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Formulation, Development and Evaluation of Mouth Dissolving Tablets of Pioglitazone HCL

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Snehal T Hase*, Nalanda T Rangari, Sanjay R Chaudhari, Preetilata D Deshmukh

Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner.
Dist-Ahmednagar-422608, Maharashtra, India.

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ABSTRACT

The purpose of this research work was to develop antidiabetic mouth dissolving tablets of Pioglitazone HCL. Tablets containing pioglitazone, sodium starch glycolate & crospovidone were prepared by direct compression technique. The tablets were evaluated for weight variation, hardness, percentage friability, wetting time and disintegration time. Eight formulation having superdisintegrants in different concentration levels were prepared to access their efficiency and critical concentration level. Tablets containing sodium starch glycolate along with crospovidone is showing excellent results as compare to other formulations.

INTRODUCTION

Scientists have developed innovative drug delivery systems known as "melt in mouth" or "mouth dissolve (MD)" tablets. Fast dissolving tablets disintegrate/dissolve/disperse quickly in saliva. Fast dissolving tablets can be administrated without water, anywhere, anytime to geriatric and paediatric patients. They are also suitable for mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice[1-2]. Pioglitazone is a prescription drug of the class thiazolidinedione with hypoglycemic (antihyperglycemic, antidiabetic) action. Pioglitazon HCL is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. Pioglitazon HCL is a basic (pKa = 12.06) which is practically insoluble in water and alkaline buffer solutions, but as per the Biopharmaceutical Classification System (BCS) Pioglitazon HCL categorized as class II drug. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 3-7 hrs. Formulations for Pioglitazon HCL for better control of blood glucose levels to prevent hypoglycemia enhance clinical efficacy and patient compliance. Pioglitazone HCL reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream. Following oral administration, in the fasting state, Pioglitazone HCL is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

MATERIALS

The drug Pioglitazone HCL was a generous gift sample from Concept Pharmaceuticals Pvt. Ltd., Aurangabad. Sodium starch glycolate, crospovidone, HPMC, xylitol, magnesium stearate, Talc were supplied by S. D. Fine Chemicals (Mumbai). Other reagents and organic solvents used were of analytical grade.

METHODS

Mouth dissolving tablet of Pioglitazone HCL was prepared by direct compression method by using superdisintegrant sodium starch glycolate, crospovidone together with binding agent like HPMC. Magnesium stearate and talc were used as lubricants.

PREPARATION OF MOUTH DISSOLVING TABLET

Direct compression, one of these techniques, requires the incorporation of a superdisintegrants into the formulation, or the use of highly water-soluble excipients to achieve fast disintegration of tablets[3-4]. Pioglitazone mouth dissolving tablets were prepared according to the formulae given in Table 1. The raw materials were passed through a sieve (40 mesh) prior to mixing. Pioglitazone HCl (30 mg) was mixed with the other excipients and compressed on a 8 station tablet machine (Jaguar JM-D) equipped with round 8 mm punches[5].

Table No.1 Preparation of Mouth Dissolving Tablet

Formulation ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)
Pioglitazone	30	30	30	30	30	30	30	30
Sodium starch glycolate	-	6	6	10	8	4	6	8
Crosprovidone	5	–	5	10	7.5	7.5	5	8
HPMC	90	90	90	90	90	90	90	90
Xylitol	70	69	65	55	59.5	63.5	55	56
Mg.Stearate	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2

DRUG EXCIPIENT INTERACTION STUDY

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT-IR)

FT-IR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drug and polymers. Physical mixtures comprising of drug and polymers

in a ratio of 1:1 were prepared by triturating in mortar and pestle. Samples were subjected to FT-IR studies using Brucker alpha instrument and the IR spectrum of pure drug and drug-excipient mixtures were compared to find any interaction between drug and excipients used for the formulation of mouth dissolving tablets of Pioglitazone HCl.

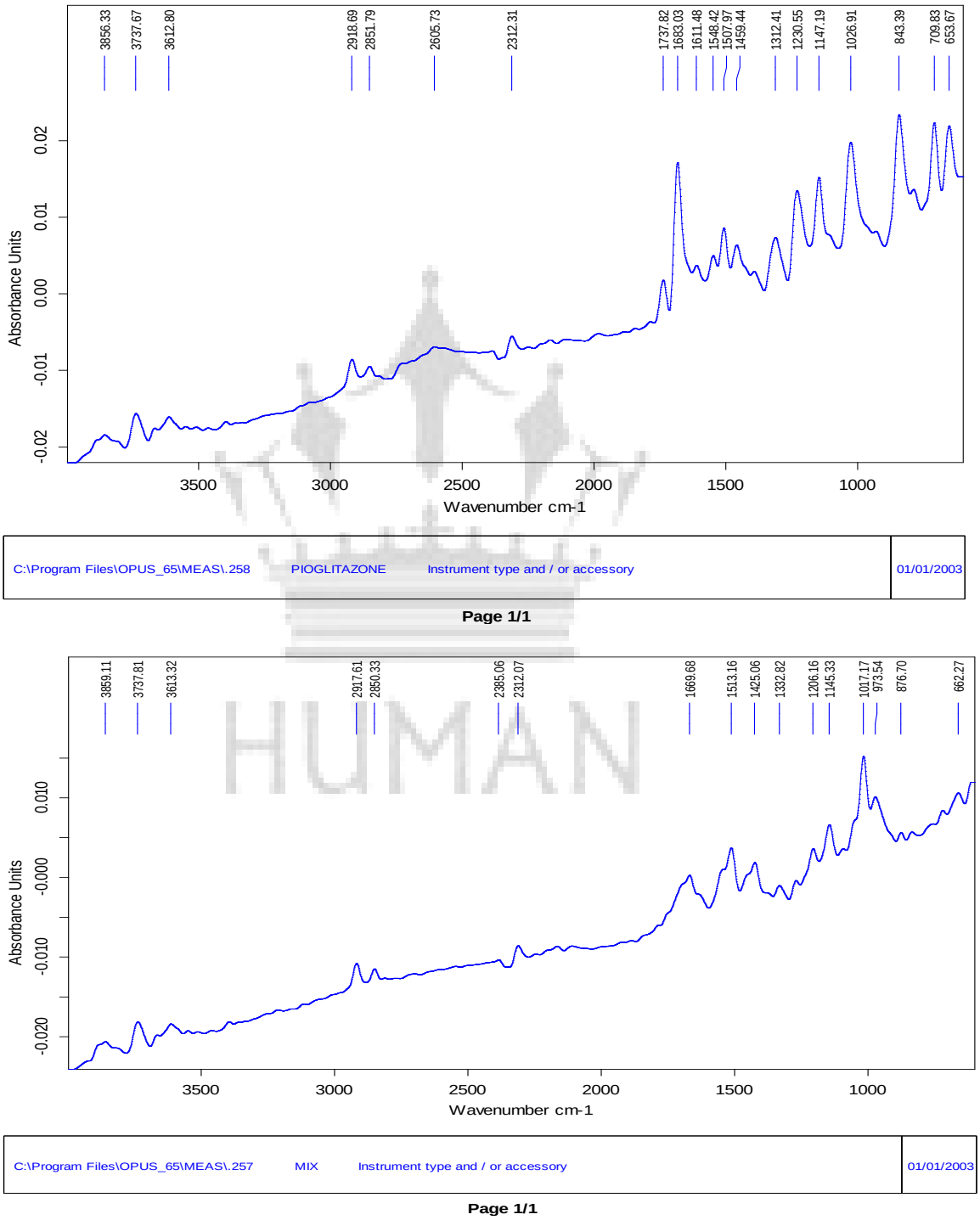

Fig No. 01: FTIR Data of Pure Drug and excipients

MICROMERITICS STUDIES OF BLEND

The blend were characterized by their Micromeritics properties, such as, bulk density, tapped density, Carr's compressibility index, Hausner ratio and flow property.

Bulk Density

The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm^3. The sample of about 10 cm^3 of powder was carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$\mathbf{D_f = M / Vp}$$

Where, D_f = bulk density

M = weight of samples in grams

Vp = final volumes of granules in cm^3.

Tapped Density

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. The sample of about 10 cm^3 of powder is carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$\mathbf{D_o = M / Vp}$$

Where, D_o = bulk density

M = weight of samples in grams

Vp = final tapped volumes of granules in $cm.^3$

Carr's Index

The percentage compressibility of microspheres was calculated according to equation given below:

$$\% \text{ Compressibility} = \frac{D_o - D_f}{D_o} \times 100$$

Where, D_f = bulk density; Do = Tapped density.

Table No. 02: Relationship between % compressibility and flowability

% Compressibility	Flowability
5 - 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 - 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

Hausner ratio

The hausner ratio of a microsphere was calculated according to equation given below:

$$\textbf{Hausner ratio} = D_o / D_f$$

D_o = Tapped density

D_f = bulk density

Angle of repose

The Angle of repose (θ) i.e. flow property of the microspheres, which measures the resistance to particle flow, was calculated as

$$\tan \theta = 2H / D$$

Where, 2H / D is the surface area of the freestanding height of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

Table No 03. Micromeritics Analysis of Blend

Parameter	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	Compressibility Index	Angle of Repose
F1	0.385±0.003	0.447±0.003	1.117±0.004	14.96±0.003	23.35±0.001
F2	0.395±0.025	0.449±0.004	1.109±0.002	14.50±0.003	23.50±0.002
F3	0.401±0.004	0.452±0.003	1.115±0.003	14.60±0.002	24.50±0.003
F4	0.388±0.002	0.510±0.003	1.120±0.003	14.90±0.002	23.90±0.004
F5	0.420±0.002	0.447±0.004	1.16±0.002	15.2±0.003	24.10±0.004
F6	0.396±0.003	0.449±0.004	1.210±0.003	14.90±0.004	24.01±0.003
F7	0.366±0.004	0.463±0.003	1.178±0.003	15.1±0.002	23.98±0.004
F8	0.402±0.005	0.482±0.002	2.014±0.002	14.78±0.003	24.20±0.004

***Each sample was analyzed in triplicate (n = 3).**

EVALUATION OF PHYSICAL PROPERTIES OF MOUTH DISSOLVING TABLET[6-7]

WEIGHT VARIATION

Twenty tablets were randomly selected and weighed to determine the average weight and compared with individual tablet weight. The percentage weight variation was calculated.

THICKNESS

Thickness of tablets was measured with Verniar caliper.

HARDNESS

Hardness of the tablet was tested using Monsanto hardness tester for each trial. The hardness range was determined for five tablets of each batch. The hardness of tablet was expressed in kg/cm^2.

FRIABILITY

Friability of the tablet of each tablet was determined by using Roche Friabilator. For this test ten tablets were weighed and placed in friabilator which was operated for 100 revolutions at the speed of 25 revolutions per minute. The tablets were then dusted and reweighed.

DISINTIGRATION

Disintegration time of 6 tablets per batch was measured by using Electrolab Disintegration apparatus.

WETTING TIME

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10 cm diameter. Ten millilitres of water containing methylene blue, a water-soluble dye was taken in the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

Table No. 03: Evaluation of the prepared formulation batches

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Hardness (kg/cm3)	4.1+0.2	4.1+0.1	3.6+0.2	4.2+0.3	3.5+0.1	3.8+0.2	4.0+0.1	4.0+0.3
Disintegration time (sec)	62±1	59±0.5	58±0.6	59±0.4	52±0.6	61±0.5	60±0.5	67±1
Friability (%)	0.190 ±0.02	0.180 ±0.05	0.109 ±0.03	0.190 ±0.02	0.192 ±0.05	0.189 ±0.04	0.193 ±0.04	0.192 ±0.02
Weight variation	200±10	210±10	190±10	200±10	200±10	190±10	200±10	190±10
Wetting time (sec)	49±0.5	48±0.5	48±0.6	51±1.2	40±1	47±0.9	49±1.2	52±1

*** Each sample was analyzed in triplicate (n = 3).**

IN VITRO DISSOLUTION STUDIES

The *in vitro* dissolution study was performed by using aelectrolab paddle apparatus at a rational speed of 50 rpm. Exactly 900 ml pH 6.8 Phosphate buffer was used as the dissolution medium and the temperature was maintained at 37^0C. A sample (1 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 30 min and the same volume was then replaced with pre-warmed dissolution media. The samples were diluted to suitable concentration with Buffer. Absorbance of these solutions was measured at 269 nm using a UV spectrophotometer (Lab India) [11, 12].

Table No. 04: Cumulative % drug release of prepared formulation batches

Time (min)	5	10	15	20	25
	% Drug Release				
F1	70.43±0.23	78.52±0.2	89.5±0.22	90.23±0.23	93.5±0.24
F2	73.52±0.25	77.56±0.27	82.56±0.24	89.2±0.26	91.5±0.27
F3	72.98±0.26	78.2±0.24	86.6±0.23	90.2±0.25	92.6±0.26
F4	73.25±0.22	80.2±0.27	85.2±0.27	91.3±0.26	93.6±0.27
F5	79.2±0.23	86.28±0.26	93.2±0.25	96.7±0.25	98.97±0.23
F6	78.2±0.26	82.2±0.27	89.3±0.26	95.4±0.23	97.2±0.27
F7	80.2±0.25	86.2±0.26	89.9±0.24	92.8±0.23	96.7±0.26
F8	79.9±0.24	86.5±0.23	90.3±0.23	95.8±0.25	97.02±0.25

***Each sample was analyzed in triplicate (n = 3).**

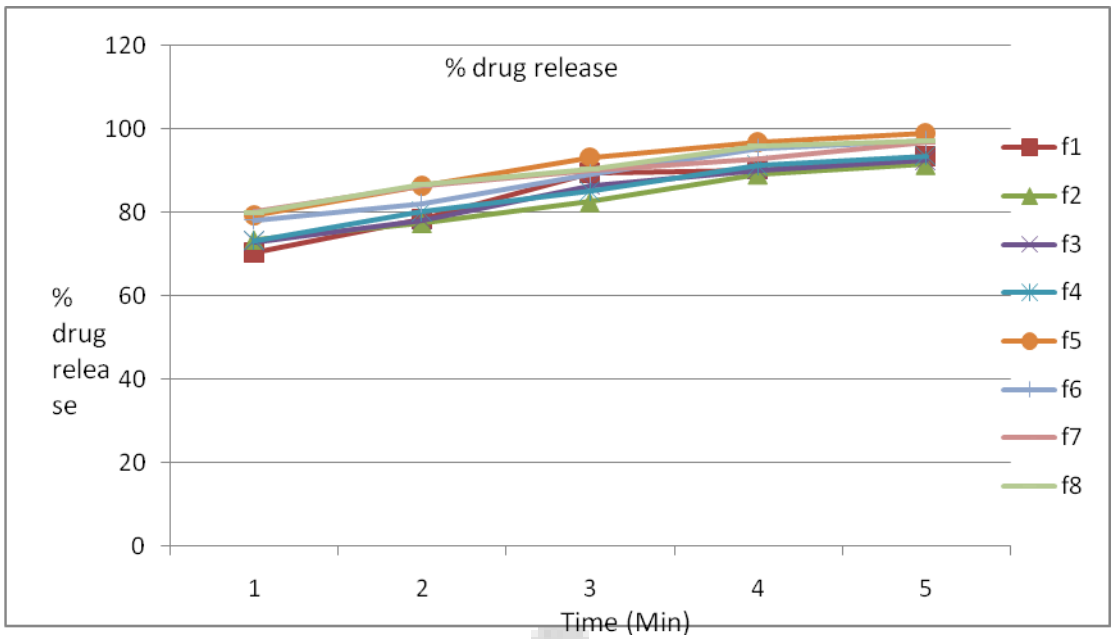

Fig No. 2: Cumulative % drug release of prepared formulation batches

RESULTS AND DISCUSSION

The preparation of fast dissolving tablets with the use of superdisintegrants is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration is reported to have an effect on dissolution characteristics as well. In this research work we have formulated total eight batches which are coded as F1, F2, F3, F4, F5, F6, F7, and F8. Out of this eight batches, batch F5 show the satisfactory result of hardness of 3.5 kg/cm^3 $\pm$ 0.2, friability 0.192$\pm$ 0.05, average weight 200 mg $\pm$10, wetting time 40 $\pm$ 1sec, disintegration time 52$\pm$ 0.6 sec and 98.97 $\pm$ 0.23% drug release. A prepared fast dissolving tablet gets dispersed in the mouth quickly and released the drug as early as compared to its formulated conventional tablets. Two different superdisintegrants namely sodium starch glycolate and crospovidone were tried to achieve fast dispersion of tablets which has been satisfactorily proved by batch F5.

CONCLUSION

In summary, it is concluded that the formulation of the Pioglitazone HCL gives satisfactory results and by the use of superdisintegrants, we achieved the Pioglitazone HCL fast dissolving

tablets. Tablets containing sodium starch glycolate along with crospovidone formulation F-5 shown fastest disintegration, as shown in (Table 1). Characteristics of tablets are further tabulated in Table 2. The study shows that the dissolution rate of Pioglitazone HCL can be enhanced to a great extent by direct compression technique with the addition of mixture of superdisintegrant.

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