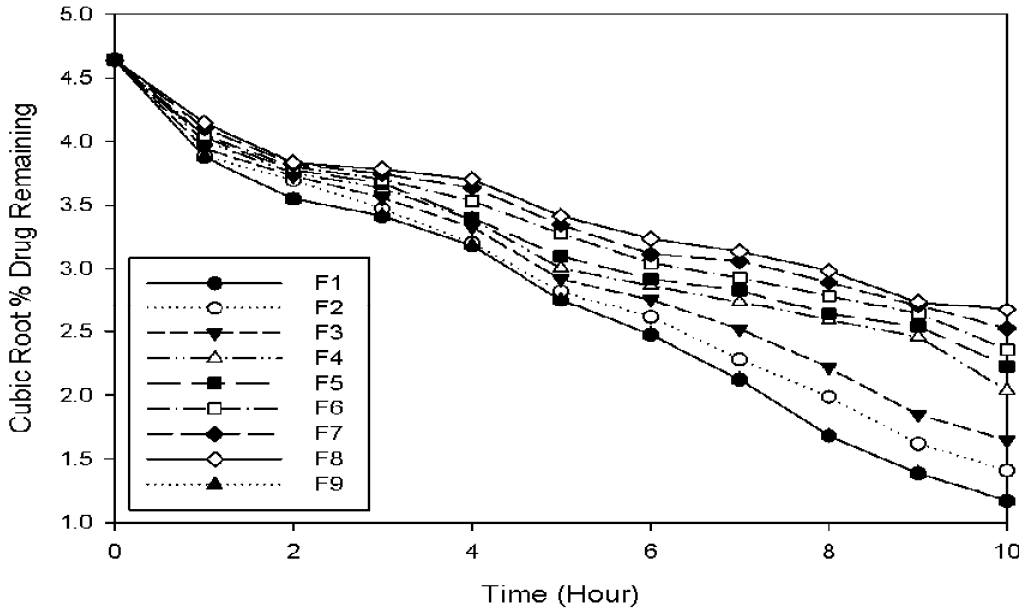

Fig. 10. Hixson-Crowell release model of metformin HCl extended release formulation

Considering the overall data of release kinetics, it can be stated that the formulations follows Hixson-Crowell release kinetics, showing high linearity in this model (r^2= 0.964 – 0.988). From this, we can infer that in the formulations, as dissolution progresses, the surface area and diameter of the drug matrix change with time [17].

4. CONCLUSION

Metformin Hydrocholoride is a poorly compressible active pharmaceutical ingredient that presents huge challenge to manufacture tablets by direct compression method. In the present study sustained released matrix tablets of Metformin Hydrochloride were successfully prepared using hydrophilic polymers, Methocel K100 MCR Premium and Xanthan gum, as the release retarding materials, by direct compression method. Higher amount of polymer decreased the drug release. Among the prepared formulations, F-4 was deemed as most suitable. An extended release formulation of Metformin Hydrocholoride not only will increase the efficacy of the treatment of diabetes patients, but will also improve patient convenience by lowering the dosage frequency to once a day. Further study on formulation optimization & scale up, stability study and bioequivalence study is needed to confirm the appropriateness of these formulated extended release tablets.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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