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FORMULATION AND IN VITRO EVALUATION OF PIOGLITAZONE HYDROCHLORIDE MOUTH DISSOLVING TABLETS

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ABSTRACT

The purpose of this research work was to develop antidiabetic mouth dissolving tablets of Pioglitazone HCL thereby enhancing the dissolution rate. Tablets containing Pioglitazone, sodium starch glycolate & crospovidone, Croscarmellose sodium as superdisintegrants were prepared by wet granulation & direct compression techniques. The tablets were evaluated for weight variation, hardness, percentage friability, wetting time and disintegration time were showed acceptable results. Formulations F5 and F9 showed disintegration time of 23 and 22 sec respectively. Dissolution was performed in pH 1.2 Hcl buffer and formulations F5 showed maximum drug release within 30 min and drug release from F9 was more than that of the marketed drug. Hence, it could be concluded that formulation F9 showed good drug release than marketed drug. The results compared for both the technologies showed that the Pioglitazone HCL tablets prepared using wet granulation was found to have good technological properties and satisfying and reproducible drug dissolution profiles. Moreover the drug release was found to be comparable to the marketed dispersible tablet.

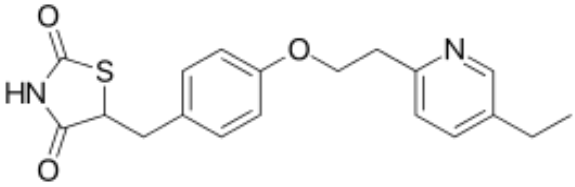
KEYWORDS: Mouth dissolving tablets, Pioglitazone, Direct compression, Wet granulation, dissolution enhancement.

INTRODUCTION

Pioglitazone hydrochloride is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus. Pioglitazone hydrochloride is a basic (pKa = 12.06) which is practically insoluble in water and alkaline buffer solutions, but as per the Biopharmaceutical Classification System (BCS) Pioglitazone 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. Delivery Systems (NDDS) aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. One such approach is oral dispersible tablet. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. Mouth dissolving tablets are also called as fast dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapid melts, porous tablets, quick dissolving etc. Mouth dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva the faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

Diabetes Mellitus (DM) is a group of syndromes and chronic metabolic disorder characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins because of a lack of or ineffective use of the hormone insulin and associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications and diminished quality of life. A fasting blood glucose level of 126 mg/dl and 200 mg/dl post prandial (oral Glucose load) is considered as indication of DM. In present work, an investigation was made to use crospovidone and sodium starch glycolate, Croscarmellose sodium as superdisintegrants in the design of mouth dissolving tablets.

Structure: Pioglitazone Hydrochloride.



Chemical name: Pioglitazone hydrochloride; 112529-15-4; Pioglitazone Hcl; U72107A; Pioglitazone (hydrochloride); 5-(4-(2-(5-Ethylpyridin-2-yl) ethoxy) benzyl) thiazolidine-2, 4-dione hydrochloride.

Pioglitazone contains not less than 90.0 per cent and not more than 110.0 per cent of C19H2ON2O3S.HCl, calculated on anhydrous basis. It is a Thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. PG is a potent and highly selective agonist for peroxisome proliferators-activated receptor-gamma (PPARg). The drug decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Thus the mouth dissolving tablets of Pioglitazone may be prepared with Croscarmellose, crospovidone and sodium starch glycolate, the well proven and acceptable polymers having least limitations.

MATERIALS AND METHODS

Materials: Pioglitazone hydrochloride was obtained as a gift sample from the Cadila Pharma Ltd., Ahmadabad, India. Sodium starch glycolate, crospovidone& Croscarmellose sodium were received as a gift sample from Hetero Pharma, Hyderabad. Other materials used were of analytical grade, and procured from commercial source.

METHODS OF PREPARATION

Development of standard calibration curve

Accurately weighed 15 mg of drug, dissolved in sufficient volume of methanol and then made up volume up to 100 ml with 0.1 N HCl, phosphate buffer and then working solutions of different concentrations (2, 4, 6, 8, 10 and 12 µg/ml) were prepared. The absorbance was obtained at λmax 269.4nm and calibration curve was plotted between concentration and absorbance.

Drug polymer compatibility studies

The pure drug and physical mixture of drug and polymers were subjected to IR spectroscopic study by using Perkin Elmer FT-IR spectrophotometer Shelton USA. KBr disc method was employed. The spectra were scanned over the wave number range from 4000 – 400 cm- ^{1}.An obtained IR spectrum of pure drug was compared with the IR spectra of its physical mixtures to know the chemical interactions between drug and excipients used in the formulation.

Formulation Development

Total of 12 Pioglitazone hydrochloride mouth dissolving tablets formulations were prepared and evaluated. Six formulations (F1 to F6) of which were prepared by direct compression method in which Crospovidone, Croscarmellose sodium & Sodium starch glycolate superdisintegrants were used. Six formulations were prepared by wet granulation method in which same superdisintegrants were used as direct compression in different ratios.

Tablets prepared by superdisintegrants addition method by direct compression method

Tablets containing 15 mg of PGTZN were prepared by direct compression method and the various formula used in this study are shown in (table 1). The drug and diluents were passed through sieve on 40. All the materials were transferred to a mortar and triturated till it was uniform.. Talc and magnesium stearate were passed through mesh number 80, mixed well and blended with initial mixture in a poly-bag .The resulting powder blend was evaluated for angle of repose, bulk density, tap density and compressibility index and compressed into tablets using single punch tablet machine.

Table 1: Composition of mouth dissolving tablets by direct compression method.

Sl.no	Ingredients	F1	F2	F3	F4	F5	F6
1	PGTZN	15mg	15mg	15mg	15mg	15mg	15mg
2	Crospovidone	4.5	-	-	4.5	-	4.5
3	Croscarmellose sodium	-	4.5	-	4.5	4.5	-
4	Sodium starch glycolate	-	-	4.5	-	4.5	4.5
5	Microcrystalline cellulose	94	94	94	90	90	90
6	Lactose	30	30	30	30	30	30
7	Talc	2.5	2.5	2.5	2	2	2
8	Magnesium stearate	2	2	2	2	2	2
9	Aspartame	2	2	2	2	2	2
	Total weight in mg	150	150	150	150	150	150

All the quantities are in mg.

Tablets prepared by superdisintegrants addition method by wet granulation method

Tablets containing 15 mg of PGTZN were prepared by wet granulation method and the various formulae used in the study are shown in the (table 2). The drug and diluents were passed through sieve no 12 and all the above ingredients were properly mixed together (in a poly-bag). Talc and magnesium stearate were passed through mesh number 80, mixed well and blended with initial mixture in a poly-bag. The resulting powder blends was evaluated for angle of repose, bulk density, tap density and compressibility index and compressed into tablets using single punch tablet machine.

Table 2: Composition of mouth dissolving tablets by wet granulation method.

Sl.no	Ingredients	F7	F8	F9	F10	F11	F12
1	PGTZN	15mg	15mg	15mg	15mg	15mg	15mg
2	Crospovidone	4.5	4.5	-	3	-	-
3	Croscarmellose sodium	4.5	-	4.5	3	3	3
4	Sodium starch glycolate	-	4.5	4.5	-	3	3
5	Microcrystalline cellulose	90	90	90	93	93	93
6	Lactose	30	30	30	30	30	30
7	Talc	2	2	2	2	2	2
8	Magnesium stearate	2	2	2	2	2	2
9	Aspartame	2	2	2	2	2	2
	Total weight in mg	150	150	150	150	150	150

All the quantities are in mg.

Evaluation of Mouth Dissolving Tablets of Pioglitazone Hydrochloride

Determination of precompression characteristics

Angle of repose

It is determined by allowing a powder to flow through a funnel and fall freely on to a surface. Further addition of powder is stopped as soon as the pile touches the tip of the funnel. A circle is drawn around the pile without disturbing it. The height and diameter of the resulting cone are measured. The same procedure is repeated three times and the average value is taken. Angle of repose is calculated by using the following equation:

$\tan \theta = h/r$

Where, h = height of the powder cone; r = radius of the powder

Bulk density

The bulk density of the formulated powder was evaluated using a bulk density apparatus. It is expressed in gm/ml and is calculated by formula,

Bulk density (ρb) = Mass of the powder (M)/Volume of the bulk powder (Vb)

Tapped density

Accurately weighed quantity of powder is introduced into a measuring cylinder. Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester at a nominal rate of 300 drops/min. Tap the cylinder 500 times and measure the tapped volume (Va).Repeat the operation for an additional 750 tappings and again measure the tapped volume as (Vb).

If the difference between Va and Vb is <2%, Vb is the final tapped volume (Vf). If the difference is higher, repeat the tapings for an additional 1,250 times, and then the tapped density can be calculated using the following formula,

Tapped density = M/Vf

Where, M = weight of the sample taken; Vf = Final tapped volume

Carr's index

The compressibility index of powder can be determined using Carr's compressibility index, and can be determined by the following formula:

Carr's index (%) = (Tapped density – Pour density)/Tapped density × 100

Hausner ratio

The Hausner ratio can be determined using the following formula:

Hausner ratio(%) = Tapped density/Pour density × 100

Determination of Post Compression Characteristics

Thickness and dimension

Tablets of each batch were selected and measured for thickness and diameter using digital screw gauge.

Hardness of the tablets

The Hardness of the tablet was determined using a Monsanto Hardness tester. It is expressed in kg / cm^2.

Friability of tablets

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. Ten tablets were weighed and loss in weight (%) was calculated.

Weight variation test

Twenty randomly selected tablets were weighed individually and all together. The average weight and the percentage deviation were calculated. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percentage deviation was calculated using the following formula:

Percentage Deviation = Individual weight – Average weight x 100 Average weight

As per Indian Pharmacopoeia (IP), permissible limit of weight variation is 7.5% for tablet weight of 200 mg (Table 3).

Table 3: It shows IP (2007) standards for percentage weight variation.

Average Weight of Tablet	± Percentage Deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

Drug content estimation

Five tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend. Then, the samples were transferred to 100 ml volumetric flasks and were diluted up to the mark with phosphate buffer pH 6.8. The content was shaken periodically and kept for one hour to dissolve of drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at 269.4 nm against blank.

Wetting time and water absorption ratio

Wetting time of dosage form is related with the contact angle. A lower wetting time implies a quicker disintegration of the tablet. Five circular tissue papers of 10 cm diameter were placed in a petridish with 10 cm diameter. 10 ml of water containing Eosin, a water soluble dye, was added to the petridish, tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as wetting time.

Water absorption ratio (R) was calculated using the formula,

$R = 100 \times [Wa - Wb] / Wb$,

Where, Wa = weight of tablet after absorption Wb = weight of tablet before absorption

Dissolution studies

The release rate of PGTZN was determined by using USP dissolution apparatus type-II (Paddle) (Electro Lab TDT-06N USP dissolution apparatus, India). The dissolution test was performed using 900 ml of pH 6.8 phosphate buffer solution for 30 min which was maintained at 37 ± 0.2°C and rate of stirring at 50 rpm. At each time point of analysis, 5 ml sample was withdrawn and replaced with freshly prepared dissolution media maintained at same conditions. Sample solution was filtered, drug content of the filtrate was determined spectrophotometrically.

RESULTS AND DISCUSSION

Table 4: Standard calibration curve in 0.1N HCl (pH 1.2) at λmax 269.4 nm.

Concentration(µg/ml)	Absorbance
5	0.168
10	0.205
20	0.446
30	0.706
40	0.976
50	1.251

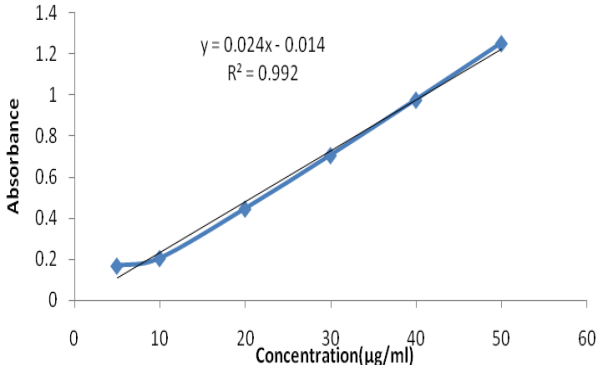


Fig. 1: Standard calibration curve in 0.1N HCl.

Drug polymer compatibility studies

The IR spectrum of pure drug and its physical mixture were studied. The characteristic absorption peaks of PGTZN like NH str, C-H str, C-O Str and C -H bond were obtained at wave numbers 3474.20 cm-1, 3085.05 cm-1, 1149.01 cm-1, 849.66 cm-1 respectively and also those peaks were observed in IR spectra of physical mixtures (Figure 2). Hence, it indicates there were no chemical interactions between the pure drug and its physical mixture.

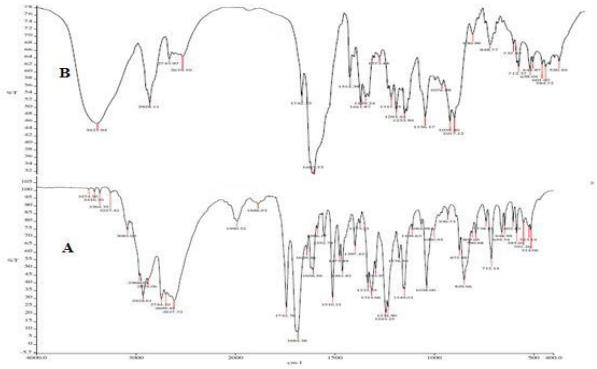


Fig 2: FT-IR spectrum of a) pure Drug Pioglitazone hydrochloride.

b) IR Spectra of physical mixture

Precompression studies

The powder blends have the bulk density ranging from 0.290 to 0.462 and tapped density from 0.330 to 0.569. The cars index values are ranged from 5.1 to 18.18 are said to be excellent ,good and fair.Hausner's ratio of powder blend was found to be in the range of 1.05 to 1.22 (H.R.= 0-1.2 indicating free flowing property).The angle of repose of granules of all the formulations was found to be ≤30˚, hence are freely flowing . Powder blend also showed acceptable dispersibility and porosity results (Table 5).

Table 5: Flow properties of various formulations.

	Direct compression						Wet granulation					
Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Bulk density (gm/cc)	0.45	0.45	0.44	0.46	0.44	0.39	0.29	0.34	0.35	0.37	0.40	0.36
Tapped density (gm/cc)	0.54	0.54	0.55	0.54	0.56	0.54	0.33	0.36	0.37	0.39	0.43	0.44
Porosity%	18.3	26.7	28	18.3	25	28	16.2	24.2	18.2	24.1	24	25.2
Carr's index	16.7	15.3	14.1	16.9	17.0	15.1	12.1	5.5	5.40	5.1	16.9	18.1
Hausner's ratio	1.17	1.21	1.18	1.18	1.18	1.17	1.13	1.05	1.05	1.05	1.07	1.22
Dispersibility (%)	70.3	68.3	70.3	70.3	56.8	66.3	80.5	65.3	70.2	68.2	54.2	65.2
Angle of repose (0)	31.2	29.6	30.2	29.1	28.2	29.1	37.2	29.6	28.6	27.9	34.2	37.5

POST COMPRESSION STUDIES

Post compression parameters like hardness, friability, weight variation, disintegration time and wetting time were studied and reported in table 6 & 7. Hardness was ranged from 3.5 to 5 kg/cm2 and supports sufficient mechanical strength to the tablets. Friability was lies between 0.14 to 0.97 % and complied with the pharmacopoeial limits. Tablets posses uniform thickness and passed weight variation test. Drug content showed by all the formulations was complied with the official limits and results were very close to the marketed drug as shown in table 8.

Disintegration time

The most important parameter that is needed to be optimized during the development of MDTs is disintegrating time of tablets (Table 6 & 7). The disintegration test of the tablets was conducted in pH 6.8 phosphate buffer and showed disintegration time from 22 to 34 sec. However, disintegration time of the tablets prepared with of superdisintegrants (1:1) is in the acceptable range with no much deviation due to the combinational effect of super disintegrated mixture.

Wetting time

Wetting time of tablets containing the mixture of superdisintegrants (1:1) with various concentrations are in the range of 11-24 sec (Table 6 & 7). Usually the crospovidone having the low swelling rate has also showed the fast wetting effect due to the combinational effect of superdisintegrants. This is also due to the synergistic effect of crospovidone along with other superdisintegrants will modify the wetting property of crospovidone and formulations prepared with the mixture of it. It was observed that there was no significant change in the wetting time with increase in the concentration of superdisintegrants mixture and however, the formulations with mixture of superdisintegrants like Croscarmellose sodium and Sodium starch glycolate showed least disintegration time.

Table 6: Evaluation of post compression parameters.

Direct Compression						
Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Hardness (kg/cm2)	3.7	3.9	3.8	5.0	4.1	3.9
Friability (%)	0.68	0.69	0.67	0.21	0.97	0.14
Weight variation	Pass	Pass	pass	Pass	Pass	Pass
Thickness (mm)	4.23	4.22	4.21	4.25	4.25	4.24
Disintegration time (sec)	34	32	31	30	23	26
Wetting time (sec)	26	28	25	18	13	15
Drug content (%)	98.3	98.5	99.6	100.2	98.0	101

Table 7: Evaluation of post compression parameters.

Wet Granulation						
Parameters	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Hardness (kg/cm2)	3.5	4.6	3.63	4.8	4.9	4.0
Friability (%)	0.74	0.68	0.75	0.40	0.20	0.95
Weight variation	Pass	Pass	Pass	Pass	Pass	Pass
Thickness (mm)	4.25	4.33	4.23	4.32	4.20	4.32
Disintegration time (sec)	27	24	22	31	28	29
Wetting time (sec)	14	14	11	22	16	17
Drug content (%)	96.5	98.6	102.0	96.9	99.2	100.4

Table 8: Evaluation of precompression and post compression parameters of Marketed drug.

Precompression parameters		Post compression parameters	
Bulk density (gm/cc)	0.446	Hardness (kg/cm2)	3.9
Tapped density (gm/cc)	0.36	Friability (%)	0.21
Porosity%	28	Weight variation	pass
Carr's index	5.41	Thickness (mm)	4.25
Hausner's ratio	1.172	Disintegration time (sec)	24
Dispersibility (%)	70.2	Wetting time (sec)	29
Angle of repose (0)	31.4	Drug content (%)	102.4

***In vitro* release studies**

The rapid increase in dissolution (Table 9 & 10) of PGTZN in F5 and F9 may be due to the rapid swelling of Croscarmellose and sodium starch glycolate. The increase in the concentration of Croscarmellose and sodium starch glycolate increased the swelling and disintegration of tablets rapidly into apparently small particles. While tablets formulated with sodium starch glycolate disintegrated by rapid up take of buffer, followed by rapid and enormous swelling into primary particle but more rapidly due to the change in viscous gel layer of sodium starch glycolate by Croscarmellose.

Table 9: In-vitro dissolution profiles of PGTZN MDTs of direct compression.

Direct compression						
Time interval (min	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
5	31.42	28.32	32.22	67.71	65.41	62.85
10	37.52	34.22	36.43	71.33	71.32	75.04
15	40.52	38.33	40.22	79.48	76.31	80.91
20	48.32	45.09	47.43	81.65	82.47	82.79
25	52.44	52.11	54.33	86.40	93.88	92.73
30	58.24	57.42	61.49	93.33	96.22	94.38

Table 10: In-vitro dissolution profiles of PGTZN MDTs of wet granulation.

Wet granulation						
Time interval (min	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
5	63.71	69.42	70.85	62.87	64.21	62.57
10	67.86	73.07	76.52	66.42	69.02	66.42
15	83.46	80.94	84.131	71.10	81.46	75.41
20	85.93	83.11	92.93	78.67	84.21	81.85
25	87.55	88.16	94.004	86.28	88.40	88.33
30	94.35	95.53	98.53	92.21	94.34	93.71

Table 11: *In-vitro* dissolution profiles of marketed drug.

Marketed Drug	
5	68.31
10	75.43
15	83.18
20	90.15
25	93.33
30	96.77

CONCLUSION

From this study, it can be concluded that wet granulation method showed better disintegration and drug release as compared to direct compression method. The main aim of formulating mouth dissolve tablets was to achieve instantaneous dispersion without the aid of water. By seeing *in vitro* dissolution time and disintegration, it can be clearly stated that the objective has been achieved. Above all, most of the formulations showed 80% drug release within 30 min, hence decreasing the lag time for absorption. By seeing this, it can be clearly seen that there is more chance for pre gastric absorption, thereby reducing first pass metabolism. Therefore, overall oral bioavailability can be increased. As the target patients are children and elderly, the addition of sweeteners increased the appeal and patient compliance.

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