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Formulation and Evaluation of Metformin Hydrochloride Sustained Release Tablet

Talha Suhel, Vivek Jain, Pushpendra Kumar Khangar, Rupesh Kumar Jain*

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001

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*Address for Correspondence:

Rupesh Kumar Jain, Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001

Abstract

Metformin hydrochloride (MET) is an oral hypoglycemic agent which improves glucose tolerance in patients with type 2 diabetes and diminishes basal plasma levels of glucose. The aim of this study was to develop and optimize MET matrix tablets for SR application. The SR matrix tablet of MET was prepared by wet granulation technique using Polyvinyl pyrrolidone K30 and hydroxyl propyl methylcellulose of different viscosity grades (HPMC K4M, HPMC K15M, and HPMC K100M). The influence of varying the polymer ratios was evaluated. The excipients used in this study did not modify physicochemical properties of the drug. MET has relatively short plasma half-life, low absolute bioavailability. The need for the administration 2 to 3 times a day when larger doses are required can decrease patient fulfillment. SR formulation that would maintain plasma level for 8-12 h might be sufficient for daily dosing of MET. SR products are needed for MET to prolong its duration of action and to improve patient compliances. The development of oral sustained release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. From all the formulation trial batches, formulation F3 shows the best results. It has been observed that HPMC K100M alone cannot give satisfactory drug release profile but the blend of HPMC K100M and Polyvinyl pyrrolidone K30 together give the best drug release kinetics. Thus, sustained release matrix tablets of metformin hydrochloride can be expected to reduce the frequency of administration and decrease the dose dependent side effects.

Keywords: Metformin hydrochloride, SR matrix tablet, HPMC K100M, Wet granulation technique

Introduction

Sustained-release (SR) oral delivery systems are designed to attain therapeutically effective concentrations of drug in systemic circulation over an extended period of time[1] towards novel drug delivery of pharmaceutical technology; SR matrix tablets have given a new development[2]. Reservoir type of dosage forms designed to release drug constantly and continuously over satisfactory prolonged period of time to maintain plasma drugs concentration within therapeutic level[3]. Drug products designed to reduce the occurrence of dosing by modifying the rate of drug absorption are available since many years. Among various dosage forms, matrix tablets are widely accepted for oral sustained release (SR) as they are effortless and easy formulate. Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed. In fact, matrix is defined as a well complex of one or more drugs with a gelling agent i.e. hydrophilic polymer[4-6]. It is estimated that by 2025 around 300 million people will be diagnosed with diabetes[7, 8]. Metformin hydrochloride (MET) is an oral anti-hyperglycaemic drug used in the treatment of Type 2 diabetes in patients who cannot manage the disease with only diet and exercise[9]. Different from Insulin and the Sulfonylurea, MET does not promote weight gain; therefore it becomes the first choice for treatment of type 2 diabetes and is even used in obese patients with type 1 diabetes to reduce insulin resistance[10]. Chemically, MET is (N, N-dimethyl imidodi carbonimidic diamide hydrochloride) belongs to the class of biguanides, hydrophilic, BCS class- III drug[11, 12]. It improves glucose tolerance by lowering both basal and postprandial glucose by decreasing intestinal absorption of glucose, decreasing hepatic gluconeogenesis, increasing glycogenesis, lipogenesis and glucose uptake by adipocytes and muscle cells[9, 13]. MET is a highly water soluble drug (0.5 g/ml) administered up to 2.5 g/day in three separate doses given with meals to minimize possible gastrointestinal side effects such as anorexia, abdominal discomfort, nausea and diarrhea[14]. However, food also decreases the absorption of the drug [15]. The presence of side effects and the need for three-times-a-day administration could reduce patient compliance and hinder successful treatment[16]. MET does not produce lactic acidosis as seen in other biguanide drugs such as phenformin and buformin[17]. Further, MET does not bind to plasma proteins and the elimination of the unchanged drug mainly occurs by active tubular secretion through the kidneys. A single dose of 500 mg of an immediate and modified release MET showed higher plasma concentrations for the latter in the steady-state[18]. A single immediate release doses of MET exhibits a flip-flop model and a bioavailability of about 61%. The tmax and t1/2 of MET after a single immediate release oral dose of 500 mg was ~2 h and 2.6 h, respectively[19]. However, a 250 mg sustained-release MET pellet showed a tmax of 7.3 h and t1/2 of 8.3 h and a 165% increase in

bioavailability in comparison to the immediate release formulation and thus, tmax depended on the dose. For instance, tmax was 2.2 h and 1.5 h for an immediate release dose of 0.5 and 1.5 g, respectively[17]. Further, ~20% of the single immediate release dose is recovered in faeces, indicating saturable absorption and low absorption in the terminal segment of the colon[20-22]. This problem creates the need for a modified release device to modulate the release and hence, the absorption of MET. Thus, a modified release system allows for achieving an optimal therapy, improving patient compliance and safety, reducing dose dumping, plasma fluctuations and the incidence of side effects. In the present study, formulations of hydrophilic matrixes composed of MET, Polyvinyl pyrrolidone K30, HPMC, and magnesium stearate were prepared by wet granulation followed by tableting to achieve a once-a-day controlled release preparation. This provides a lower but controlled drug concentration over an extended period of time (24 h).

Materials and methods

Materials

Metformin HCl was received as a gift sample from Arbro Pharmaceuticals Ltd, New Delhi (India). Hydroxy propyl methyl cellulose, polyvinyl pyrrolidone K30, magnesium stearate was purchased from Himedia Chem. Lab, Mumbai. Talc and sodium alginate, starch was purchased from Loba Chemicals Pvt. Ltd. Mumbai. Acetonitrile, methanol and Isopropyl alcohol were of HPLC grade supplied by Merck Ltd., India. All other ingredients used were of analytical grade. Triple distilled water was generated in house.

Preformulation studies[23, 24]

Physical characteristics

By visual examination, the drug was identified for physical characters like colour, texture, odour etc.

Solubility

Solubility of the drug was determined by taking some quantity of drug (about 10 mg) in the 10 ml volumetric flasks separately and added the 10 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH, chloroform and 7.4 pH buffer) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Melting point

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

FTIR spectroscopy

The concentration of the sample in KBr should be in the range of 0.2% to 1 %. The pellet is a lot thicker than a liquid film, consequently a decrease concentration in the sample is required (Beer's Law). For the die set that you'll be the usage of, about 80 mg of the mixture is wanted. Too excessive of an attention causes typically difficulties to obtain clean pellets. FTIR spectra of the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Determination of λ_{max} of MET

MET, 100 mg was accurately weighted into a 100 ml volumetric flask, dissolved in distilled water and the volume was made up with distilled water. Pipette 1 ml of this solution into a 10 ml volumetric flask with methanol as the volume and marks it as stock. Prepare an appropriate dilution to bring the concentration down to 2-12µg/ml. The resulting solution is scanned with a UV spectrophotometer (UV-1700 Shimadzu corporation, Japan) in the range of (200-400 nm) to determine the absorption maximum (λ max). Concentration vs. absorbance was shown on a graph.

Formulation of MET sustained release (SR) tablets

Different tablet formulations were prepared by wet granulation technique. All the powders except magnesium stearate and talc were passed through 60 mesh sieves. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent (alcoholic solution of PVP) was added slowly. The composition of each tablet is shown in Table 1.

Table 1: Composition of metformin hydrochloride sustained release matrix tablets

Composition of 500 mg Metformin HCl			
Ingredient	**F1**	**F2**	**F3**
Metformin HCl	500	500	500
Hydroxy-propyl-methyl cellulose K4M	200	0	0
Hydroxy-propyl-methyl cellulose K15M	0	200	0
Hydroxy-propyl-methyl cellulose K100M	0	0	200
Polyvinyl pyrrolidone K30	50	50	70
Magnesium stearate	5	5	5
Talc	5	5	5
Isopropyl alcohol	Q.S.	Q.S.	Q.S.

Micromeritics properties[25]

Angle of repose

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface. Angle of repose can be determined by following equation:

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

Where, θ is the angle of repose, h is height of pile; r is radius of base of the pile.

Bulk density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula.

Bulk density = Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends was determined using the following formula.

TBD = Total weight of powder/Total volume of tapped Powder.

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume. Carr's compressibility index was calculated using the following formula.

Carr's compressibility index (%) = [(Tapped density-Bulk density) ×100]/Tapped density.

Hausner's ratio

Hausner's ratio can be determined by the following equation.

Hausner's ratio = TBD / BD

Where, TBD -Tapped bulk densities & BD- bulk densities

Evaluation of tablets[26]

Weight variation

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeial specification, tablets with an average weight between 80-250 mg, the percentage deviation should not more than ± 7. 5 % and tablets with an average weight more than 250 mg should not be more than ±5 %.

Friability test

Twenty tablets were selected at random; their surfaces cleaned with a hair brush to remove any adhering dust, weighed and placed in the friabilator (Electro Lab USP EF-2). They were then allowed to fall freely 100 times from a height of 6 inch at a speed of 25 rpm for 4 min. The tablets were then dusted and weighed. Any loss in weight due to fracture or abrasion was recorded as a percentage weight loss. The replicate determinations of each formulation were averaged. Friability was calculated by the following formula.

$$F = 100\left[\frac{W_0 - W}{W}\right]$$

F = Friability, W = Final weight, Wo = Initial weight

Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm^2. Ten tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Uniformity of thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using digital vernier calliper.

Determination of drug content in tablets

Twenty tablets were weighed and its average weight was taken which was crushed in motor and pestle. The powder weight equivalent to single tablets i.e. 500 mg was dissolved in 10 ml water in a 100 ml volumetric flask and allowed to stand for 10 min. To that 75 ml of methanol was added initially followed by addition of sufficient methanol to produce 100 ml which was then filtered through whatman filter paper. 5 ml of this resulting solution was further diluted to 50 ml with 7.2 pH phosphate buffer: methanol (1:1). Again 5 ml was diluted to 50 ml by the same solvent. The absorbance of each of the standard and sample solution was taken in UV-visible spectrophotometer at 234nm using equal volumes of methanol as blank.

In vitro dissolution studies

In Vitro dissolution study of all the formulated tablets and market sample was carried out for 8 h in USP dissolution apparatus II (paddle) at 37 ± 2°C and 100 rpm in 900 ml 0.1 N HCl. Sample of 10 ml was withdrawn at pre-determined time intervals and replaced with the same volume of dissolution media (37 ± 2°C) to maintain the constant volume. Solution samples were analysed by UV-Visible Spectrophotometer. The percentage of drug dissolved was calculated based on the concentrations of drugs.

Results and Discussions

The melting point of MET (pure drug) was found to be 223-226°C. MET was freely soluble in water, sparingly soluble in methanol and ethanol and insoluble in Acetone. Identification of MET was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Figure 1. The calibration curve of MET was found to be linear in the concentration range of 2-12 µg/ml at 234nm Figure. 2. Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and carr's index (CI) was calculated using the following equation. Carr's index = (TBD-LBD) ×100/TBD. Hausner's ratio was related to inter particle friction and could be used to predict powder flow properties. Hausner's value of the prepared granules ranged from 1.15 to 1.16 was thought to indicate good flow properties Table 2. The physical appearance, tablet hardness, friability, weight variation and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 3. Tablet hardness was found to be good (between 6 to 8 kg/cm^2) depending on the compression force applied, and friability was less than 0.5% (wt/wt). The manufactured tablets showed low weight variation and a high degree of drug content uniformity, indicating that wet granulation is an acceptable method for preparing good- quality matrix tablets of metformin HCl. Initially, tablets were prepared with HPMC K4M (F1) released 40.61% and 81.23% of metformin HCl within 1 and 4 h respectively. And the tablets with HPMC K15M (F2) shows 81.01% drug released within 4 h. The tablets prepared with K100M (F3), drug- to-polymer ratios of 5: 2 and isopropyl alcohol as granulating agent retard the release of metformin HCl 36.11%, 73.65% and 93.44 at 1h, 4 h and 8 h respectively. F3 formulation has showed an optimal formulation due to its closest profile to the target in terms of release Figure 3.

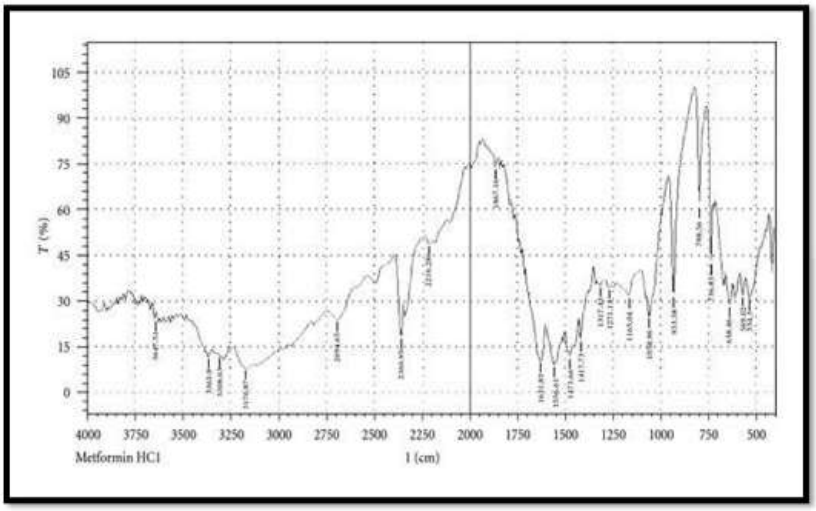

Figure 1: FT-IR spectrum of pure drug (MET)

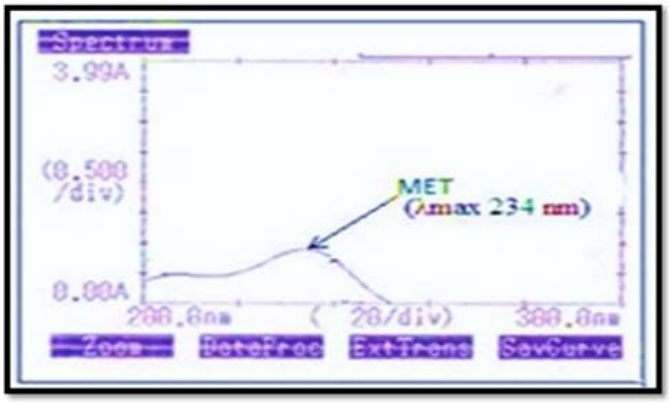

Figure 2: Wavelength maxima of MET in water

Table 2: Result of pre-compression properties of MET SR tablets

Formulation	LBD	TBD	Angle of repose	Carr'sindex	Hausner'sratio
F1	0.307	0.357	25.94±0.56	13.84	1.15
F2	0.266	0.312	26.32±0.87	14.66	1.16
F3	0.384	0.441	25.98±0.40	13.46	1.15

Table 3: Results of post compression properties of MET SR tablets

F. Code	Hardness (kg/cm²}	Thickness (mm)	Weight variation	Friability (%)	Assay (%)
F1	6-7	6.48	760	0.1	96.74
F2	7-8	6.52	760	0.1	99.4
F3	6-7	6.51	780	0.1	99.5

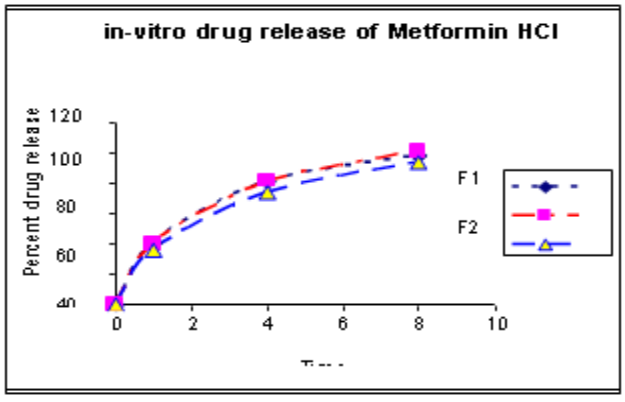

Figure 3: *invitro* cumulative percentage of drug release

Conclusions

In our study, to reach an intended target release profile, SR formulation of metformin HCl tablets were developed with polymer substance such as HPMC K100M. It has been revealed that excipient such as HPMC K100M with polyvinyl pyrrolidone can be used with wet granulation method. This application has shown similar results with other studies in the literature in terms of SR formulation preparations. However, in developing SR formulations containing metformin HCl, it has been shown that HPMC K100M provides a better result in preparation of SR formulation prepared by wet granulation method. F3 formulation (5:2 ratios) has showed an optimal formulation due to its closest profile to the target in terms of release.

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