ORIGINAL ARTICLE

Effect of Hydrophilic Polymer and Binder on Drug Release of Metformin HCL in Sustained-Release Matrix Tablet

Sudarshan B. Kakad[1]*, Punit R. Rachh[2]

[1]Research Scholar, Bhagwant University, Ajmer, Rajasthan, India, [2]Department of Pharmaceutical Sciences, Bhagwant University, Ajmer, Rajasthan, India.

Abstract

Aim: The aim of this study was to develop a sustained release formulation containing Metformin HCl. **Methods:** The sustained-release Metformin HCl tablet was prepared by wet granulation technique, using different grades of hydroxyl propyl methylcellulose (HPMC) in different concentration and by varying binder concentrations. Formulation optimization was done by three ways to select optimum formula for preparing sustained-release matrix tablet. The trail batches were prepared by varying the concentration of the binder and hydrophilic polymers, and they were all analyzed for pre-and post-compression parameters. To determine the concentration of HPMC K4M in the first step, three trial batches are produced. The following three batches are, then, analyzed to measure the concentrations of HPMC K15M and K100M in the second and third steps, respectively. The HPMC amount was optimized at 240 mg. **Results:** Each optimized HPMC batch's drug release was assessed in an in vitro drug release trial using phosphate buffer solution at pH 6.8 and compared to the drug release of the commercial formulation. Drug identification was performed by melting point determination, Fourier transform infrared, UV, and solubility determination. After pre-compression and post-compression evaluation, we get the appropriate result in B3, B6, and B9 batches. In vitro drug release of these three batches was studied and compare with the marketed formulation. Formulation when compared to the reference sustained-release Metformin HCl tablet, batch B9's drug release, was very similar. Batch B9 is therefore an optimized formulation. **Conclusion:** The hydrophilic polymer HPMC K100M is useful for making tablets of metformin HCl with sustained-release. With an increase in hydrophilic polymer content, the drug release was prolonged, and the PVP K30 binder gave the tablet the right amount of hardness.

Key words: Sustained-release tablet, Hydrophilic, Hydroxyl propyl methylcellulose and PVP K30

INTRODUCTION

The most common method of medication delivery is through the oral route and widely used method of drug delivery due to its efficient patient compliance, cost and availability, flexibility in dosage form design, and ease of manufacture. However, this distribution strategy has substantial physiological limitations, including a quick gastrointestinal transit time, variable gastric emptying rates, and the occurrence of an oral bioavailability for a variety of drugs in the upper gastrointestinal tract.[1,2] Due to these challenges, researchers created the gastroretentive drug delivery system, a delivery method that enables the medication to stay in the stomach for an extended and predictable period of time.[3] Oral sustained-release (SR) delivery systems are made to deliver therapeutically effective medication concentrations in the bloodstream for a prolonged length of time. Therapeutic benefits of a properly designed SR dosage form may also include low cost, simple processing, greater effectiveness, less side effects, variability in terms of the variation of release profiles possible, increased convenience, and patient compliance.[4,5]

Diabetes is a chronic illness that originates when the pancreas either produces insufficient amounts of insulin or when the body cannot fully utilize the insulin that it does. Diabetes is a serious issue in India, where it influences an estimated 8.7% of people in the age group of 20 and 70. Effective

Address for correspondence:
Sudarshan B. Kakad, Research Scholar,
Bhagwant University, Ajmer, Rajasthan, India.
E-mail: sudarshankakad1990@gmail.com

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clinical maintenance of type II diabetes needs continuous administration of oral hypoglycemic medications. Better systemic drug availability, maintaining drug plasma concentrations, and patient adherence to recommended treatments are all necessary for better control of the illness.[6]

Metformin HCl, single most important biguanide still in use today, is efficacious in minimizing hepatic glucose production and peripheral insulin resistance in people with Type II diabetes. It is an oral anti-hyperglycemic regimen with a 6.2-h plasma half-life, 50% to 60% absolute bioavailability, and inadequate gastrointestinal absorption.[7,8]

The medications are placed in a matrix system, which is the method of drug release control that is most often used. The versatility of hydrophilic polymer matrix systems in achieving a desired drug release profile, economic effectiveness, and regulatory approval makes them commonly used in oral controlled drug delivery. The major objective of this research was to develop metformin HCl hydrophilic polymer-based matrix SR tablets with controlled drug release.

MATERIALS AND METHODS

Metformin HCl was received as gift sample, while all other chemicals of analytical grade were procured from the market.

Preformulation studies

Drug Identification and Characterization[9,10]

1. Melting point determination
2. Fourier transform infrared (FTIR) analysis
3. UV spectrophotometric analysis
4. Solubility determination

Preparation of granules and optimization of formulation

Preparation of granules for compression[11,12]

Through a wet-granulation technology, sustained-release Metformin HCl matrix tablets were developed. Different formula was designed using varying hydrophilic polymers and its concentration as well as its binder concentration. Weigh Metformin HCl, HPMCK100M, and Avicel as per composition [Table 1], mixed homogeneously and passed through sieve. Prepare the mass of mixture using PVP K30 binder solution. Wet mass passed through a sieve to get a uniform size granules and dried at 60°C. The obtained granules mixed with magnesium stearate, Aerosil. After evaluation of pre-compression parameters, compression was done on eight stations single rotary press machine. Formulations were evaluated for post-compression parameters.

Evaluation of pre-compression parameters[13]

Bulk density: Bulk Density was calculated by employing the formula below.

$$\text{Bulk density} = \frac{M}{Vb}$$

Where, M = mass/weight of powder taken (g) and Vb=bulk Volume (cm^3)

Tapped density: Tapped density was calculated using following formula

$$\text{Tapped density} = \frac{M}{Vt}$$

Where, M = mass/weight of powder taken (g) and Vt = tapped volume (cm^3)

Carr's index or compressibility index: It was calculated from bulk density and tapped density as per following formula:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio: Ratio of tapped density to bulk density is also a measure of flow properties and is termed as Hausner ratio.

$$\text{Hausners ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose: Angle of repose is determined by funnel method using following formula.

$$\tan\theta = \frac{h}{r}$$

h = height of the pile and r = radius of powder cone

Evaluation of post-compression parameters[14,15]

Weight variation: The average weight of 20 tablets was calculated after each one was weighed. The weight of each tablet was compared to the weight of all tablets combined. For sustained-release tablet, tablet weight is 850.00 mg and the maximum percent difference allowed is 5.0%, that is ±42.5 mg.

Friability test: Friability for the sustained-release tablets was determined by 100 revolutions at 25 rpm. Friability of the tablets should be <1%.

Hardness: Tablet was selected at random from individual formulations and hardness was measured using digital hardness tester.

Assay: Standard solution of Metformin HCl (100PPM) was prepared by dissolving 10 mg of drug in 100 ml distilled water. For preparation of sample solution, ten tablets are crushed in mortar and pestle. Tablet powder equivalent to

10 mg of drug was weighed and dissolve in 100 ml distilled water. Take absorbance on UV at 232 nm and concentrations were determined.[16]

Dissolution test: The tablets were evaluated for *in vitro* drug release was carried out using USP dissolution apparatus.

The following conditions were applied.

USP Dissolution apparatus: Type II (Paddle)

Media: pH 6.8 buffer

Volume of dissolution medium: 900 ml

Speed of paddle rotation: 75 RPM

Temperature: 37 ± 0.5°C

Sampling point: 1, 2, 4, 6, 8, 10 and 12 h

The dissolution profiles of test batches were compared with marketed product. Comparison between marketed product and test batches was done using two statistical factors called difference factor (f1) and similarity factor (f2).

The difference factor (f1) calculate the percentage difference between two profiles, that is, standard dissolution profile and test sample dissolution profile at each sampling points and corresponds to a relative error measure between the two profiles.

f1 value should lie between 0 and 15. Ideally, it should be as closer as possible to 0.

The similarity factor (f2) was defined by CDER and FDA as the"logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products".

It was calculated from the mean dissolution data according to the following equation.

$$F_2 = 50 \text{ X } \log \{[1- (1/n) \Sigma^{n}_{t=1}(R_t - T_t)^2]^{-0.5} \text{ X } 100\}$$

n - Number of time points
R_t - The reference profile at the time point t
T_t - The test profile at the same point.

RESULTS AND DISCUSSION

Drug identification and characterization

1. Melting point determination: Melting point of the drugs was found 223–226ºC.
2. FTIR analysis: A FT-IR spectrum of pure drug as shown in Figure 1.

FTIR of Metformin HCl showed characteristic sharp peaks at 3119, 3290, 3356 cm-1 due to N-H stretching vibrations, 1059 and 1156 cm-1 corresponding to C-N stretching, and 634 cm-1 due to N-H wagging. The peaks observed in the FTIR spectra of pure drug were found to be matching with reported values for Metformin HCl, thus confirming identity and purity of drug.

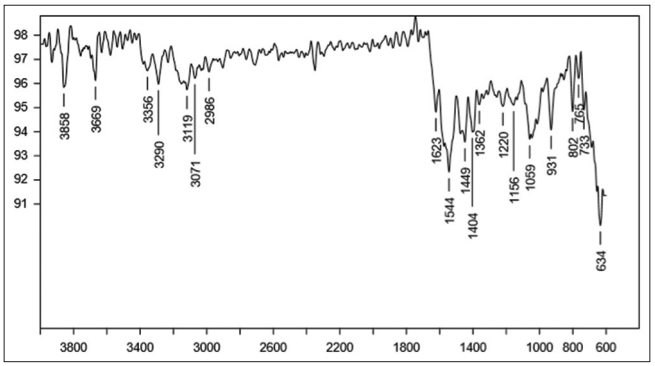

Figure 1: FTIR of pure metformin HCl

Table 1: Metformin HCl sustained-release formulations

Ingredients	Quantity/tablet (mg)								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
Metformin HCl	500	500	500	500	500	500	500	500	500
HPMC K4 M	160	200	240	-	-	-	-	-	-
HPMC K15M	-	-	-	160	200	240	-	-	-
HPMC K100 M	-	-	-	-	-	-	160	200	240
Lactose monohydrate	145	90	35	145	90	35	145	90	35
PVP K30	15	30	45	15	30	45	15	30	45
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Avicel	15	15	15	15	15	15	15	15	15
Total (mg)	850	850	850	850	850	850	850	850	850

Table 2: Evaluation of pre-compression parameter

Batch No.	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index(%)	Hausner ratio
1	27.59	0.8169	0.9541	14.38	1.1679
2	26.00	0.8064	0.9293	13.22	1.1524
3	25.51	0.7861	0.8992	12.57	1.1438
4	27.07	0.8143	0.9433	14.22	1.1657
5	26.02	0.8064	0.9259	12.49	1.1526
6	25.01	0.7886	0.8896	11.35	1.1280
7	27.07	0.8116	0.9328	12.99	1.1493
8	26.00	0.8012	0.9191	12.82	1.1471
9	24.07	0.7812	0.8650	9.68	1.1072

Table 3: Evaluation of post-compression parameter

Batch No.	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	Assay (%)	Friability (%)
1	852±1.52	7.00±0.01	7.6	99.6	0.56
2	853±1.33	7.10±0.02	7.7	101.3	0.48
3	848±1.52	6.90±0.01	7.9	100.5	0.42
4	854±1.15	7.10±0.01	7.3	98.8	0.52
5	851±1.76	7.00±0.01	7.4	100.2	0.47
6	849±1.15	7.00±0.01	7.8	102.6	0.43
7	854±1.45	7.10±0.01	7.6	98.9	0.51
8	851±1.20	7.00±0.01	7.8	99.7	0.47
9	849±0.88	6.90±0.01	7.9	100.2	0.39

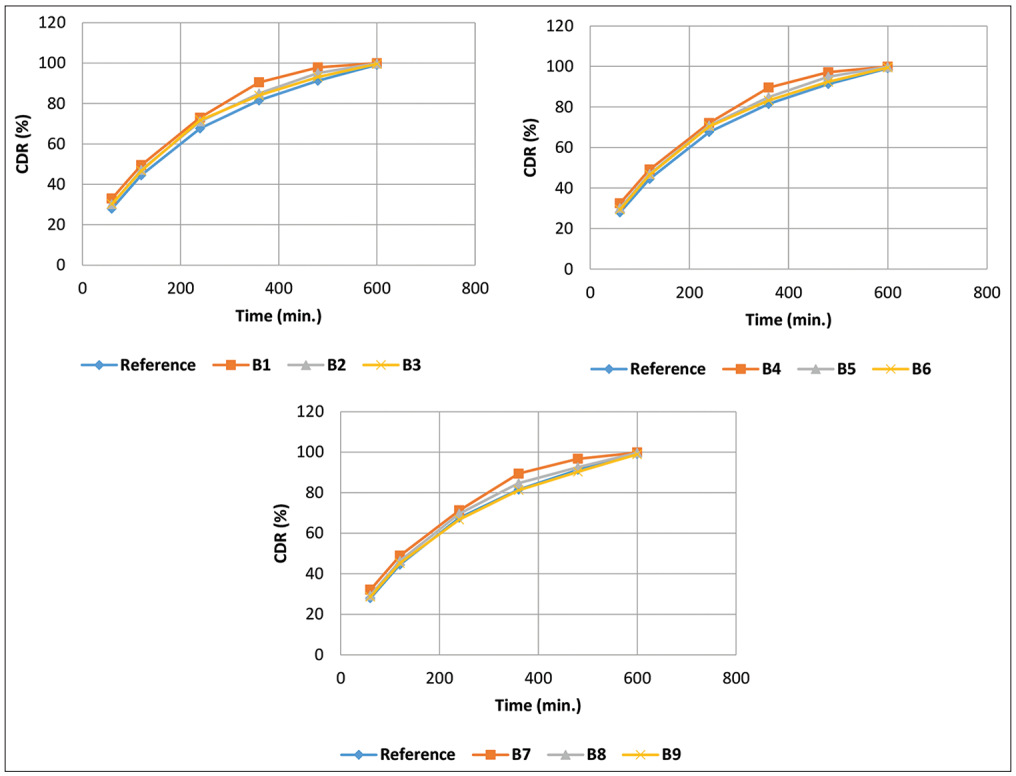

Figure 2: *In vitro* drug release of metformin HCl from trial formulations

Table 4: Dissolution profiles

Time (min.)	% Cumulative drug release									
	Reference	B1	B2	B3	B4	B5	B6	B7	B8	B9
60	27.92	32.92	30.16	30.24	32.46	30.08	29.32	32.14	29.28	28.62
120	44.46	49.46	47.08	46.66	49.14	46.96	46.54	48.9	46.36	45.24
240	67.64	73.02	71.14	71.78	72.06	70.82	70.43	71.26	69.68	66.76
360	81.48	90.44	84.96	83.98	89.58	84.86	83.23	89.42	84.72	81.24
480	91.28	97.84	95.06	93.12	97.12	94.96	92.44	96.74	92.58	90.34
600	99.12	99.98	99.86	99.54	99.92	99.82	99.42	99.86	99.76	98.96

Optimization of formulation

Pre-compression parameter evaluation

Pre-compression Parameters: It was observed that with increase in concentration of HPMC polymer the flow properties of granules were improved from B1 to B9 batch, exhibiting good flow properties and compressibility. Angle of repose, Carr's index and housner's ratio increases with increasing concentration of hydrophilic polymer. Granules of B9 batch showed excellent flow and compression properties [Table 2].

Post-compression parameter evaluation

Post-compression Parameters: Evaluation of post compression parameters of tablet formulations showed that increase in amount of concentration of HPMC polymer and binder concentration PVP K30 increases hardness and decreases % friability of tablets. Batch S3 showed more hardness [Table 3].

In vitro drug release

In contrast to conventional sustained-release tablets of metformin HCl, trial batches made using various hydrophilic polymer types and concentrations as well as changing binder concentrations had their cumulative drug release measured in percent (%). In comparison to the other trial batches, the drug release for batches B3, B6, and B9 was delayed [Table 4]. The release profile of the commercial formulation was equivalent to the *in vitro* drug release of metformin HCl in batches B6 and B9. However, the formulation B9's drug release was highly comparable to that of the reference sustained-release Metformin HCl tablet [Figure 2].

CONCLUSION

The purpose of the present study was to formulate and evaluate sustained-release matrix tablet of Metformin HCl containing hydroxyl propyl methylcellulose as hydrophilic polymer and PVP K30 binder. Using the wet granulation process, sustained-release tablets were developed. Three trial batches are prepared to optimize the concentration of HPMC K4M in the first stage. The concentration of HPMC K15M and HPMC K100M is optimized in the second and third stages in the same manner. The PVP K30 and HPMC amounts are good. For an *in vitro* drug release analysis in phosphate buffer solution at pH 6.8, the drug release of each modified HPMC batch was compared to that of the commercial formulation. The best formulation for exhibiting sustained drug release at 10 h was Formulation B9. Obtained result conclude that, with increase in concentration of HPMC, it controls drug release in developed formulation and HPMC K100M is the best hydrophilic polymer for sustained-release matrix tablet.

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