Research Article

Design and Evaluation of Pioglitazone Hydrochloride Matrix Tablet

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ABSTRACT

The objective of this study was to design oral controlled release matrix tablets of pioglitazone using different proportion of HPMCK-100M, Guar gum and Xanthan gum as the retardant polymer and study the effect of formulation factor such as polymer proportion on the in vitro release of drug. The granules were evaluated for angle of repose, bulk density, tapped density and compressibility index, shows satisfactory results. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, thickness, friability, hardness, swelling, erosion behaviour and In vitro dissolution studies. All the formulation showed compliance with Pharmacopoeial standards. In vitro drug release studies were carried out using USP XXII dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer, maintained at 37+0.5C The release kinetics were analyzed using the zero-order, first-order model equation, Higuchi's square-root equation, and the Korsmeyer-peppas model.from invitro release study batch F5 selected as optimized batch for stability study.

KeyWords: Pioglitazone Hydrochloride, Xanthan gum, Guar gum, Matrix Tablet.

INTRODUCTION

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug delivery systems[1] Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance[2, 3]. Matrix type sustained delivery systems are popular because of their ease of manufactures. It is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form[4, 5]

Diabetes mellitus is a chronic metabolic disorder characterized by high glucose concentration in blood, caused by Insulin deficiency, often combined with Insulin resistance[6]. Pioglitazone hydrochloride is an oral hypoglycaemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus[7].

Pioglitazone hydrochloride is a basic (PKa = 12.06) which is practically insoluble in water and. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 3-7 h, Pioglitazone hydrochloride is reported to have a short biological half-life requiring it to be administered in 2 to 3 doses of 15 to 45 mg per day[8] SR formulations that would maintain plasma levels of drug for 8 to12 hrs might be sufficient for once a day dosing for pioglitazone. SR products are needed for pioglitazone to prolong its duration of action and to improve patient compliance.

MATERIALS AND METHODS

Pioglitazone was obtained as gift sample from cadila pharmaceutical ltd. Ahamadabad,The pharmacopial grade Guar gum,Xanthan Gum was obtained from Rajesh chemical ,Mumbai.other materials used were of analytical grade,and procured from commercial source.

Preparation of matrix tablets

Different tablet formulations were prepared by wet granulation technique[9] (Table 1). All the powders were passed through sieve number 80. Required quantities of drug and polymer were

mixed thoroughly and a sufficient volume of granulating agent was added Povidone in isopropyl alcohol, slowly. After enough cohesiveness was obtained the mass was sieved through sieve number 22. The granules were dried at 55±5 °C for one hour. Once dried the granules retained on sieve number 44 were mixed with magnesium stearate for 2 min. The practical weight of tablets, were calculated based on the drug content of the granulations and the tablets were compressed.

Table 1: Composition of Matrix Tablets of Pioglitazone hydrochloride

Ingredient (mg)	Batches					
	F1	F2	F3	F4	F5	F6
Pioglitazone	50	50	50	50	50	50
Xanthan gum	200	---	----	100	----	100
Gaur gum	----	200		100	100	-----
HPMCK100M	------	-----	200	----	100	100
PVPK30	10	10	10	10	10	10
Mg.Stearate	5	5	5	5	5	5
Talc	10	10	10	10	10	10
Lactose	50	50	50	50	50	50
Total wt.	325	325	325	325	325	325

Evaluation of *Granules*

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in funnel. The height of the funnel was adjusted in such away that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the granules were measured the angle of repose was calculated using following formula[10].

. **Tan Q= h/r**

Where, "h" is height of the heap and "r" is the radius of the heap of granules.

Bulk density

An accurately weighed quantity of granules (W) was carefully transferred into 250 ml measuring cylinder and initial volume (V0) was measured. The bulk density is calculated by using following Formula.

Bulk Density = Mass of the granules (W)/ Initial volume of the granules (V0)

Tapped density

An accurately weighed quantity of granules (W) was carefully transferred into 250 ml measuring cylinder. The cylinder is then allowed to tap on to a wooden surface from the height of 2.5 cm at one second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (Vf). The tapped density is calculated by the following formula[11].

Tapped Density = Mass of the granules (W)/ Tapped volume of the granules (Vf).

Compressibility index and Hausner ratio[12]

The compressibility index and the Hausner ratio are determined by measuring both the bulk density and tapped density of the granules. A quantity of 2g of granules from each formulation, filled into a 10mLof measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the granules

The compressibility index and the Hausner ratio were calculated as follows:

Compressibility Index = {(pt-po)/pt} x100

Where, pt= tapped density.Po=bulk density

Hausner Ratio = Tapped density/ Bulk density

Evaluation of tablet

All the formulations of Pioglitazone matrix tablets prepared were evaluated for the following parameters

Hardness test

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage, transportation, and handling before

usage depends upon its hardness. for each formulation, the hardness was determined using Monsanto hardness tester.

Friability test:
Ten tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (W_{final}). The % friability was then calculated by following formula

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X100$$

Uniformity of weight
This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (5%).

Drug content
An accurately weighed equivalent amount 100 mg of Pioglitazone hydrochloride into the matrix tablets. Extracted with 0.1 N HCl and the solution was filter. The absorbance was measured at 270 nm after suitable dilution.

Swelling behaviour of matrix tablets
The extent of swelling was measured in terms of % weight gain by the tablet[13]. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a petridish containing phosphate buffer of pH 7.4. At the end of 2 hours, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 1 hour till the end of 6 hours. The % weight gain by the tablet was calculated by equation.

$$S.I = \left\{ \frac{(M_t - M_0)}{M_0} \right\} \times 100$$

Where, S.I = Swelling Index, M_t = Weight of tablet at time't' and M_0 = Weight of tablet at time 0.

***In Vitro* Dissolution studies**
The *in vitro* dissolution studies were carried out in 900 ml of phosphate buffer ph 7.4 using USP XXII Dissolution test apparatus employing paddle stirrer. One tablet was placed inside the dissolution medium and the paddle was rotated at 50 rpm. 5ml samples were withdrawn at specific time intervals and the same volume was replaced to maintain sink conditions..The samples were analyzed for drug content spectrophotometrically at 265.5 nm.

Kinetic modelling of drug release
Analysis of drug release from swell able matrices must be performed with a flexible model that can identify the contribution to overall kinetics The dissolution profile of all the batches was fitted to various models such as zero-order, [14]Higuchi,Korsmeyer and Peppas to ascertain the kinetic modelling of drug release[15,16].The raregiven in table no4.

STABILITY STUDIES
To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines[17]. Optimized formulation F5, sealed in aluminium packaging coated inside with polyethylene and various replicates were kept in the humidity chamber maintained a 45±2°C and 75±5% RH for 3 month at the end of studies; samples were analyzed for the drug content, *in vitro* dissolution.given in table no.5.

IR Analysis
The spectral analysis was done using FT-IR (Schimadzu 8400 SCCE).The dry sample of Pioglitazone, and optimized formulation (F5) was mixed by triturating with dry potassium bromide (A.R. Grade) and placed in sample cell.

RESULT AND DISCUSSION
Granules of the different formulations were evaluated for angle of repose, loose bulk density tapped bulk density, and compressibility index. The results of angle of repose and compressibility index (%) ranged from (20.05 ± 1.25 to 27.15) and (10.93 to 16.32), respectively. The results of loose bulk density and tapped bulk density ranged from (0.367to 0.412) and (0.369 to 0.0.412), respectively. The results of angle of repose (< 30) indicate good flow properties of granules. This was further supported by lower compressibility index values. The lowest compressibility index is 5-15% which indicates excellent flow properties in Table 2.

Table 2: Evaluation of granules

Batches	Parameters				
	Bulk density (gm/cc^3)	Tapped density (gm/cc^3)	Angle of repose	Compressibility index (%)	Hausner ratio
F1	0.313	0.374	24.39	16.31	1.19
F2	0.326	0.384	23.50	15.10	1.17
F3	0.367	0.412	24.65	10.95	1.12
F4	0.332	0.394	20.05	15.73	1.18
F5	0.323	0.374	27.15	13.63	1.15
F6	0.326	0.369	21.45	11.65	1.13

The physical properties of different batches of developed matrix tablets are given in Table3. The thickness of the tablets ranged from (3.52 to 3.78) mm. All the batches showed uniform thickness. The average percentage deviation of 20 tablets of each formulation was less than (5%), and hence all formulations passed the test for uniformity of weight The hardness of all the formulation ranged from (5.4± 0.21 to 6.5 ± 0.20) kg/cm^3. Tablets hardness is, however, not an absolute indicator of strength. The percentage friability of the tablets of all the formulations ranged from (0.036 to 0.061). In the present study, the percentage friability for all for formulations was below 1% w/w, indicating that the friability is within the prescribed limits. Drug content was found to be uniform among different formulations of the tablets and ranged from (97.82 ± 0.41 to 99.12 ± 0.18).

Table 3: Evaluation of tablets of Pioglitazone

Batch	Physical parameters				
	Hardness* ($kg./cm^3$)	Weight Variation*	Friability*	% Drug content*	Thickness
F1	5.4± 0.21	0.325±0.49	0.036	98.96±0.62	3.57
F2	4.9±0.20	0.325±0.42	0.049	97.93±1.50	3.39
F3	5.7±0.17	0.325±0.44	0.061	97.98±1.47	3.46
F4	6.9±0.20	0.325±0.38	0.061	98.23±1.61	3.78
F5	6.2±0.21	0.325±0.38	0.062	98.45±1.12	3.54
F6	6.6±0.15	0.325±0.39	0.048	98.26±0.96	3.45

*All values are expressed as mean ± SD, (n=3)

The results of the dissolution studies for formulations F1 to F6 are shown in the Figure 1. The cumulative percentage drug release for F1, F2, F3, F4, F5 and F6 (91.84, 83.09, 93.75, 89.53, 98.78, 94.67) at the end of 12hrs respectively. Among all the formulation F5 shows highest drug release (98.75%) in 12hrs which contain HPMC K-100M And xanthan gum, where as in batch F1 and F2 contain gaur and xanthan gum gives less release it may be due to the hardness of tablet .in batch F4, F5, F6 combination of polymer were used.it gives 89.53, 96.78, 94.67 % drug release in 12 hr respectively. Here we observed that on increasing the quantity of xanthan gum and the proportion of HPMC K-100, it retards the drug release from matrix. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. Formulation F5 met the needed theoretical drug release profile and has the sustain action i.e., retarding the drug release so the release is for a long time and thus more bioavailability; for these reasons, it was considered the best formulation among all the six formulations of this series.

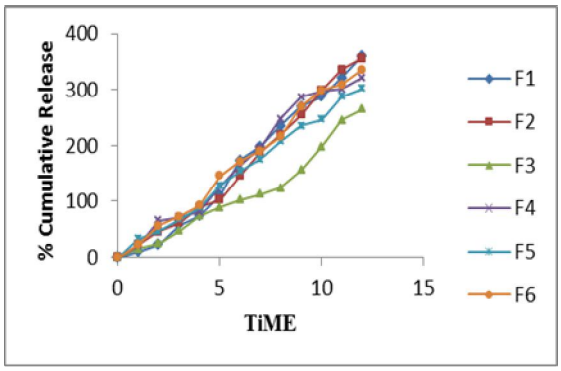

Fig. 1: In-vitro dissolution profile of F1 to F6 formulation

The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of

hydration The direct relationship was observed between swelling index and gum concentration, as gum concentration increases, swelling index was increased. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of guar gum. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix, where hydration of individual Xanthan gum particles results in extensive swelling. As a result of Rheology of hydrated product, the swollen particles coalesce this result in a continuous viscoelastic matrix that fills the interstices maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium. Swelling studies carried out for gain of uptake water given in Fig.No-2.

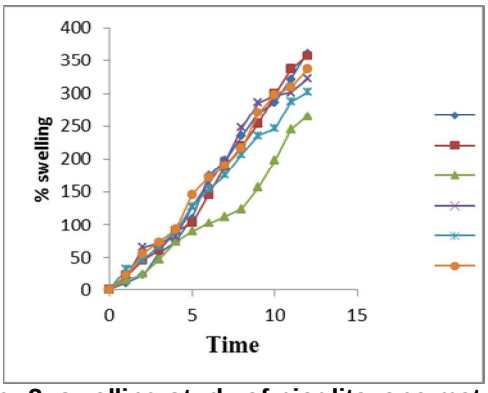

Fig. 2: swelling study of pioglitazone matrix tablet

In view of the potential utility of the formulation, stability studies were carried out on optimized formulation F5 at 45±2 °C and 75±5% RH for three months to assess their long-term stability. The protocols of stability studies were in compliance with the guidelines in the WHO document for stability testing of products intended for the global market. After storage, the formulation was subjected to a drug assay and *in vitro* dissolution studies (Table.No-4). The stability study showed no significant change after storage at 45 °C and75% RH for three month.

Table 4: Characteristic of optimized formulation F5 before and after storage

Parameters	% Drug content	Hardness Kg/cm^3	% Drug release
Before storage	97.98±1.47	5.7±0.17	98.75
After storage	97.07±0.78	5.4±0.85	97.99

To analyze the mechanism of the drug release rate kinetics of the dosage form, All the formulations were fitted for the release kinetics. The data were processed for regression analysis using Microsoft excell statistical function.

It may be concluded that the release of the drug follows Korsmeyers – Peppas reaction. The n values of all the formulations ranged between 0.230.0.435. Values of slope between0.976-0.969 suggest that release of pioglitazone from matrix tablet followed fickian transport mechanism given in table no.5.

Table 5: Release kinetics parameters of d esigned matrix tablets of Pioglitazone

Batch	Zero order plot	First order plot	Higuchi plot	Korsmeyer plot peppas	
				Slope(n)	R^2
F1	0.852	0.974	0.963	0.332	0.954
F2	0.931	0.955	0.979	0.435	0.969
F3	0.735	0.979	0.923	0.235	0.961
F4	0.914	0.952	0.979	0.452	0.965
F5	0.879	0.967	0.981	0.345	0951
F6	0.786	0.959	0.949	0.282	0.949

Fig. No.3, 4 shows IR spectra for Pioglitazone, and formulation F5. Major functional groups of Pioglitazone (3083.95) NH Stretching, (2927.73) CH Stretching, (2742.57) CH Stretching, (1741.59) C=O Stretching, (1643.73) C=O Stretching, (1242.07) C-O Stretching Ar. Group can be seen in spectra of individual drugs as well as in spectra of formulation. So there is no interaction between Pioglitazone and polymers used.

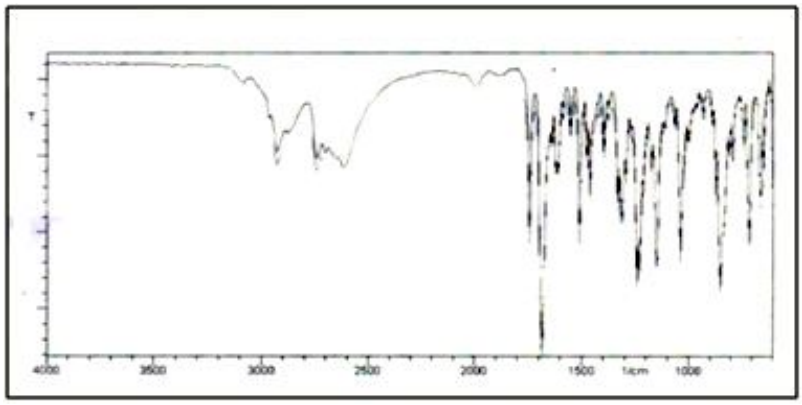

Fig. 3: IR Spectrum of Pioglitazone

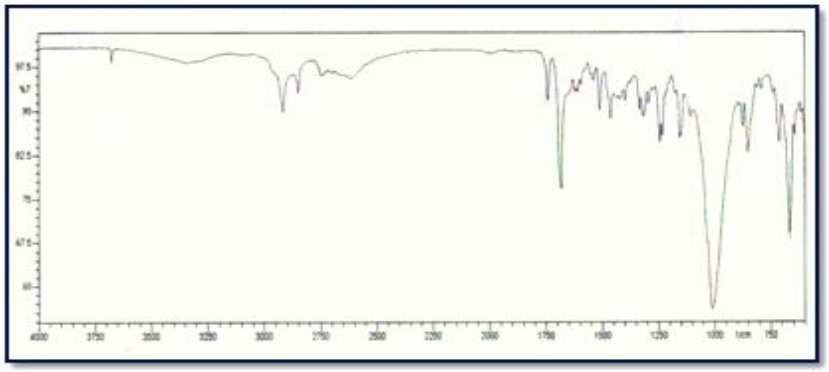

Fig. 4: IR.Spectrum of Optimized formulation (F4)

CONCLUSION

The present study was carried out to develop the matrix tablet of pioglitazone for sustained release to provide an effective and safe therapy for Diabetes mellitus with a reduced dose and reduced length of treatment. *In vitro* dissolution studies of optimized F5 tablets formulation showed controlled release of pioglitazone for 12 hr. by maintaining the zero order release. Thus, results of the current study clearly indicated a promising potential of the pioglitazone matrix system as an alternative to the conventional dosage form.

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