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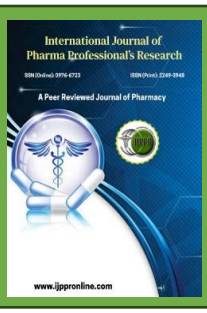

Fabrication, Evaluation and Comparison of Metformin Tablets by Using Different Binders Effect on The Dissolution Rate

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ABSTRACT

The objective of the present study is to evaluate the effect of commonly used binders on the dissolution rate of metformin tablets. Tablets each containing 100 mg of Metformin hydrochloride were formulated employing commonly used binders namely acacia, starch paste, polyvinyl 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 in30 and 40sec 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.

Keywords: *Metformin hydrochloride, Tablets, Binder, Dissolution rate*

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1. Introduction

Diclofenac Sodium is sodium salt of [o-(2, 6-dichloro aniline) phenyl] acetate and is a potent Non-Steroidal Anti-Inflammatory Drug (NSAID).[1] DS or sodium 2-[(2,6-dichlorophenyl) amino]phenyl- acetate, is a broadly used non-steroidal anti-inflammatory drug for the treatment of inflammatory conditions such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[2] NSAIDs are agents having anti-inflammatory, analgesic and antipyretic effects. These drugs are used frequently and commonly in humans as well as in animals to manage pain, fever and inflammation for the treatment of different clinical conditions such as rheumatic disorders, musculoskeletal disorders, sports injuries, muscular cramps and other syndromes involving pain and inflammation. Its pharmacological effects are believed to be due to blocking the conversion of arachidonic acid to prostaglandins by inhibiting cyclo-oxygenase enzymes. Diclofenac Sodium is almost completely absorbed after oral administration. However, due to its first-pass metabolism, only about 50% of the absorbed dose is systematically available. The half-life of Diclofenac Sodium in plasma varies from1-3h, with mean peak plasma levels of approximately 0.5µg/ml and 1.0µg/ml occurring after about 2 h after a single dose of 25 mg and 50 mg of enteric-coated tablets respectively. About 99% of the drug is bound to human plasma proteins, mainly albumin.[3] It is 99% bound to human serum proteins. It diffuses into and out of synovial fluid. It is eliminated through urinary and biliary excretion of the glucuronide and the sulphate conjugates of the metabolite. Diclofenac Sodium has little anti-microbial activity and is under investigation for the treatment of tuberculosis. This is also used to treat chronic pain associated with cancer. It may prevent the development of Alzheimer disease if given daily in small doses for many years. Diclofenac Sodium also acts asanti- uricosuric agent. Dosage form testing, development of the improved dosage form and determination of drug in biological samples is required in pharmaceutical industry and research.[4] It is available in the various formulations such as injections, tablets, gel, suppositories and powdered form (Figure 1).[5-6]

C3	100	86.18	0.391

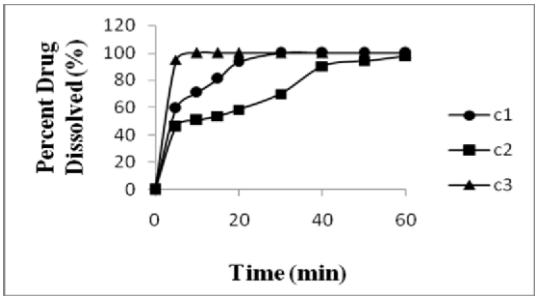

Figure 1: Dissolution profiles of commercial brands of metformin tablets

2. Materials and Methods

2.1 Materials:

Metformin hydrochloride was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Lactose, acacia, potato starch as paste (10% w/w), polyvinyl pyrollidine (PVP K30), sucrose, methyl cellulose LV and hydroxy propyl methyl cellulose (HPMCE5LV), 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, C2: Okamet-500 (tablets each containing 500mg of metformin hydrochloride manufactured by Cipla Ltd, C3: Almetfor -500 (tablets each containing 500mg of metformin hydrochloride manufactured by Alkem Laboratories. All other materials used were of pharmacopoeial grade.

2.2 Methods:

2.2.1 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.

2.3 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 meshno.80 and collected onto 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.

Table1:Formulae of MetforminTablets Prepared EmployingVariousBinders

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	-	-	-	-	-
PVPK30	-	4.6	-	-	-	-
Potato starch as paste (10%w/w)	-	-	4.6	-	-	-
Methylcellulose LV	-	-		4.6	-	-
HPMCE5LV	-	-	-	-	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

Table2: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

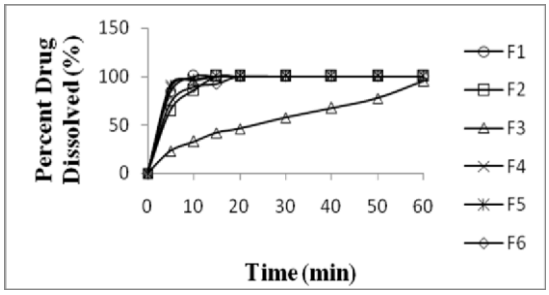

Figure 2: Dissolution profiles of metformin tablets prepared with various binders

2.4 Evaluation of Tablets

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

2.4.1 Hardness:

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

2.4.2 Friability:

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

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

2.4.3 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 6.8 and assayed for metformin hydrochloride at 233 nm.

2.4.4 Disintegration time:

The disintegration time of the tablets was determined using a single-unit disintegration test apparatus (Make: Paramount) employing water as the test fluid. Dissolution Rate Study:

The dissolution rate of metformin hydrochloride tablets prepared was studied in phosphate buffer of pH 6.8(900 ml) employing a station dissolution rate test apparatus (LAB INDIA, DS8000) using a paddle stirrer at 50rpm 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).

2.5 Analysis of Data:

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

3 Result and Discussion

The objective of 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, polyvinyl pyrollidine (PVP K30), sucrose, methylcellulose 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 within 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 inFig.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 > starchpaste > 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 K30as 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.

Conclusion

All the metformin tablets prepared using various binders disintegrated within 2 minutes, with those formulated using acacia and sucrose as binders disintegrating particularly rapidly, in 30 and 40 seconds, respectively, compared to others. Significant variations were observed in the dissolution characteristics of the prepared metformin hydrochloride tablets and the commercial brands tested. The choice of binder had a notable effect on the dissolution rate, with tablets formulated using acacia and the commercial product C3 showing rapid and higher dissolution of metformin hydrochloride. The increasing dissolution rate (K1) observed for different binders was in the order: acacia = C3 > starch paste > sucrose > methyl cellulose > PVP K30 > C1 > C2 > HPMC. Tablets formulated with HPMC as a binder, along with commercial brands C1 and C2, demonstrated relatively low dissolution rates for metformin hydrochloride. However, all the metformin tablets prepared and the three commercial brands tested met the dissolution rate specification of NLT 70% in 45 minutes, as prescribed for metformin tablets in IP 2010. Consequently, acacia, starch paste,

polyvinylpyrrolidone (PVP K30), sucrose, and methyl cellulose LV are recommended as suitable binders for the preparation of metformin hydrochloride tablets.

4. Conflict of interest

The authors have no conflict of interest.

5. Acknowledgement

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