

Research Article

Formulation of Extended-Release Metformin Hydrochloride Matrix Tablets

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Abstract

Purpose: To develop and characterize an oral extended-release matrix tablet of metformin hydrochloride using a combination of a hydrophobic carrier and a hydrophilic polymer, and two types of formulation techniques.

Methods: Various metformin hydrochloride formulations containing a hydrophobic carrier (stearic acid) and a hydrophilic polymer (polyethylene oxide) were prepared using a 3² factorial design. Two types of formulation techniques – melt granulation and direct compression – were evaluated. The influence of the carrier, polymer and preparation method on metformin release from the formulations *in vitro* as well as other physicochemical properties were studied. The release data were subjected to various release kinetic models and also compared with those of a commercial brand.

Results: The physicochemical characteristics of all the granules and tablets were generally satisfactory. Optimization results indicate that the release rate of metformin HCl was directly proportional to the levels of stearic acid (SA) and polyethylene oxide (PEO) in the tablet formulations. Release rate was also dependent on the method of granulation used. Kinetic analysis showed that the formulation containing 30 %w/w of polymer exhibited release similar to that of the commercial brand with a similarity factor (*f*₂) of 81.1. Melt granulation was more effective in extending drug release than direct compression. Release mechanism followed most closely the Korsmeyer-Peppas model with a correlation coefficient (*r*²) and 0.991.

Conclusion: The use of a hydrophobic carrier along with a hydrophilic polymer effectively controls the initial rapid release of a highly water soluble drug such as metformin HCl. Hot melt granulation method was especially more effective in achieving this than the direct compression method.

Keywords: Metformin hydrochloride, Matrix tablets, Polyethylene oxide, Stearic acid, Hot melt granulation, *In vitro* release.

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INTRODUCTION

The major therapeutic goals in subjects with type 2 diabetes are to optimize blood glucose control, reduce overweight, and normalize lipid disturbances and elevated blood pressure. It has been shown that intensive management of type 2 diabetes reduces the risk for chronic complications. However, pharmacological treatment with oral hypoglycemic agents (OHAs) or insulin is often required [1].

Biguanides, in particular, metformin HCl, increase sensitivity to insulin in peripheral tissues of the hosts. It is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis and inhibition of fatty acid oxidation [2]. It has an absolute oral bioavailability of 40 to 60 % and gastrointestinal absorption is apparently complete within 6 h of ingestion. An inverse relationship is observed between the dose ingested and relative absorption with therapeutic doses (0.5 to 1.5 g), suggesting the involvement of active, saturable absorption process [3].

Plasma half-life of metformin HCl is 1.5 - 4.9 h [4]. Suitable dosage regimens of the drug include unit doses of 500 mg two to three times daily and can even be built up to five times daily or 850 mg once or twice daily. Such multiple dosing regimens are not preferred since they lead to patient non-compliance, potential side effects and danger of overdosing. There is, therefore, the need to provide formulations and processes that would deliver extended release of metformin HCl from the dosage form when consumed.

Furthermore, metformin HCl presents formulation challenges due to its inherently poor compressibility, high dose and high water solubility (> 300 mg/ml at 25 °C). It belongs to class III of Biopharmaceutical Classification System (BCS) having high water solubility and low permeability [5]. For drugs that are highly water soluble, both

hydrophilic and hydrophobic matrix systems are widely used in oral controlled release drug delivery to obtain a desirable drug release.

A direct compression method was reported for the preparation of metformin HCl 500 mg extended-release tablet [6] but on a commercial scale, this may create problems of powder flow down the hopper which would lead to weight variation, as well as poor content uniformity, hardness and friability due to its poor compressibility of metformin HCl. Sustained release microcapsulated preparation of metformin HCl using ethyl cellulose has been reported to give *in vitro* release up to 22 h; however, preparation of microcapsules on commercial scale as well as optimization are time-consuming and challenging [7]. Several matrix formulations of metformin HCl have been reported based on the use of a hydrophilic (hydroxypropyl methylcellulose or carbopol) and/or hydrophobic polymers (e.g., ethylcellulose) but no effort has been made to compare the effectiveness of the production methods.

Waxes have been extensively investigated for sustaining the release of drugs. In formulating wax matrix systems, different processing methods, such as dry blending, wet granulation, melt granulation and extrusion spherulization, have been used [8-9]. Melt granulation method can be used for granulating water sensitive material and producing sustained release granulations. This technique fulfills today's pharmaceutical industry need because of its simplicity, continuous and efficient process as well as many advantages over conventional methods of granulations such as wet and dry granulation [10,11].

The aim of this work was to prepare matrix tablet containing metformin HCl, as a model water-soluble drug, using a combination of hydrophilic and hydrophobic polymers and evaluate its release characteristics. A secondary objective was to assess the effect

of granulation method on the release of the drug from matrix tablets.

EXPERIMENTAL

Metformin HCl powder was a gift from USV Ltd, Mumbai, India while polyethylene oxide (Polyox) was obtained from Colorcon India. Microcrystalline cellulose and magnesium stearate were purchased from Signet Chemicals, India. Other materials used were of analytical grade. Glycomet SR 500 mg tablets (USV Ltd, Mumbai, India), used as the reference metformin sustained release tablets, were purchased from a local pharmacy.

Full factorial design

Two factors were evaluated, each at three levels, and experimental trials were performed at all possible concentrations. The contents of polyethylene oxide (PEO) and stearic acid (SA) were selected as independent variables. The diffusion exponent (n) and percent drug release at 1 (Q_1), 2 (Q_2), 4 (Q_4), 8 (Q_8), 10 (Q_{10}) and 12 h (Q_{12}) were selected as dependent variables. The experimental design used is outlined in Table 1.

Table 1: Formulation of Metformin HCl matrix tablet as per 3^2 factorial design [12-13]

Factorial design 3^2		PEO		
		ρ_1	ρ_2	ρ_3
SA	α_1	M1	M2	M3
	α_2	M4	M5	M6
	α_3	M7	M8	M9

Polyethylene oxide (PEO) concentration: $\rho_1 = 10\%$; $\rho_2 = 20\%$; $\rho_3 = 30\%$; stearic acid (SA) concentration: $\alpha_1 = 4\%$; $\alpha_2 = 8\%$; $\alpha_3 = 12\%$; each formulation contained: metformin HCl – 500 mg, colloidal silicon dioxide – 0.55 %, magnesium stearate – 0.55 %; microcrystalline cellulose - quantity sufficient to 900 mg

Preparation of matrix tablets by melt granulation

Hot melt granulation technique was used to prepare the drug-wax matrix formulations. First stearic acid was melted in a stainless steel vessel at 75°C . Metformin HCl was sieved through a $850\ \mu$ aperture screen, and heated, spread on a metal tray in an oven at 75°C . Melt granulation was carried out by transferring the molten metformin HCl to a high shear mixer-granulator (model-Mini RMG, Kevin, India) and then slowly adding the molten stearic acid. Granulation speed was 100 rpm for the impeller and 1500 rpm for the chopper while granulation time was 5 min. The granules were allowed to cool to room temperature by spreading them on metal trays and then sieved through a $850\ \mu$ aperture screen.

The melt granules were mixed with PEO (pre-sieved through a $850\ \mu$ screen) and microcrystalline cellulose (pre-sieved through a $600\ \mu$ screen), mixed with colloidal silicon dioxide (pre-sieved through a $425\ \mu$ screen) and magnesium stearate (pre-sieved through $425\ \mu$ screen). The blend was compressed into 19×9.7 mm oblong tablets in an 8-station Cadmach compression machine.

Preparation of matrix tablets by direct compression

Batch M6 was selected for this purpose. The drug and microcrystalline cellulose were sieved through a $850\ \mu$ screen and manually blended for 5 min. Colloidal silicon dioxide (pre-sieved through a $425\ \mu$ screen) was added next and blended for 3 min. Finally magnesium stearate (pre-sieved through a $425\ \mu$ screen) was added and mixed for additional 2 min. The final blend was compressed into 19×9.7 mm oblong tablets in an 8-station Cadmach compression machine.

Physicochemical characterization of granules

The granules were evaluated for various physicochemical parameters including angle of repose, bulk density, tap density, compressibility index and Hausner ratio.

Angle of repose

The fixed-funnel method was used to determine angle of repose. The granule formulation was carefully poured through a funnel until the apex of the conical pile just touched the tip of funnel. The height (h) of the pile of the powder and the radius (r) of its conical base were measured and applied to compute the angle of repose (θ) as in Eq 1 [14].

$$\theta = \tan^{-1} h/r \dots\dots\dots (1)$$

Bulk and tap densities

A 30 g quantity of the granule samples was placed in a 100 ml dry measuring cylinder and volume, V_0 , occupied by it, without tapping, was determined. The cylinder was then given 500 taps using a tap density apparatus (model ETD-1020, Electrolab, India,) and the resulting volume, V_{500} , was noted determined [15-16]. The bulk and tap densities were calculated using Eqs 2 and 3, respectively.

$$\text{Bulk density} = W/V_0 \dots\dots\dots (2)$$

$$\text{Tapped density} = W/V_{500} \dots\dots\dots (3)$$

where W is the weight of the granules.

Compressibility index

This parameter was calculated fitting bulk and tap density data (TD and BD, respectively) into Eq 4 [15-16].

$$\text{Compressibility (C\%)} = 100 (TD - BD)/TD \dots (4)$$

Hausner ratio

This parameter was calculated as the ratio of tap density to bulk density of the granules [15-16].

Physicochemical characterization of tablets

The tablets were evaluated for assay, hardness and friability.

Determination of drug content

Randomly selected tablets (20) from each batch were weighed and powdered. A quantity of the powder, equivalent to 100 mg of metformin HCl, was transferred to a 100 ml volumetric flask and extracted with water. A quantity (1 ml) of filtered solution was diluted to 100 ml with water and the absorbance measured at 233 nm (model UV1201, Shimadzu). Each measurement was carried out in triplicate and the mean taken. Drug concentration was calculated from the calibration curve of a standard (concentration range: 0 to 10 $\mu\text{g/ml}$).

Determination of tablet hardness

The hardness of each of 10 tablets randomly selected from each batch was measured with a tablet hardness tester, and the mean and standard deviation evaluation.

Determination of tablet friability

Tablet friability was assessed using a friabilator (model EF-2, Electrolab, India) at 25 rpm for 4 min. The weight of ten tablets before and after the test, and the percent loss in weight recorded as friability.

Evaluation of *in-vitro* drug release

In-vitro drug release assessment was performed using USP type I (basket) apparatus in 900 ml of 0.1M HCl at $37 \pm 5^\circ\text{C}$ for the first hour and then with phosphate buffer pH 6.8 for a further 11 h, with the apparatus rotating at 100 rpm throughout the test. Samples were withdrawn at predetermined time intervals and replaced with an equivalent volume of fresh dissolution medium. The withdrawn samples were filtered through a 0.45 μm membrane filter,

suitably diluted and analyzed at 233 nm for metformin HCl by UV-spectrophotometer (Shimadzu UV1201). The content of drug and the cumulative percent drug release were derived from a standard metformin HCL calibration curve.

Kinetic analysis of drug release data

To analyze the *in vitro* release data, various kinetic models, including zero order (Eq 5) [17], first order (Eq 6) [18], Higuchi (Eq 7) [19], and Hixson-Crowell cube root law (Eq 8) [20].

$$C = k_0t \dots \dots \dots (5)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log } C = \text{Log } C_0 - k_0t/2.303 \dots \dots \dots (6)$$

where, C_0 is the initial concentration of the drug and K is first order rate constant.

$$Q = Kt^{1/2} \dots \dots \dots (7)$$

where, K is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \dots \dots \dots (8)$$

where, Q_t is the amount of drug released in time t , Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

Mechanism of drug release

A simple relationship, Korsmeyer–Peppas model [21], was applied to determine the mechanism of drug release as in Eq 9.

$$M_t/M_\infty = Kt^n \dots \dots \dots (9)$$

where M_t/M_∞ is the fraction of drug released at time t , K is the rate constant and n is the release exponent. The n value was used to characterize different release mechanisms for cylindrical shaped matrices.

Assessment of similarity factor

Similarity factor (f_2), computed as in Eq 10, was used to compare differences in drug release profile. Similarity factor (f_2) values

between 50 and 100 indicate equivalence of two sets of release data [22-23].

$$f_2 = 50 \log \{ (1 + 1/n \sum_{t=1}^n (R_t - T_t)^2)^{-0.5} \times 100 \} \dots \dots \dots (10)$$

where R_t and T_t represent the dissolution values of the reference and test products, respectively.

Data analysis

Statistical evaluation was performed by analysis of variance (ANOVA) using Microsoft Office Excel 2003. The confidence limit was set at 95%. Regression coefficient (R^2) was used to determine how well a regression model describes the release data. Mean \pm SD for tablet thickness, weight and hardness were calculated by using Microsoft Office Excel 2003.

RESULTS

Evaluation of granules

Table 2 summarizes the physicochemical properties (bulk density, tapped density, angle of repose, Carr’s index and Hausner ratio) of the granules.

Table 2: Physicochemical properties of metformin granules

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Carr’s index (%)	Hausner ratio
M1	0.53	0.66	39.8	19.7	1.25
M2	0.56	0.69	36.6	18.8	1.23
M3	0.61	0.74	38.0	17.6	1.21
M4	0.54	0.67	38.1	19.4	1.24
M5	0.57	0.7	37.3	18.6	1.23
M6	0.63	0.76	35.8	17.1	1.21
M7	0.55	0.67	37.2	17.9	1.22
M8	0.59	0.73	37.5	19.2	1.24
M9	0.65	0.78	35.6	16.7	1.20
DC	0.51	0.64	41.2	20.3	1.25

The bulk density of the granules ranged from 0.51 - 0.65 gm/ml and tapped density from 0.64 - 0.78 g/ml. The angle of repose of the granules prepared by melt granulation

method was in the range 35.6 - 39.8^o while it was 41.2^o for the direct compression granules. The compressibility (Carr's index) for all the formulations was < 25 % while Hausner ratio was in the range 1.20 - 1.25.

Physicochemical characteristics of metformin tablets

Table 3 indicates the results of the various physicochemical tests (hardness, friability and assay) performed on the tablet formulations.

Table 3: Physicochemical evaluation of metformin HCl tablets

Formulation code	Hardness (N) ^a , n=10	Friability (%), n=10	Assay (%) n=20
M1	80 ± 4	0.21	99.92
M2	78 ± 4	0.25	99.96
M3	74 ± 4	0.31	100.10
M4	75 ± 2.83	0.28	100.02
M5	74 ± 3.95	0.26	99.97
M6	76 ± 2.07	0.19	99.95
M7	79 ± 2.62	0.21	98.20
M8	75 ± 4.14	0.23	99.20
M9	70 ± 4.58	0.28	97.85
DC	66 ± 5.74	0.42	99.58

^aMean ± SD

The hardness of the tablets produced by melt granulation (formulation M1 – M9) and direct compression (formulation DC) was in the range 70 - 80 N for the former and 66 N for the latter. All the formulations showed less than 1 % friability which is within the prescribed limit. Drug content was uniform within each batch and ranged from 97.85 – 100.10 % of the theoretical value.

Evaluation of in-vitro release

The *in-vitro* drug release results for the test and reference (commercial brand) tablets are shown in Figs 1 and 2.

The release results for the formulations composed of polyethylene oxide (PEO) in the range of 10, 20, 30 % w/w and stearic acid (SA) in the range of 4, 8, 12% w/w are shown

in Figs 1 and 2. Over the period of 12 h, the drug release rate for M1 and M9 formulations decreased as the concentration of polyethylene oxide increased.

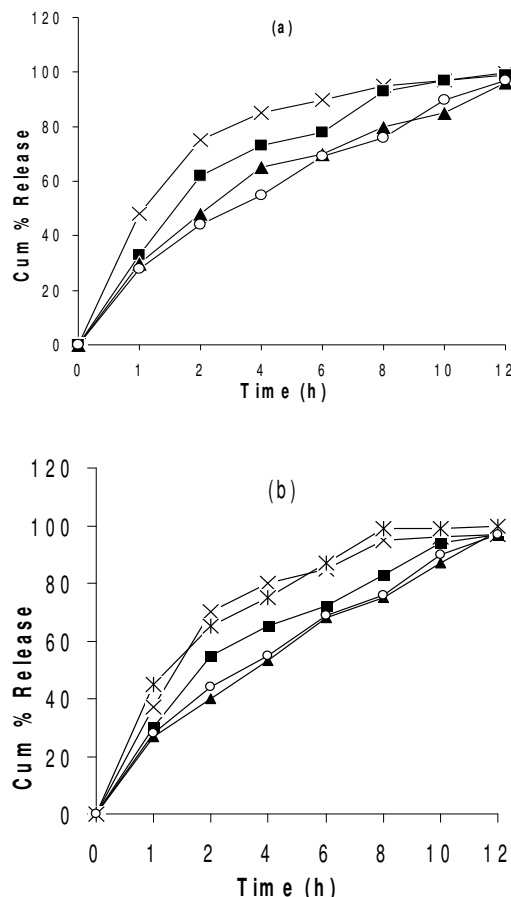


Fig 1: Comparative release profiles of metformin HCl tablets with varying PEO content (a): M1= X; M2 = ■; M3 = ▲; and (b) M4= X; M5 = ■; M6 = ▲; DC = ✕; reference (commercial) product = ○

The release profile of M6 formulation (which contains 30 %w/w of PEO and 8% w/w of SA) is similar to that of the reference (commercial) product based on the similarity factor (f2) value of 81.08. Kinetic analysis of the release data indicates that formulation M6 fitted best to both Higuchi and Korsmeyer-Peppas models with correlation coefficients of 0.9780 and 0.9910, respectively, and n value of 0.4967.

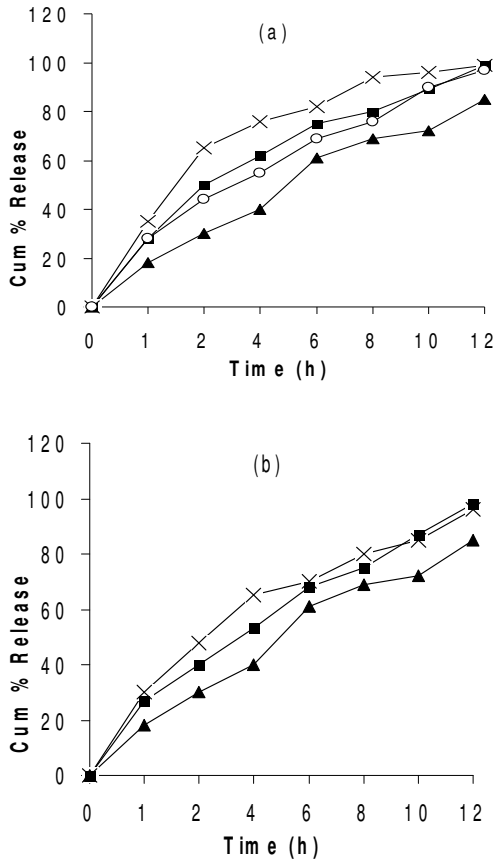


Fig 2: Comparative release profiles of metformin HCl with (a) varying PEO content: M7 = X; M8 = ■; M9 = ▲; reference (commercial) product = ○; and with (b) varying SA content: M3 = X; M6 = ■; M9 = ▲

DISCUSSION

A suitable extended release metformin HCl dosage form would not only enhance therapeutic efficacy and patient compliance but also produce more desirable blood drug levels and lower incidence of adverse effects.

The density of a material depends on the shape and size of the particles. The density is normally proportional to the number of spherical particles present in the bulk, and inversely proportional to the size of particles [24]. Notwithstanding this, out of all the nine

granule formulations, M9 (the optimized formulation) had the largest granules, as well as the highest bulk and tapped densities (Table 2). M9 granules were probably more regular in shape, producing a more uniform distribution, with smaller void spaces between the particles. Carr's index (CI) is usually indicative of the flowability and degree of packing of the material; these are important parameters when filling a matrix formulation into the die of the tablet press. A CI of < 15 % indicates adequate granule flow and stable packing, while values > 25 % are characteristic of poor flow properties. The Hausner ratio is usually related to the compressibility of powder and values < 1.25 are indicative of good compressibility. All the formulations had CI < 25 % and Hausner ratio ≤ 1.25 indicating good to passable flow irrespective of the method of granulation.

The drug content of all the formulations ranged from 98.2 -100.1 %, indicating the presence of an acceptable amount of drug in the formulations. Furthermore, all the formulations showed satisfactory hardness and friability.

The decrease in drug release rate as the concentration of polyethylene oxide increase is consistent with the findings of Rajkumar et al [25], which indicate that the presence of a highly water soluble compound in polyethylene oxide matrix results in a faster rate of polymer swelling and a large increase in gel thickness to prevent immediate tablet disintegration, and thus controlling the diffusion of the drug. Increase in polymer concentration not only caused increase in the viscosity of the gel but also led to a decrease in the diffusion of drug and, therefore, a reduction in the drug release rate [26]. Other factors at play in relation to polymer content probably include change in water penetration rate, water absorption capacity and polymer swelling [27].

Also, the decrease in drug release rate when the stearic acid content of the matrix was increased may be due to slower penetration

of the dissolution medium in matrices as a result of increased lipophilicity [28] while the initial burst release from the matrix can probably be attributed to the dissolution of drug from the tablet surface. Further, penetration of dissolution fluid was hindered by the hydrophobic coating of stearic acid around the drug particles, leading to diminished drug release over an extended period [29].

The slower drug release from the tablets derived by melt granulation (compared with those prepared by direct compression) could be due to the formation of a more uniform, and hence, a more effective and rigid hydrophobic coating of stearic acid around the hydrophilic drug particles during hot melt granulation.

An ideal matrix formulation should contain polymers and diluents at amounts as little as possible, and release its drug content in a sustained release profile over a reasonable length of time, preferably by zero-order kinetics [30]. On fitting M6 data into various release models, the highest regression coefficients, 0.9780 and 0.9910, were for Higuchi and Korsmeyer-Peppas models, respectively, with n value of 0.4967 which indicates a coupling of diffusion and erosion mechanism, so-called anomalous diffusion. This indicates, therefore, that drug release from the tablets was controlled more by polymer swelling, followed by drug diffusion through the swollen polymer, and then slow erosion of the tablet matrix.

CONCLUSION

An extended release tablet formulation of metformin HCl was successfully developed using a combination of hydrophobic and hydrophilic polymers. The matrix tablet formulation demonstrated the desired drug release profile. Melt granulation is more effective than direct compression for controlling the release of a highly water soluble drug such as metformin HCl.

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