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Research Article

AN ADVANCEDFORMULATION FOR ANTIDIABETIC DRUG BY MATRIX TECHNOLOGY

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ABSTRACT

This research was aimed to prepare and evaluate the matrix tablet of Metformin, to overcome its poor biopharmaceutical property and therapeutic efficacy. Metformin is biguanide derivatives of the antihyperglycemic category. Although metformin shows excellent water solubility after reaching the gastrointestinal tract, the drug values are lower in the plasma. This indicates that metformin has very low bioavailability (1-2.5 hours). To prolong the duration of action and also to improve patient compliance; it is formulated into a matrix tablet. The overall objective of this research work was to develop a matrix tablet of metformin to sustain its action by using polymers of different ratios such as Starch 1500, HPMC, K4M, Crospovidone XL, MCC 102. The tablet was formulated using the wet granulation technique. Invitro drug dissolution study was performed to estimate the amount of drug released from the prepared matrix tablet. The drug release study revealed that crospovidone XL and MCC 102 in ration 2:1 were best suited as a matrix tablet giving a release rate of 86% for 9hrs by using selected grades of HPMC at selected proportion.The experimental and predicted results for optimum formulations were found to be in close agreement.

Keywords: Matrix tablet, Polymers, Wet granulation, Drug dissolution, Sustained release

1. INTRODUCTION

Oral drug delivery system has been known for decades as the most widely utilized route of administration among all routes that have been explored for systemic delivery of drugs in case of different dosage forms. The advantages of administering a single dose of a drug is that release over an extended period. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as the enhanced clinical efficacy of the drug for its intended use. Introduction of matrix tablet as the sustained release (SR) has given a breakthrough for novel drug delivery systems (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and the drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Metformin hydrochloride is a biguanide derivative of highly water-soluble oral antihyperglycaemic agents used in the treatment of type II non-insulin dependent diabetic Mellitus. It is slowly and incompletely absorbed from the gastrointestinal tract due to its relatively low 50-60% bioavailability together with its short biological half-life 1.5-4.5 hrs [1]. Metformin is not metabolized initially; its main sites of concentration are the intestinal mucosa. The plasma concentration of drugs at steady-state ranges about 1 to 2 mcg/ml and a relatively narrow absorption window. Administration of sustained-release Metformin Hydrochloride form could reduce the dosing frequency and improve patient compliance. Despite the clinical response and lack of significant drawback, chronic therapy with Metformin Hydrochloride suffers problems of which high dose (1-3g/day) and enhancing the incidence of metallic taste, gastrointestinal tract *i.e.,* lactic acidosis, to improve the pharmaceutical formulation of Metformin hydrochloride. To achieve optimal therapy, the effort mainly focuses on the formulation of a sustained release matrix tablet of Metformin hydrochloride dosage forms [2].

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$. HCl and a molecular weight of 165.63 gm. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform.

Matrix devices were used due to their chemical inertness, drug embedding ability, and drug release character, and have gained steady popularity for sustaining the release of a drug. The preparation of sustain release formulation by matrix technique is a commonly employed method because of ease of preparation, flexibility, and cost efficiency [3].

The objective of this study was to prepare sustained release matrix Metformin HCl tablets using various hydrophilic and hydrophobic polymers. Metformin hydrochloride was entrapped within the polymer matrix so that its sustained release could be achieved. The polymer concentration played a crucial role for sustained delivery of the drug. The precompression evaluation was done to obtain an optimum flow of granules. After formulation, the tablets were evaluated for their weight uniformity, hardness and drug dissolution.

2. MATERIAL AND METHODS

Metformin hydrochloride was obtained from Harman finochem limited, Aurangabad. Microcrystalline cellulose (MCC)101 was purchased from JRS Pharma,HPMC K100M, HPMC K200M were obtained as a giftsample from Colorcon Asia private ltd. All other ingredients used were of laboratory reagents and were used as such without further testing.

Fluid Bed Dryer TG 200 - Retsch GMBH (Inkarp) was used for drying. The blending of powder mixture was done using Multimill- Betcochem Eng. and Octagonal Blender-Anchor Mark Private. The tablet compression was facilitated by Compression Machine (Cadmach CMD4). The tap density was measured using Tap Density Apparatus-Electropharma. Moreover, the time for complete disintegration of tablets were measured using Disintegration Tester-Electropharma and friability by Friability Tester- Electropharma. The strength of the tablet was measured by Hardness Tester- Pharmatron and coating of the prepared tablets were done by Coating machine-Gansons Ganscoater.

2.1. Preparation of standard calibration curve of metformin

2.1.1. Preparation of standard stock solution

Accurately weighed 100mg of metformin HCl was transferred in to a 100ml volumetric flask, dissolved in 50ml of distilled water and made upto a standard stock solution of 1000µg/ml drug concentration. From this Standard stock solution of metformin HCl, 100 µg/ml (stock solution) was prepared by pipetting 10ml of stock solution to a100 ml volumetric flask and making up to 100ml with distilled water.

2.1.2. Determination of Wavelength maximum of Metformin HCl

10ml of the above solution was diluted to 100ml with the same solvent to get 10µg/ml of concentration. The UV spectrum of final solution was scanned in the range of 200-400 nm against distilled water as blank. The λ_{max} was found at 233.8 nm

2.1.3. Standard curve of Metformin HCl

One mille litre (1 ml) of the standard stock solution was taken and diluted to 10ml with distilled water (100µg/ml), from the above solution 0.2,0.4,0.6,0.8 and 1 ml were pipetted out and diluted to 10ml with distilled water to get the final concentration of 2,4,6,8 and 10µg/ml respectively. The standard curve of Metformin HCl was then plotted whose regressed value was around 0.991 (Fig. 1).

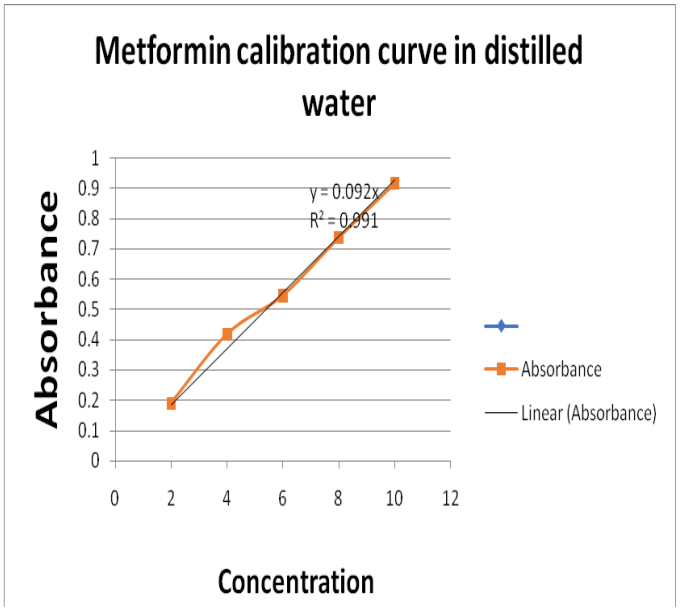

Fig. 1: Standard curve of Metformin HCl

2.2. Preparation of Tablets

Various batches of tablets were prepared by wet granulation technique [4]. The steps involved in tablet preparation includes mixing of metformin and aerosol, which were passed through sieve 30# and after proper mixing the powder mixture was transferred to rapid mixer granulator (RMG) and mixed for 10 minutes. After this, binder was prepared by adding PVA in purified water. Granules were dried in Retsch Dryer

until Loss on drying (LOD) reached below 2%. Starch 1500, HPMC K4M, HPMC K100M, Cross Povidone XL 10, MCC 102 were added in dry granules and mixed in octagonal blender for 15minutes at 24rpm for perfect blending. Magnesium Sterate (lubricant) was added at last and mixed for 5 minutes. The prepared tablets with varying concentration of polymers are tabulated below (Table 1).

Table 1: Formulation table for matrix tablet

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin	60	60	60	60	60	60	60	60	60
Aerosil	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
PVA	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Starch 1500	16.09	16.09	32.18	8.045	40.235	16.09	-	20.11	20.11
HPMC K100 M	16.09	32.18	16.09	8.045	40.235	16.09	40.235	20.11	-
HMPC K4M	16.09	8.045	16.09	16.09	-	8.045	-	20.11	20.11
Crosspovidone	16.09	8.045	8.045	32.18	-	8.045	40.235	-	20.11
MCC102	16.09	16.09	8.045	16.09	-	32.18	-	20.11	20.11
Magnesium Stereate	3.53	3.53	3.53	3.53	3.53	3.53	3.53	3.53	3.53
Total weight (mg)	150	150	150	150	150	150	150	150	150

2.3. Precompression Parameters

2.3.1. Angle of repose

Angle of repose is defined as, "the maximum angle possible between the surface of pile of Powder and horizontal plane". The angle of repose for powder of each formulation was determined by the fixed funnel method [5]. A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface.[6]The funnel bottom was closed and 10 gm of sample powder was filled in funnel. After filling, the bottom of funnel was opened and a conical heap of powder was formed. The height and radius of the conical heap was measured using normal scale.

The value of angle of repose was calculated by using the following formula: $\theta = \tan^{-1} = h/r$,

Where, h- height of the heap, r-radius of the heap

2.3.2. Moisture content

LOD test is to measure the amount of water and volatile matters in the sample when the sample is dried under specific conditions. The quantity of moisture present in the API was determined by using moisture analyzer and was calculated as follows.

LOD =**Fehler!***100

2.3.3. Bulk density

The powder sample (blend) under test was screened through sieve #20 and the sample equivalent to 20g was accurately weighed and filled in a 100ml graduated cylinder and the powder was levelled and the unsettled volume (Vo) was noted. The bulk density was calculated in g/cm^3 by the formula,

Bulk density (PO) = M/Vo

Where,

M = Mass of powder taken

Vo = apparent untapped volume

2.3.4. Tapped density

After carrying out the procedure as given in the measurement of bulk density [7], the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provided 100 drops per minute and this was repeated until the difference between succeeding measurement was less than 2 %. The tapped volume, V was measured to its nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

2.3.5. Compressibility index

The compressibility Index was calculated by using measured values for bulk density and tapped density. Table 2 shows the scale of flowability of the prepared granules.

Compressibility Index(%)

=**Fehler!***100

Table 2: The scale of Flowability

Compressibility index (%)	Flow character
>10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

2.4. Post Compression Parameter

2.4.1. Weight variation test

The weight variation test was done by weighing 20 tablets of each batch using an electronic balance. After that, the average weight was calculated. The tablets were then weighed individually and the percentage deviation from the average weight was calculated.

% weight Variation = (Individual weight/Average weight) *100

The tablets meet the USP test if not more than two tablets are outside the percentage limits, and no tablet differs by more than 2 times the percentage limit (Table 3).

2.4.2. Friability test

The friability of tablets was measured in a Roche friabilator. 20 tablets of known weight (Wo) were taken in a drum for 4 minutes (100 revolutions) and weight (W) again. Percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not be more than 1% w/w.

Friability percentage = (Initial weight – Final weight)/Initial weight * 100

2.4.3. Hardness of tablet

Tablet hardness has been defined as, "the force required breaking a tablet in a diametric Compression test". For each formulation, the hardness of three tablets was determined using Monsanto hardness tester.

The tablet was placed in "Monsanto hardness tester'' vertically and the force was applied with the help of screw, the end point was detected by breaking the tablet.

2.4.4. Thickness

The thickness of tablet was determined using Vernier Calliper. Six tablets from each batch of formulation were used and mean thickness value and SD was calculated for each formulation.

3. RESULTS AND DISCUSSION

3.1. Evaluation of granules

Table 4 summarizes the physicochemical properties (bulk density, tapped density, angle of repose and Carr's index) of the granules.

Table 4: Physiochemical properties of the granules

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of repose(°)	Carr's Index (%)
F1	0.453±0.005	0.403±0.006	27.52±0.45	16.53± 0.53
F2	0.35±0.045	0.363±0.001	28.22±0.52	17.43± 1.78
F3	0.33±0.015	0.373±0.023	26.52±0.45	15.46± 2.49
F4	0.31±0.045	0.383±0.033	25.20±0.12	18.88± 0.11
F5	0.33±0.025	0.383±0.021	26.33±0.55	18.76± 0.58
F6	0.32±0.005	0.393±0.022	25.23±0.56	16.44± 0.36
F7	0.34±0.045	0.363±0.026	27.22±0.19	19.34± 1.55
F8	0.345±0.045	0.401±0.034	28.56±0.29	18.01± 0.26
F9	0.35±0.055	0.355±0.025	26.54±0.44	17.12± 0.33

3.2. Physicochemical characteristics of Metformin tablets

Table 5 indicates the results of the various physicochemical tests (hardness, thickness, friability and percentage weight variation) performed on the tablet formulations.

3.3. *In-vitro* drug release study

This study was performed using USP dissolution test apparatus type 2(paddle type) at 50 rpm using 900 ml of pH 1.2 HCl solution maintained at 37±0.50 °C as dissolution medium. The results were shown in Table 6. From the data, it is evident that as the proportion of polymers in the formulation increases, the percent drug

released was found to be reduced. After formulation of tablets, we observed that controlled release of the drug can be obtained with an equivalent amount of polymers concentration (Starch 1500, HPMC K100 M, HPMC K4M, Crosspovidone XL, MCC 102). In nine formulations, F4 formulation has shown promising dissolution parameters that is 86% in 9hours.

Table 5: Physicochemical evaluation of Metformin HCl Tablets

Formulation Code	Mean hardness (Kg/cm^2)	Thickness(mm)	Friability(%w/w)	Percentage weight variation (%)
F1	3.59±0.45	3.3±0.177	0.590±0.055	6.8±1.10
F2	3.64±0.11	3.1±0.45	0.64±0.45	6.4±0.122
F3	3.55±0.76	2.8±0.035	0.61±0.45	7.2±0.65
F4	3.89±0.45	3.2±1.45	0.67±0.13	6.9±0.082
F5	4.04±0.66	3±0.35	0.52±0.85	7±0.12
F6	3.44±0.65	2.8±0.75	0.45±0.05	7.1±0.85
F7	3.98±0.54	3.1±0.45	0.64±0.45	7.2±0.65
F8	3.89±0.45	2.8±0.035	0.61±0.45	6.9±0.082
F9	4.04±0.66	3.2±1.45	0.67±0.13	7±0.12

Table 6: *In-vitro* drug release data of formulations

Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	11.14±0.97	10.85±0.75	0.54±0.26	0.87±0.75	1.46±0.35	2.45±1.24	0.77±0.75	0.24±0.26	09.85±0.75
15	18.09±0.54	21.45±0.45	3.11±0.45	5.66±0.66	4.55±0.07	12.71±0.21	4.66±0.66	4.15±0.45	19.45±0.45
30	25.45±0.06	27.39±0.49	8.45±0.36	10.99± 0.73	12.94±0.95	17.24±0.45	11.99± 0.73	8.45±0.36	22.39±0.49
60	30.15±0.56	39.17±1.45	29.63±1.22	14.28±0.01	15.36±0.55	21.55±0.85	16.45±0.01	29.63±1.22	36.17±1.45
120	35.54±0.46	46.28±0.85	30.02±0.42	21.90±1.25	18.31±0.85	37.08±0.85	23.25±1.25	30.02±0.42	42.28±0.85
180	43.70±0.88	52.54±0.88	37.41±0.45	27.39±0.75	30.02±0.36	41.16±0.66	33.39±0.75	37.41±0.45	50.54±0.88
240	55.12±0.014	59.45±1.45	44.46±0.85	39.17±1.85	42.10±0.76	53.74±0.95	39.17±1.85	49.56±0.85	59.45±1.45
300	62.45±0.46	64.23±0.75	57.99±1.45	46.28±0.45	49.52±0.42	58.76±0.45	46.28±0.45	57.99±1.45	64.23±0.75
360	73.14±0.75	66.18±0.45	60.19±0.36	52.62±1.21	61.73±0.12	62.45±0.12	55.22±1.21	61.19±0.36	66.28±0.65
420	76.98±0.36	70.45±0.11	65.14±0.85	69.15±0.85	65.85±0.85	65.11±0.45	69.15±0.85	65.14±0.85	72.45±0.31
480	81.22±0.49	75.52±0.45	73.42±0.54	78.39±0.54	70.56±0.21	70.37±0.45	78.39±0.54	74.42±0.54	75.52±0.75
540	---	79.00±0.93	76.4±0.31	86.00±0.54	---	76.99±0.99	85.02±0.54	78.4±0.31	77.00±0.23

4. CONCLUSION

Metformin hydrochloride is a biguanide derivative of highly water-soluble oral antihyperglycaemic agents used in the treatment of type II non-insulin dependent diabetic Mellitus. It is slowly and incompletely absorbed from the gastrointestinal tract due to its relatively low 50-60% bioavailability together with its short biological half-life 1.5-4.5 hrs. Therefore, the present investigation was concerned with the development of the sustained release matrix tablets, which after oral administration were designed to prolong the duration of action. Various formulations were developed by using release rate controlling and matrix forming polymers like Starch 1500, HPMC K100M, HPMC K4M, Cross povidone XL and MCC by direct compression method [8]. Different proportion of HPMC and Starch 1500 was associated with a decrease in the overall cumulative drug release rate. Thus, we conclude that from among all the developed formulations, F4 formulation sustained the drug release for a longer period of time over 9 h and percentage drug release was found to be 86% when compared to other formulations. So, F4 was selected as the best formulation. From the result, it is evident that Crosspovidone and MCC 102(2:1) by forming a matrix with selected grades of HPMC retards the release rate of the drug and the tablet made by using these polymers can be used as the sustained release dosage form. Thus, the objective of the present work was formulating a sustained release dosage form of Metformin by using different proportions of a release rate controlling polymers has been achieved with success. The method of wet compression utilizes minimum machinery and manpower. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product.

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