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Research Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF PIOGLITAZONE

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Abstract: This study aims to fabricate and optimize mouth dissolving tablets prepared by direct compression to not only have sufficient mechanical strength/hardness to withstand manual handling, but also have a rapid disintegration time. This research was to develop fast dissolving tablets of pioglitazone. Tablets containing pioglitazone, β-Cyclodextrin and Sodium starch glycolate were prepared by direct compression technique. The tablets were evaluated for thickness, weight variation, hardness, percentage friability, wetting time, disintegration time and drug release studies. Formulations having superdisintegrants in different concentrations levels were prepared to access their efficiency. Tablets containing β-Cyclodextrin is showing excellent results as compare to other formulations.
Key**words:** pioglitazone, β-Cyclodextrin, Sodium starch glycolate, Excepients

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as mouth dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the 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 made these tablets popular as a dosage form in the current market[1].

Mouth dissolving tablets are novel types of tablets that disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and paediatric patients. They are also suitable for the 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 in the current market[2] .many elderly patients have difficulty in swallowing tablets, capsules or powders. To alleviate this problem, these tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. Criteria for Fast dissolving Drug Delivery System: The tablets should not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds, be compatible with taste masking, be portable without fragility concern, have a pleasant mouth feel, leave minimum or no residue in the mouth after oral administration, exhibit low sensitive to environmental condition as temperature and humidity[3]. The various technologies adopted to prepare oral disintegrating tablets are freeze drying/lyophilization, moulding, sublimation, spray drying, mass extrusion, direct compression[4].

Diabetes mellitus is often simply considered as diabetes, a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycaemia). The two most common forms of diabetes are type 1diabetes (diminished production of insulin) and type 2 diabetes (impaired response to insulin and b-cell dysfunction). Both lead to hyperglycaemia, excessive urine production, compensatory thirst, increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism.

T2DM is a complex heterogeneous group of metabolic conditions characterized by increased levels of blood glucose due to impairment in insulin action and/or insulin secretion (Das & Elbein 2006). Physiologically, the pancreatic b-cells constantly synthesize insulin, regardless of blood glucose levels. Insulin is stored within vacuoles and released once triggered by an elevation of the blood glucose level. Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells, including skeletal muscle cells and adiposities. Insulin is also the major signal for conversion of glucose to glycogen for internal storage in liver and skeletal muscle cells. A drop in the blood glucose level results in a decrease in release of insulin from the b-cells and an increase in release of glucagon from the a-cells, which stimulates the conversion of glycogen to glucose. Following an overnight fast, glucose is largely produced by glycogenolysis and gluconeogenesis[5].

Pioglitazone is a prescription drug of the class thiazolidinedione with hypoglycemic (anti hyperglycemic, anti diabetic) action. Pioglitazone 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 glaciated hemoglobin in the bloodstream. Following oral administration, in the fasting state, pioglitazone 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[6]. The aim of this study is to formulate and evaluate Pioglitazone mouth dissolving tablets.

MATERIALS AND METHODS

MATERIALS

Pioglitazone hydrochloride was received as gift samples from Strides Arco Lab Pvt. Ltd, Bangalore, India. Sodium starch glycolate was supplied by BIO PLUS Pvt. Ltd. Bangalore, India. Other materials were used analytical grade.

PREPARATION OF PIOGLITAZONE TABLETS

Various techniques can be used to formulate rapidly-disintegrating or dissolving tablets[7, 8]. 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. Watanabe *et al*[9] and Bi *et al*[10] were the first to evaluate the ideal excipients proportions and other related parameters using a superdisintegrant in order to formulate durable fast disintegrating tablets for oral administration.

Pioglitazone mouth dissolve tablets were prepared according to the formulae given in Table 1. The raw materials were passed through a screen (40 mesh) prior to mixing. Pioglitazone (30 mg) was mixed with the other excepients and compressed on a single-punch tablet machine (REMIK, mini press, B-tooling machine, India) equipped with round 6-mm punches.

PREFORMULATION STUDIES:

Angle of Repose[11, 12]

The angle of repose of powder was determined by funnel method. The accurately 1.2 g weighed powder were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\theta = \frac{\tan^{-1} h}{r}$$

Where, θ = angle of repose, h = height of cone, r = radium of the conc.

Bulk Density[13]

Bulk density (BD) and tapped density (TD) were determined. Specified quantity of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to tap by using the Tap density tester (USP) for the 100 taps and then final volume was observed. Bulk density and tapped density is calculated by using formula:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density = Weight of the powder/Tapped volume of the powder

Carr's Index [14]

The Carr's index of the powder mix was determined by using formula:

$$\text{Carr's index (\%)} = \frac{(TBD - LBD)*100}{TBD}$$

Where, LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of packing

Hausner's Ratio[15]

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following

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

EVALUATION OF PHYSICOCHEMICAL PARAMETERS:

Thickness [16]

Thickness was measured using screw gauge on randomly selected samples.

Hardness[17]

5 tablets were randomly the hardness of tablet of randomly selected 5 tablets each formulation was measured by Pfizer hardness tester. Tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Friability[18]

Electro lab friabilator was used for testing the friability. Tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min. the tablets were weighed and the percentage loss in tablet weigh was determined. The equation of the friability is shown below

$$\text{\% Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} * 100$$

Weight Variation [19]

Twenty Tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per Indian Pharmacopoeia.

Wetting Time[20]

A piece of tissue paper folded twice was placed in a small Petri-dish (internal diameter of 5 cm.) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. It is measured in the unit of second.

Water Absorption Ratio[21]

Initially, the initial weight (Wa) of the tablet has been measured. After the completion of the wetting time the wetted tablet was then weighed and is denoted by Wb. Water absorption ratio 'R' was determined using the equation [13]

$$R = \frac{100\ (Wb - Wa)}{Wa}$$

Where, Wa is weight of tablet before water absorption Wb is weight of tablet after water absorption.

***In-Vitro* Dissolution Studies**[22]

In vitro release studies were carried out using tablet USP XXIII dissolution test apparatus. Two objectives in the development of in-vitro dissolution tests was to show that, i) Release of the drug from the tablet is as close as possible up to 100% and Rate of drug release is uniform from batch to batch and is the same as the release rate from those proven to be bioavailable and clinically effective. Cumulative percentage drug release rate was evaluated.

FTIR study

This study was carried out to check incompatibility between drug and excepients by using IR spectrophotometer.

RESULTS AND DISCUSSION

F1 to F7 formulations were prepared using β-Cyclodextrin and superdisintegrant sodium starch glycolate in different concentrations. The values of the pre-compression parameters evaluated were within prescribed limit and indicate good flow properties. (Table 2)

Mouth dissolving tablets were prepared by direct compression and evaluated for thickness, hardness, weight variation, friability, content uniformity, wetting time and disintegration time. The % drug content was found in the range of 97.55±0.4% to 101.01±0.11% which shows good content uniformity. Wetting time was found in the range of 37.13±0.32 to 150.12±1.32sec. Hardness was found between 3.05±0.06 to 3.37±0.15kg/cm^2 which indicate good mechanical strength. Friability was found below 1% indicating good resistance against mechanical shear. (Table 3)

The most important parameter that needs to be optimized in the development of mouth dissolving tablets is the disintegration time. In the present study disintegration time was found in the range of 26.12±0.12 – 78.2±0.1sec (Table 3). It was observed that the disintegration time of the tablets decreased with the increasing level of β-Cyclodextrin and where as it is increased with increasing level of sodium starch glycolate (SSG). As increase in the level of SSG, it produces viscous gel layer which might have formed a thick barrier to further penetration of the disintegration medium and hindered the disintegration of the tablet contents.

All the seven formulations were subjected for *in vitro* dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed. The results obtained in the in vitro drug release for the formulations F1 to F7 are tabulated in Table 5. In all formulations the drug release was nearer to 100 % within 12 minutes except F7. F1, F2 and F3 showed good drug release than other formulations. IR spectral revealed about Pioglitazone hydrochloride.

TABLE 1: FORMULATION CHART

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Pioglitazone	30	30	30	30	30	30	30
MCC	45	35	25	45	35	25	55
Starch	15	15	15	15	15	15	15
PVP	15	15	15	15	15	15	15
Mannitol	35	35	35	35	35	35	35
β-Cyclodextrin	10	20	30	0	0	0	0
SSG	0	0	0	10	20	30	0

TABLE 2: MICROMERITIC PROPERTIES

Formulation code	Angle of repose(°) ± SD	True density	Bulk density	Carr's index (%)± SD	Hausner's ratio ± SD
F1	24.23±0.57	0.33±0.002	0.398±0.004	15.12±1.25	1.25±0.019
F2	24.65±1.00	0.33±0.003	0.398±0.003	16.82±1.27	1.18±0.011
F3	24.85±0.84	0.33±0.002	0.396±0.004	17.57±1.62	1.20±0.018
F4	24.83±0.84	0.33±0.002	0.395±0.003	15.76±0.82	1.21±0.024
F5	24.57±1.80	0.33±0.003	0.398±0.003	16.82±1.27	1.18±0.011
F6	24.59±0.57	0.33±0.002	0.396±0.004	17.84±1.48	1.20±0.018
F7	24.55±0.49	0.33±0.002	0.395±0.004	17.45±1.26	1.21±0.011

TABLE 3: POST COMPRESSION PARAMETERS

Formulation code	Thickness (mm) ± SD	Hardness (kg/mm^2) ± SD	Friability (% loss)	Weight variation (mg) ± SD	Drug content (%)
F1	0.3±0.05	3.37±0.01	0.2652±0.01	147.55±0.02	98.53±0.43
F2	0.3±0.02	3.37±0.15	0±0.01	148.23±0.12	98.23±0.41
F3	0.3±0.03	3.05±0.06	0.1360±0.02	148±0.01	97.55±0.4
F4	0.3±0.01	3.12±0.03	0.1340±0.08	149±0.12	98.83±0.33
F5	0.3±0.02	3.32±0.12	0.1336±0.04	148.2±0.013	98.54±0.23
F6	0.3±0.04	3.13±0.06	0.2706±0.03	149.9±0.03	101.01±0.11
F7	0.3±0.012	3.33±0.09	0.1345±0.07	149.99±0.03	99±0.12

TABLE4: Disintegration Time, Wetting Time and Water Absorption Ratio

Formulation code	Wetting time (sec) ± SD	Disintegration Time (sec) ± SD	Water absorption ratio
F1	39.11±0.11	28.11±1.00	50.12±0.34
F2	38.13±0.15	27.12±0.13	48.12±0.21
F3	37.13±0.32	26.12±0.12	53.14±0.54
F4	41.14±0.16	30.13±0.11	49.13±0.15
F5	48.32±0.24	33.12±0.1	57.98±0.67
F6	47.13±1.21	35.13±0.2	59.12±0.65
F7	150.12±1.32	78.2±0.1	61.34±0.12

TABLET5: *in vitro* cumulative % of drug release profile data of the formulations

Formulation Code	cumulative % of drug released in minutes			
	2	4	6	8
F1	36.56±0.5	67.8±0.6	90.25±0.7	98.2±0.46
F2	46.83±2.5	79.33±2.6	98.11±0.6	
F3	67.41±1.3	100.1±0.7		
F4	37.69±0.6	78.11 ±0.8	83.85±1.4	93.1±0.19
F5	42.27±1.3	66.98±2.1	78.12±1.3	90.7±0.8
F6	31.98±0.8	65.45±0.8	72.2±1.1	88.15±0.23
F7	19.42±0.4	43.62±0.6	66.98±2.1	78.91±0.9

CONCLUSION

Mouth dissolving tablets of Pioglitazone hydrochloride is type 2 anti-diabetic agent can be efficiently and successfully formulated using novel co processed super disintegration by direct compression. The moth dissolving tablets of Pioglitazone using β-Cyclodextrin and sodium starch glycolate as superdisintegrants have sufficient hardness, disintegration time and dissolution rate so this can be used in patients having swallowing problem and geriatric and pediatrics patients. Overall results suggested that F3 formulation containing β-Cyclodextrin was satisfy all the criteria of mouth dissolving tablets.

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