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EFFECT OF SIX BINDERS ON THE DISSOLUTION RATE OF METFORMIN HYDROCHLORIDE TABLETS

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ABSTRACT

The objective o the present study is to evaluate the effect of six commonly used binders on the dissolution rate of metformin tablets. Tablets each containing 100 mg of Metformin hydrochloride were formulated employing six commonly used binders namely acacia, starch paste, poly vinyl pyrollidine (PVP K30), sucrose, methyl cellulose LV and hydroxy propyl methyl cellulose (HPMC E5LV). For comparison purpose all the binders were used at the same strength, 2% w/v in the formula. The tablets were prepared by wet granulation method. All the tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods. All the metformin tablets prepared using various binders disintegrated with in 2 min. Tablets formulated using acacia and sucrose as binders disintegrated very rapidly in 30 and 40 sec respectively when compared to others. Many variations were observed in the dissolution characteristics of the metformin hydrochloride tablets prepared and commercial brands tested. The binder used has significantly influenced the dissolution rate of metformin tablets prepared. Among all, tablets formulated using acacia and commercial product C3 gave rapid and higher dissolution of metformin hydrochloride. The order of increasing dissolution rate (K_1) observed with various binders was acacia = C3 > starch paste > sucrose> methyl cellulose > PVP K30> C1 > C2 > HPMC. Tablets formulated using HPMC as binder and commercial brands C1and C2 gave relatively low dissolution of metformin hydrochloride. All the metformin tablets prepared and the three commercial brands tested fulfilled the dissolution rate specification of NLT 70% in 45min prescribed for metformin tablets in IP 2010. Hence acacia, starch paste, poly vinyl pyrollidine (PVP K30), sucrose and methyl cellulose LV are recommended as binders for the preparation of metformin hydrochloride tablets.

Key words: Metformin hydrochloride, Tablets, Binder, Dissolution rate

INTRODUCTION

Metformin hydrochloride is a widely prescribed oral anti diabetic drug used for the treatment of type II diabetes mellitus. Metformin hydrochloride and its tablets are official in IP 2010. Though metformin hydrochloride is freely soluble in water, IP 2010 prescribed a dissolution rate test specification of NLT 70% in 45 min for metformin tablets. In the case of tablet dosage form the formulation additives or excipients greatly influence the dissolution rate of poorly soluble as well as freely soluble drugs. In tablet formulation the binder and disintegrant are critical ingredients that influence the dissolution rate of drugs from tablets[1]. Several studies reported[2-7] the effect of binders and disintegrants on the dissolution rate of drugs from tablet dosage forms. When three brands of metformin tablets procured from the local market were tested for dissolution rate, much variation was observed as shown in Fig.1. The differences observed in the dissolution rate of different brands of metformin tablets are due to formulation variables. The objective of the present study is to evaluate the effect of Six commonly used binders on the disintegration and dissolution rate of metformin tablets. Metformin tablets were formulated and prepared employing six binders namely acacia, starch paste, poly vinyl pyrollidine (PVP K30), sucrose, methyl cellulose LV and hydroxy propyl methyl cellulose (HPMC E5LV) and the tablets were evaluated for various tablet parameters including dissolution rate to evaluate the effect of binders.

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EXPERIMENTAL

Materials:

Metformin hydrochloride was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Lactose, acacia, potato starch as paste (10% w/w), poly vinyl pyrollidine (PVP K30), sucrose, methyl cellulose LV and hydroxy propyl methyl cellulose (HPMC E5LV), Primojel, talc, magnesium stearate were procured from commercial sources. The following three brands of Metformin tablets were procured from local market. C1: Glyciphage (tablets each containing 500mg of metformin hydrochloride manufactured by Franco India, B.No. GA14074; Mfg Dt.04/2014; Exp. Dt. 03/2017). C2: Okamet-500 (tablets each containing 500mg of metformin hydrochloride manufactured by Cipla Ltd, B.No. AH3461; Mfg Dt.11/2013; Exp. Dt. 10/2017).

C3: Almetfor -500 (tablets each containing 500mg of metformin hydrochloride manufactured by Alkem Laboratories, B.No. ATMT1206; Mfg Dt.08/2012; Exp. Dt. 07/2015). All other materials used were of pharmacopoeial grade.

Methods:

Estimation of Metformin hydrochloride:

An UV Spectrophotometric method based on the measurement of absorbance at 233nm in phosphate buffer of pH 6.8 was used for the estimation of metformin hydrochloride. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 1.2 % and 1.60% respectively. No interference by the excipients used in the study was observed.

Preparation of Metformin hydrochloride Tablets:

Metformin hydrochloride (100 mg) tablets were prepared by wet granulation method as per the formula given in Table 1 using six different binders. The required quantities of metformin hydrochloride, lactose and binder as per the formula in each case were blended thoroughly in a dry mortar and granulated with water (q.s) as granulating fluid. The wet mass formed was pressed through mesh no.12 to obtain wet granules. The wet granules were dried at 60^0 C for 1hour. The dried granules were passed through mesh no.14 to break the aggregates formed and to obtain discrete granules. Super disintegrant, Primojel, talc and magnesium stearate were passed through mesh no.80 and collected on to the bed of tablet granulations prepared and mixed. The tablet granules were blended thoroughly in a closed polyethene bag and compressed in to 230 mg tablets using an 8- station RIMEK tablet punching machine employing 9 mm flat punches.

Evaluation of Tablets:

Metformin hydrochloride tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods.

Hardness:

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability:

The friability of the tablets was measured in a Roche friabilator using the formula

Friability = [(Initial weight- Final weight) / (Initial weight)] x 100%

Drug Content:

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of metformin hydrochloride was taken into 100 ml volumetric flask, dissolved in water and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8and assayed for metformin hydrochloride at 233 nm.

Disintegration time:

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study:

Dissolution rate of metformin hydrochloride tablets prepared was studied in phosphate buffer of pH 6.8(900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for metformin hydrochloride at 233 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data:

The dissolution data were analysed as per zero order and first order kinetic models. Dissolution efficiency (DE_{20}) values were estimated as suggested by Khan [8].

RESULTS AND DISCUSSION

The objective o the present study is to evaluate the effect of six commonly used binders on the dissolution rate of metformin tablets. Tablets each containing 100 mg of Metformin hydrochloride were formulated employing six commonly used binders namely acacia, starch paste, poly vinyl pyrollidine (PVP K30), sucrose, methyl cellulose LV and hydroxy propyl methyl cellulose (HPMC E5LV). For comparison purpose all the binders were used at the same strength, 2% w/v in the formula. The tablets were prepared by wet granulation method as per the formulae given in Table 1.

All the tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods. The physical parameters of the metformin hydrochloride tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.74 % in all the cases. Metformin hydrochloride content of the tablets prepared was within 100±3 %. All the metformin tablets prepared disintegrated with in 2 min. Tablets formulated using acacia and sucrose as binders disintegrated very rapidly in 30 and 40 sec respectively. Dissolution rate of metformin hydrochloride from the tablets prepared was studied in phosphate buffer of pH 6.8 as prescribed in IP 2010. For comparison three commercial brands of metformin tablets were also evaluated for dissolution rate. Much variation was observed in the dissolution characteristics of the metformin hydrochloride tablets prepared and commercial brands tested. The dissolution profiles of the metformin tablets prepared and commercial tablets are shown in Figs.1-2 and the dissolution parameters are given in Table 3. Dissolution of metformin hydrochloride from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.945. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. When three brands of metformin tablets procured from the local market were tested for dissolution rate, much variation was observed as shown in Fig.1. The differences observed in the dissolution rate of the three brands of commercial metformin tablets are due to formulation variables. The dissolution profiles of metformin tablets prepared employing various binders are shown in Fig.2. The dissolution parameters are summarized in Table 3. Though all the binders were used at the same strength of 2% w/w,

difference were observed in the dissolution parameters of tablets prepared. The binder used has significantly influenced the dissolution rate of metformin tablets prepared. Among all tablets formulated using acacia and commercial product C3 gave rapid and higher dissolution of metformin hydrochloride. The order of increasing dissolution rate (K_1) observed with various binders was acacia = C3 > starch paste > sucrose> methyl cellulose > PVP K30> C1 > C2 > HPMC. All the dissolution parameters estimated (PD_{10}, $K_1$and DE_{20}) indicated rapid dissolution of metformin hydrochloride from the commercial brand C3 and tablets formulated using acacia, starch paste, sucrose, methyl cellulose and PVP K30 as binders. Tablets formulated using HPMC as binder and commercial brands C1and C2 gave relatively low dissolution of metformin hydrochloride. However all the metformin tablets prepared and the three commercial brands tested fulfilled the dissolution rate specification of NLT 70% in 45min prescribed for metformin tablets in IP 2010. Hence acacia, starch paste, poly vinyl pyrollidine (PVP K30), sucrose and methyl cellulose LV are recommended as binders for the preparation of metformin hydrochloride tablets.

CONCLUSIONS

1.All the metformin tablets prepared using various binders disintegrated with in 2 min. Tablets formulated using acacia and sucrose as binders disintegrated very rapidly in 30 and 40 sec respectively when compared to others.

2. Much variations were observed in the dissolution characteristics of the metformin hydrochloride tablets prepared and commercial brands tested.

3. The binder used has significantly influenced the dissolution rate of metformin tablets prepared.

4. Among all, tablets formulated using acacia and commercial product C3 gave rapid and higher dissolution of metformin hydrochloride.

5. The order of increasing dissolution rate (K_1) observed with various binders was acacia = C3 > starch paste > sucrose> methyl cellulose > PVP K30> C1 > C2 > HPMC.

6. Tablets formulated using HPMC as binder and commercial brands C1and C2 gave relatively low dissolution of metformin hydrochloride.

7. All the metformin tablets prepared and the three commercial brands tested fulfilled the dissolution rate specification of NLT 70% in 45min prescribed for metformin tablets in IP 2010.

8. Hence acacia, starch paste, poly vinyl pyrollidine (PVP K30), sucrose and methyl cellulose LV are recommended as binders for the preparation of metformin hydrochloride tablets.

Table 1: Formulae of Metformin Tablets Prepared Employing Various Binders

Ingredient (mg/ tablet)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Metformin Hcl	100	100	100	100	100	100
Acacia	4.6	-	-	-	-	-
PVP K30	-	4.6	-	-	-	-
Potato starch as paste (10 % w/w)	-	-	4.6	-	-	-
Methyl cellulose LV	-	-		4.6	-	-
HPMC E5LV	-	-	-	-	4.6	-
Sucrose	-	-	-	-	-	4.6
Primogel	9.2	9.2	9.2	9.2	9.2	9.2
Lactose	107	107	107	107	107	107
Talc	4.6	4.6	4.6	4.6	4.6	4.6
Magnesium stearate	4.6	4.6	4.6	4.6	4.6	4.6
Total weight (mg)	230	230	230	230	230	230

Table 2: Physical Parameters of Metformin Tablets Prepared

Formulation	**Hardness (Kg/cm^2)**	**Friability (% Wt loss)**	**Disintegration Time (min-sec)**	**Drug Content (mg/tablet)**
F_1	5.0	0.56	0-30	99.6
F_2	4.5	0.67	1-15	99.2
F_3	4.7	0.74	1-40	100.3
F_4	5.0	0.71	1-20	100.9
F_5	4.8	0.72	1-50	98.9
F_6	5.0	0.70	0-40	99.5

Table 3: Dissolution Parameters of Metformin Tablets Prepared Employing Various Binders

Formulation	PD_{10} (%)	DE_{20} (%)	K_1 (min^{-1})
F_1	100	83.63	0.391
F_2	85.61	72.68	0.193
F_3	32.67	30.04	0.039
F_4	97.12	83.98	0.354
F_5	95.67	84.25	0.314
F_6	88.93	75.91	0.220
C1	70.78	64.43	0.123
C2	50.51	44.80	0.070
C3	100	86.18	0.391

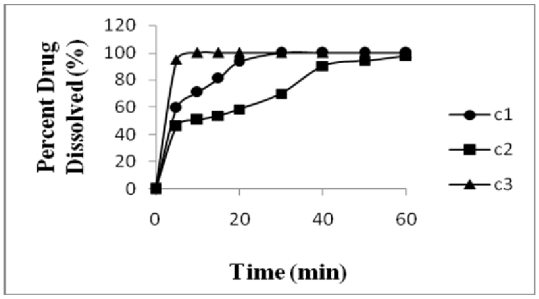

Fig.1 Dissolution Profiles of Commercial Brands of Metformin Tablets

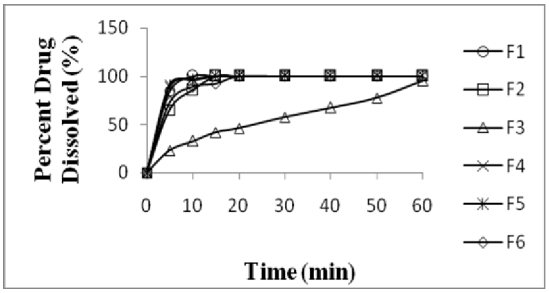

Fig.2: Dissolution Profiles of Metformin Tablets Prepared With Various Binders

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