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Formulation and Evaluation of Chronopharmaceutical Drug delivery System

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Abstract: The main objective of the present investigation was to formulate and evaluate the pulsatile drug delivery system for anti diabetic drug pioglitazone hydrochloride to control the increased blood glucose level after food consumption in diabetic patient by allowing the drug to release immediately after meals. Press coated tablets of pioglitazone hydrochloride were prpeapred by compression coating immediate release pioglitazone hydrochloride core tablets with hydrophilic and hydrophobic polymer in different ratios. The ideal concentration of hydrophilic and hydrophobic polymers were selected based on the *invitro* drug release profile and desired lag time of 7 hrs. The *invitro* drug release profile of pioglitazone hydrochloride press coated tablets containing Glyceryl behenate 100mg, Ethylcellulose 25mg and HPMC75 mg gave desired drug release profile after the lag time of 7 hrs. Hence the developed formulation was found to be suitable for the diabetic patient to manage the blood glucose levels which are high after food consumption.
Keywords: Circadian rhythm, lag time, pulsatile release, hydrophobic and hydrophilic.

Introduction

As the chronological behaviour of diabetes mellitus confirms increased blood glucose level after meal it is preferable to opt a dosage form which will provide desired concentration of the drug at particular time points. These dosage forms are designed to mimic the circadian rhythm by releasing the drug at the appropriate time, by means of an internal pre-programmed clock that is initiated when the dosage form comes in contact with gastrointestinal fluids[1,2,3].

Pioglitazone hydrochloride is a drug commonly used in the management of type 2 diabetes mellitus which are required to be administered two times a day[2]. Hence the development of pulsatile drug delivery systems will help to reduce the frequency of drug administration, as this dosage form consists two pulses of drug in an unit dosage form. So, the the aim of the present study was to formulate and evaluate the press coated pulsatile drug delivery system for anti diabetic drug Pioglitazone hydrochloride.

Materials and Methods

Materials

Pioglitazone hydrochloride was obtained as a gift sample from Orchid health care.ltd, Chennai. Sodium starch glycollate was purchased from Otto chemical-biochemika reagents,Mumbai, Avicel PH 102 was obtained from Indian research products, Chennai, HPMC, Ethylcellulose and glyceryl behenate were purchased from

Central drug house pvt.ltd, New delhi. The other chemicals and reagents used in the study were of analytical grade.

Methods

The preparation of press coated tablets of Pioglitazone hydrochloride involves 3 steps[4-7].

Step 1. Preparation of core tablets of Pioglitazone hydrochloride by direct compression with superdisintegrant for the release of second pulse.

Step 2. Compression coating of core tablets of Pioglitazone with hydrophilic (HPMC) and hydrophobic (Ethylcellulose/ Glycerylbehanate) polymer combinations to achieve desired lag time.

The core tablets were compression coated with different weight ratios(W/W) of EC/glyceryl behanate and HPMC mixtures. Intially 50% of the coat powder was placed in the die cavity then, the core tablet was carefully positioned at the centre of the die cavity which was filled with the remainder of the coat powder. It was then compressed around the core tablet by using 10mm round, flat, plain punches. The formula used for the preparation of press coated tablet were shown in the table 1.

Step 3. Coating of Immediate release layer of pioglitazone hydrochloride over the compression coated tablet using 6%W/V solution of polyvinyl pyrrolidone in water as the adhesive.

Table.1.Formula used for the compression coating of barrier layer (200mg)

S.No	Trials	Core tablet	Glyceryl behanate	Ethylcellulose	HPMC
1.	F1	100	100	_	100
2.	F2	100	_	100	100-
3.	F3	100	100	50	50
4.	F4	100	100	75	25
5.	F5	100	100	25	75

Evaluation Of Pioglitazone Hydrochloride Press Coated Tablets[6-9]

Fourier Transform infra Red spectroscopy

TIR spectroscopy was used to ensure that no chemical interaction between Pioglitazone HCl and the other excipients used in the formulation. IR spectra of Pioglitazone HCl and other excipients used in the formulation were recorded by using"Perkin-elmer FTIR". The sample for the IR spectroscopy was prepared by mixing the samples with spectroscopic grade KBr and compressed in to transparent pellets, then scanned in the IR range from 500 to 4000cm^{-1} with a resolution of 4cm. The recorded IR spectra were given from Fig .1 to Fig .4

Post compression parameters

The prepared press coated tablets were evaluated for hardness, friability, thickness, drug content, and *invitro* drug release studies. The values were given in Table 2.

***Invitro* dissolution studies**

The *Invitro* drug release study were performed using different dissolution medium such as pH 1.2 for 2 hrs, pH 6.8 for 3hrs and pH 7.4 buffers for subsequent hrs. The samples were taken at regular time intervals and the amount of drug released was calculated by measuring the absorbance of standard and sample preparations. The *Invitro* drug release study results of Pioglitazone HCl press coated tablets were given in Table 3 and lag time in Table 4.

Results and Discussion[9-12]

Drug excipients compatibility study using FTIR

- The FTIR of pioglitazone shows intense band at 1513.40 **cm^{-1}** and drug- polymer mixture also shows intense band at 1514.76, 1514.99 and 1514.78. **cm^{-1}.** From the IR interpretation results, it was

confirmed that there was no chemical interaction between drug and the polymer used in the formulations.

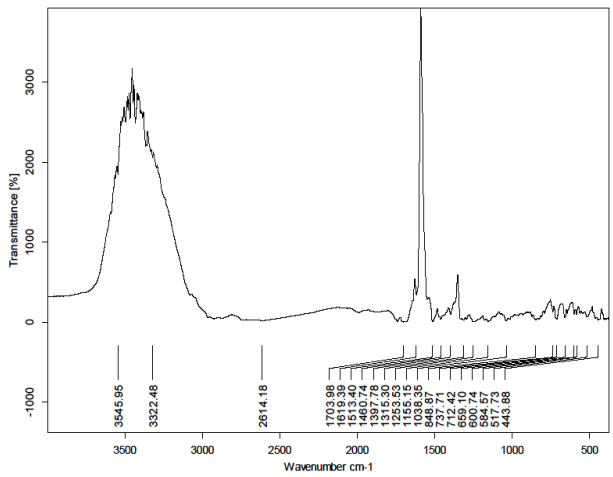


Fig .1. FTIR spectra of pioglitazone hydrochloride

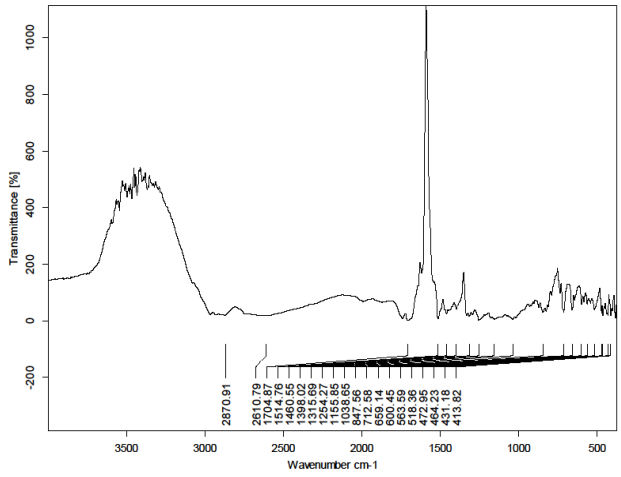


Fig .2. FTIR spectra of pioglitazone hydrochloride and ethyl cellulose

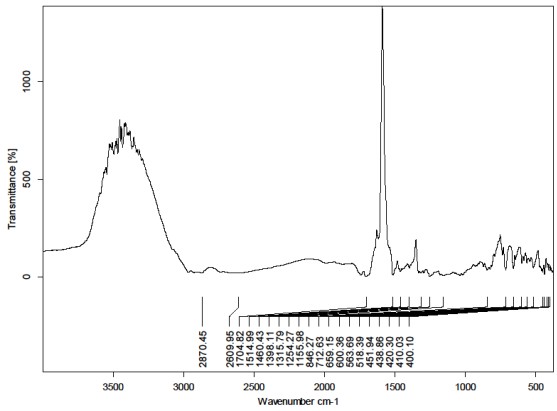


Fig .3.FTIR spectra of pioglitazone hydrochloride and glyceryl behenate

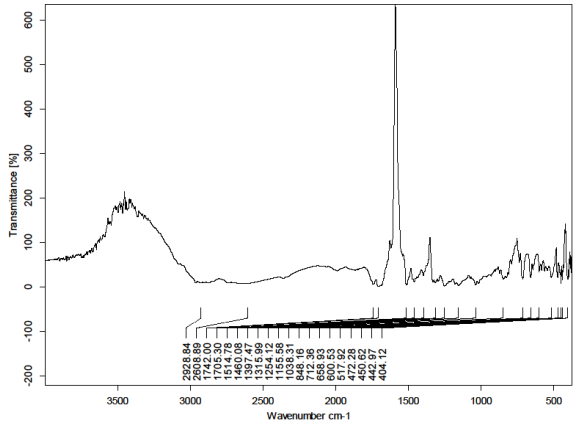


Fig.4.FTIR spectra of pioglitazone hydrochloride and HPMC

Table.2. Post-compression characteristics of Pioglitazone HCl press-coated tablets

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	394±2.76	5.8±0.01	6.14±0.01	0.39	98.25
F2	392±2.18	5.3±0.02	6.9±0.02	0.85	99.20
F3	396±1.07	5.3±0.02	6.1±0.04	0.67	99.45
F4	390±1.46	5.2±0.01	5.6±0.01	0.22	99.25
F5	396±1.23	5.4±0.01	6.3±0.01	0.59	98.48

Table .3. *In vitro* drug release results of Pioglitazone HCl press-coated tablets

Time	Cumulative percentage drug release				
In buffer pH1.2					
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
15 mts	66.15± 0.23	66.53± 0.32	67.25± 0.97	67.36± 0.61	66.55± 0.48
30mts	85.64± 0.49	86.264± 0.14	86.28± 0.19	85.64± 0.89	85.36± 0.46
45mts	96.35± 0.74	95.46± 0.36	96.45± 0.35	96.48± 0.75	97.14± 0.28
60mts	99.71± 0.13	99.58± 0.37	99.72± 0.31	99.65± 0.69	99.54± 1.06
2hr	99.75± 0.25	99.64± 0.34	99.75± 0.47	99.68± 0.57	99.59± 0.28
In buffer pH 7.4					
3hr	0	0	No release up to 10hrs	No release up to 12hrs	0
4hr	0	0	0	0	0
5hr	0	0	0	0	0
In buffer pH 6.8					
6hr	0	0	0	0	0
7hr	0	0	0	0	0
8 hr	99.28± 0.47	99.75± 0.54	0	0	0
9 hr	-	-	0	0	0
10hr	-	-	0	0	97.20± 0.25
12 hr	-	-	99.85± 0.35	0	98.60± 0.27

n=3;Mean± S.D

Table .4. Lag time of Pioglitazone HCl press-coated tablets

S.No	Trials	Core tablet	Glyceryl behanate	Ethylcellulose	HPMC	Lag time
1.	F1	100	100	_	100	5hrs
2.	F2	100	_	100	100	4hrs 45mts
3.	F3	100	100	50	50	10hrs
4.	F4	100	100	75	25	12hrs
5.	F5	100	100	25	75	7hrs

Post-compression characteristics of Pioglitazone HCl press-coated tablets

- The post compression parameters such as weight variation, thickness, hardness, friability and drug content results for all the formulations were found to be within the limits. The drug content for all the formulations were nearly 100% which indicates that there was no drug loss by manufacturing process or by excipients used in the formulation.

***In vitro* drug release studies for Pioglitazone HCl press-coated tablets**

- All the prepared Pioglitazone HCl press-coated tablets (F1-F5) shows desirable *in vitro* drug release profile in the first 2 hrs of study (pH 1.2 buffer).The cumulative percentage drug release of all the formulations in the pH 1.2 buffer were nearly 100% (first pulse)

- The barrier layer prepared with combination of hydrophobic polymer (Glyceryl behenate or Ethyl cellulose) and hydrophilic polymer (HPMC) shows the maximum lag time 12 hrs (**F4**) and minimum lag time 4 hrs 45 mts (**F2**) .

- The formulation **F5** prepared with barrier layer containing **Glyceryl behenate 100 mg, Ethylcellulose 25mg** and **HPMC75 mg** gave desired drug release profile after the lag time of 7 hrs.

- The *in vitro* dissolution study of **F5** shows the maximum drug release 99.59± 0.28 % for first pulse, 98.60± 0.27% for second pulse with desirable lag time 7 hrs. Hence the formulation **F5** was selected as an optimized batch.
- During the dissolution it was observed that when the press coated tablets contacts with dissolution medium, the immediate release layer (first pulse) dissolves and released the drug immediately.
- Then the dissolution medium gradually reaches the barrier layers which are responsible for the lag time, eroding and rupturing the barrier layer, results in the rapid releasing of drug from the press coated tablets which depends upon the concentration, hydrophobicity and hydrophilicity of the polymers used in the formation of barrier layer.

Conclusion

The active pharmaceutical ingredient pioglitazone hydrochloride was evaluated for its physical characteristics, stability and solubility. The results obtained were satisfactory and within the specified limits.

Pioglitazone hydrochloride pulsatile release tablets were prepared by first making the core tablet containing the first pulse of pioglitazone hydrochloride by direct compression method and then press coating the core tablet with hydrophobic and hydrophilic polymers namely glyceryl behenate,ethylcellulose and hydroxyl propyl methyl cellulose at various concentrations that were optimized by various trials. The optimization procedure aided in the preparation of press coated tablets of pioglitazone hydrochloride with a lag time upto 7 hrs.

The second pulse of the drug was achieved by coating the second dose of pioglitazone hydrochloride on the press coated tablets by powder layering method using PVP solution as blinder.

The *invitro* drug release profile of pulsatile tablets of pioglitazone hydrochloride showed a instantaneous release of drug followed by lag time of 7 hrs before the release of the second pulse of drug in which is considered to be the best formulation as per the treatment requisites of diabetes mellitus.

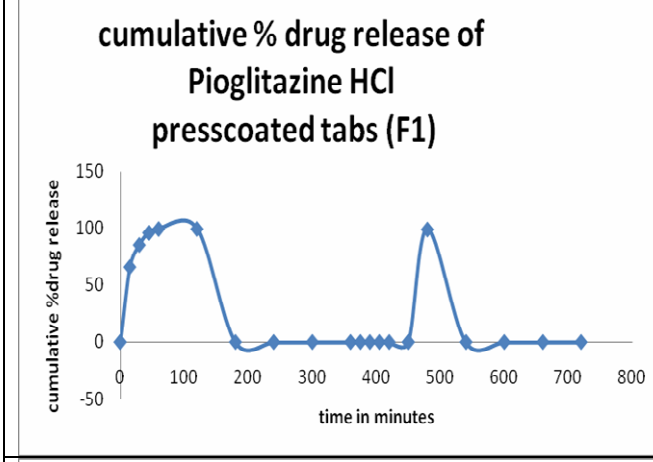
The present study was made to develop the pulsatile drug delivery of pioglitazone hydrochloride. The *invtro* dissolution study revealed that the formulated presscoated tablets of pioglitazone hydrochloride releases the desired concentration at predetermined time. Hence it can be concluded that the newly developed pulsatile drug delivery system of pioglitazone hydrochloride is considered to be ideal and effective to control the increased blood glucose level after intake of meals by allowing the drug to release after a lag time (after meals).

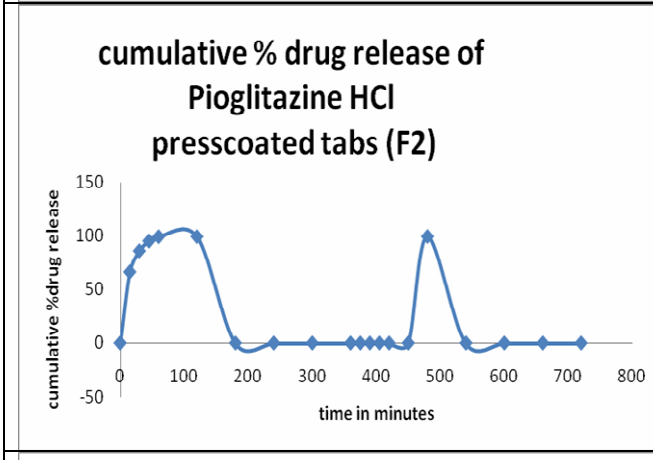
Fig.5. core tablet

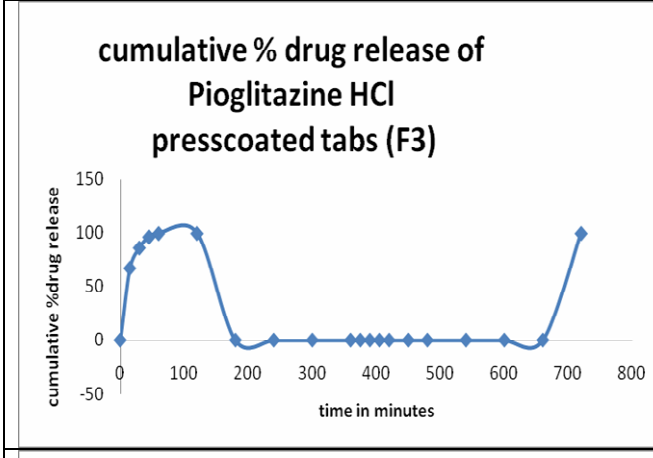
Fig.6. press coated tablet

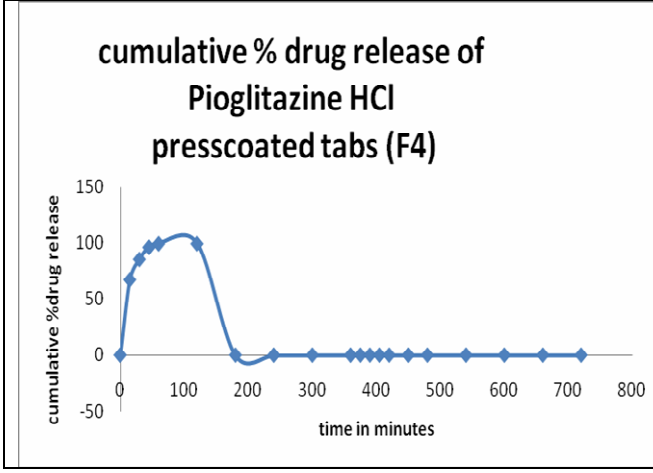
Fig.7. core tablet in press coated tablet

Fig.5-7.Images of Pioglitazone hydrochloride Press coated tablets


cumulative % drug release of Pioglitazine HCl presscoated tabs (F1)
cumulative %drug release
150
100
50
0
-50
0
100
200
300
400
500
600
700
800
time in minutes


cumulative % drug release of Pioglitazine HCl presscoated tabs (F2)
cumulative %drug release
150
100
50
0
-50
0
100
200
300
400
500
600
700
800
time in minutes


cumulative % drug release of Pioglitazine HCl presscoated tabs (F3)
cumulative %drug release
150
100
50
0
-50
0
100
200
300
400
500
600
700
800
time in minutes


cumulative % drug release of Pioglitazine HCl presscoated tabs (F4)
cumulative %drug release
150
100
50
0
-50
0
100
200
300
400
500
600
700
800
time in minutes

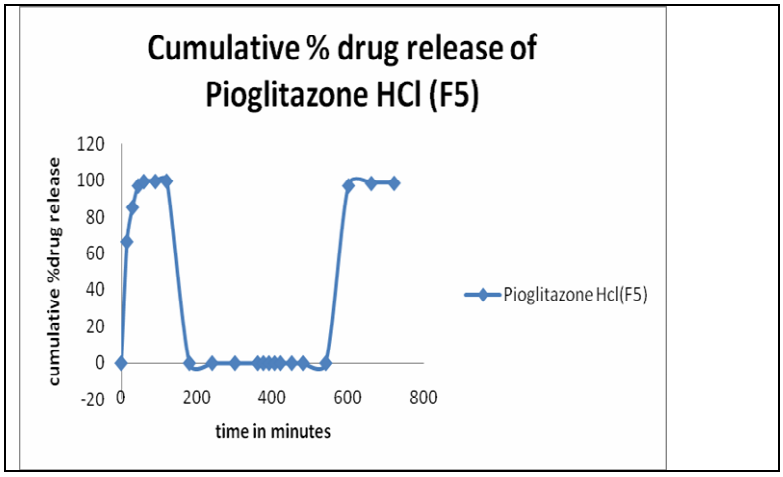


Fig. 8-12.Cumulative % drug release of Pioglitazone HCl presscoated tablets (F1-F5)

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