FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLETS CONTAINING METFORMIN HYDROCHLORIDE

Deepak Gupta[1], Shalini Sharma[1], Sukhbir Lal Khokra[1], Ram Kumar Sahu[2]

1. Manav Bharti University, Laddo, Solan-173229 (H.P.), India
2. Oriental College of Pharmacy, Raisen Road, Bhopal-462021 (M.P.), India.

For e. mail correspondence: ramsahu79@yahoo.co.in,

Summary

Sustained release formulation of Metformin HCl presents the formulator with significant challenges due to its poor inherent compressibility, high dose and high water solubility. The objective of the present study was to develop sustained release matrix tablets of Metformin HCl, an anti diabetic drug. The sustained release tablets were prepared by direct compression method and formulated using different drug and polymer ratios, formulations such as F1 to F6. Polymers like Sodium carboxymethyl cellulos (Sod. CMC), hydroxyl propyl methyl cellulose (HPMCK-100), Xanthan gum and HPMCK-4 were used. Tablets blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content. The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 16 hours using paddle method in phosphate buffer (pH 6.8) as dissolution media. Formulation F1 to F4 failed to sustain release beyond 12 hours. Among all the formulation, F6 shows 100.42% of drug release at the end of 16 hours. This finding reveals that above a particular concentration of Sod. CMC, HPMC K-100 and xanthan gum are capable of providing sustained drug release.

Key words Sod. CMC, HPMC K-100, Xanthan gum, Metformin HCl, matrix tablets

Introduction

Oral route is the most frequently preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and used by the patients and physicians alike. In long term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages. Sustained release tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs[1,2].

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral

antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. 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 day long plasma insulin response may actually decrease[3, 6]. The half-life of Metformin HCl is also short (1.5 to 4hrs) which makes it suitable candidate for sustained release formulation, moreover it reducing side effects, decreasing frequency and improve patient compliance. Keeping these factors in view it was aimed to formulate and evaluate sustained release matrix tablets, to provide a controlled and predictable release of Metformin HCl.

Materials and methods

Materials: Metformin HCl, HPMC K-100, xanthan gum, HPMC K-4 and Sod. CMC were received as gift samples from Alkem Laboratories, Himachal Pradesh. Colloidal silicon dioxide, aerosil, magnesium stearate, was of AR Grade.

Methods

Preparation of matrix tablets: All ingredients was collected and weighed accurately. Sifted Metformin HCl and polymers through sieve no. 60# and then rinsed with remaining excipients. Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#. Preblending of all ingredients (except lubricant magnesium stearate) in blended for 15 minutes. Blend then again blended for 5-6 min then added magnesium stearate blended 5 min. Lubricated powder was compressed by rotary machine having circular concave shaped and one side break line on upper punch, with pressure of 7-8 tons. Compressed tablets were examined as per official standards and unofficial tests. Prior to the compression the drug and polymers were evaluated for several tests.

Evaluation of tablet blends

Angle of repose: The angle of repose of tablet blends was determined by the funnel method. The blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where ‘h’ and ‘r’ are the height and radius of the powder cone, respectively.

Bulk density: Apparent bulk density was determined by pouring a weighed quantity of tablet blends into graduated cylinder and measuring the volume and weight.

Bulk Density = Mass of powder / Bulk Volume of the powder

Tapped bulk density: It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals.
The tapping was continued until no further change in volume was noted.

Tapped density = Weight of powder / Tapped volume of the powder

Carr's index: Carr's compressibility index CI (Carr, 1965) is defined as follows:

$CI = \rho t - \rho a / \rho t = Va - Vt / Vt$

Where ρt and ρa – tapped and poured bulk density; And Vt and Va – tapped and poured bulk volume respectively.

Hausner's ratio: A similar index has been defined by Hausner[7-10].

Hausner's ratio = Tapped density / Poured Density

Evaluation of Tablets

Thickness: The thicknesses of the tablets were determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

Uniformity of weight: Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg by using digital balance. Weight control is based on a sample of 20 tablets

Drug content: The estimation of drug content of Metformin HCl was done by UV analysis. Crushed 20 tablets and weighed equivalent to 100 mg(approx 130 mg of powered drug) of metformin HCl and dissolved in 100 ml distilled water (Solution – A) 10 ml of the solution – A was further diluted to 100 ml with distilled water. (Solution – B). From solution B, 10 ml of solution was again diluted to 100 ml (Solution – C) and read the absorbance at 233 nm with the help of UV spectrophotometer.

Hardness and friability: For each formulation, the hardness and friability of 20 tablets each were determined using the Pfizer hardness tester and Electro lab friabilator test apparatus, respectively.

***In vitro* release studies:** The *in vitro* dissolution studies were performed using USP -22 type I dissolution apparatus 37±5°C, at 50 rpm. Placed the 900 ml of pH 6.8 phosphate buffer in the vessel of apparatus and assembled, equilibrate the dissolution medium to 37 ±0.5 °C. Placed 1 tablet in basket and immediately operated the apparatus at 100 rpm. Withdrawn the 5 ml samples at 1 hour, 2 hours, 4 hours, 8 hours, 12 hours and 16 hours, from midway between the surface of dissolution medium and the top of the rotating basket, not less than 1 cm from the vessel wall and replaced with fresh buffer solution. After appropriate dilution the samples were analyzed[11-17].

Results and Discussions

The present investigation was undertaken to design, formulate and evaluate Metformin HCL matrix tablets for sustained release dosage form. The blends of different formulations were evaluated for angle of repose, bulk density, tapped bulk density, compressibility index and hausner's ratio. The results of bulk density, tapped bulk density, compressibility index and hausner's ratio are mentioned in table 2. The bulk density of the tablet blend was in the range of 0.36± 0.04 to 0.39± 0.01 g/ml; the tapped density was in the range of 0.42± 0.02 to 0.46± 0.03 g/ml, which indicates that the powder was not bulky. The blend indicated good flow properties for all the formulation with the angle of repose values 27-29° according to fixed funnel and free standing cone method. The results of compressibility index lies between range from 16.74±0.03 to 22.17±0.08, while hausner's ratio lies between 1.14±0.08 and 1.42±0.09 indicating good to excellent flow properties. The tablets of different batches formulated were evaluated for test such as hardness, friability, thickness, uniformity of weight and drug content. The results obtained from all formulations were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values and hence all formulation passed the test for uniformity of weight. The tablets mean thickness values ranged from 7.2±0.14 mm to 7.2±0.45 mm. The hardness of all the tablets was within the range of 12±0.05 to 14±0.06 kg/cm^2. The loss in friability test was in a range of 0.07 to 0.12%. The percentage drug content for different tablet formulations were discrete from 97.12% to 99.71%, were found to be within range (table 3).

In vitro dissolution studies of all the formulations of sustained release tablets of Metformin HCL were carried out in pH 6.8 phosphate buffers for 16 hours. All the tablet formulations showed acceptable properties as shown in table 4. The result of the dissolution study indicating that F1 to F4 released almost drug at the end of 12 hrs, from the released pattern of first four formulation the 100% released was found before 16 hrs. Formulation F5 and F6 released 97.51% and 100.42% at the end of 16 hrs. Here we observed that on increasing the quantity of xanthan gum and decreasing the proportion of HPMC K-100, it retards the drug release from matrix. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. It is expected that the developed formulation should have the following theoretical drug release profile, i.e., 100% for 16 hrs. Formulations F1 to F4 failed to meet the needed theoretical drug release profile. Formulation F5 and F6 met the needed theoretical drug release profile and has the sustain action i.e., retarding the drug release so the release is for a long time and thus more bioavailability. Formulation F6 release 100% drug at the end of 16 hrs, for these reasons, it was considered the best formulation among all the six formulations of this series.

Table 1: Composition of Metformin HCl SR matrix tablet

S. No.	Ingredient	F1	F2	F3	F4	F5	F6
1.	Metformin HCL	1000	1000	1000	1000	1000	1000
2.	Sod. CMC	100	100	100	100	100	100
3.	HPMCK-100	-	-	200	150	200	150
4.	Xanthan Gum	100	150	-	-	50	100
5.	HPMC K-4	50	50	-	50	-	-
6.	Aerosil	10	10	10	10	10	10
7.	Magnesium Stearate	10	10	10	10	10	10
8.	Theoretical Weight	1270	1320	1320	1320	1370	1370

Table 2: Physical characteristics of prepared blend of Metformin HCL

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Angle of repose	27° ± 0.43	29° ± 0.27	26° ± 0.53	28° ±0.31	27° ± 0.18	29° ± 0.46
Bulk density	0.36 ± 0.04	0.38 ± 0.01	0.36 ± 0.05	0.37 ± 0.02	0.39 ± 0.01	0.37 ±0.05
Tapped bulk density	0.45 ± 0.06	0.42 ± 0.02	0.46 ± 0.03	0.43 ± 0.04	0.45 ± 0.06	0.44 ± 0.05
Compresibility Index	17.23 ± 0.11	18.41 ± 0.08	16.74 ± 0.03	19.24 ± 0.12	22.17 ± 0.08	19.34 ± 0.05
Hausner's Ratio	1.14 ± 0.08	1.18 ± 0.13	1.42 ± 0.09	1.23 ± 0.05	1.19 ± 0.11	1.21 ± 0.10

Table 3: Evaluation of Metformin HCl sustained release matrix tablet

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Uniformity of weight (mg)	1270 ± 5	1350 ± 5	1350 ± 4	1350 ± 6	1370 ± 5	1370 ± 6
Thickness (mm)	7.2±0.27	7.2±0.34	7.2±0.14	7.2±0.21	7.2±0.45	7.2±0.16
Friability (%)	0.07	0.08	0.10	0.06	0.08	0.12
Tablet Hardness (Kp)	12±0.05	14±0.03	14±0.06	12±0.07	12±0.05	14±0.03
Assay (%)	97.12	99.42	96.26	98.54	99.71	99.35

Table 4: *In vitro* drug release data

Time in	Cumulative Percent Drug Release					
Hours	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	29.14	28.72	30.24	29.48	28.35	27.91
2	48.26	51.35	49.72	47.34	45.23	46.17
4	63.18	65.62	63.51	66.29	61.19	63.28
8	84.65	79.15	82.37	86.17	77.51	75.45
12	99.37	96.43	97.60	98.21	89.62	88.34
16	-	-	-	-	97.51	100.42

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