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Research Article

Formulation and evaluation of pioglitazone hydrochloride pellets

Mahesh N*, Gnanaprakash K, Kumar B, Praveen N, Sarkar Rao K, Gobinath M

Ratnam Institute of Pharmacy, Pidathapolur, Muthukur-524344, SPSR Nellore District, Andhra Pradesh, India

ABSTRACT

The aim of the present study was to formulate and evaluate Pioglitazone hydrochloride pellets. The Pioglitazone hydrochloride immediate and controlled release pellets were prepared by solution/suspension layering technique by using croscarmellose in IR layer and three different polymers such as Ethyl cellulose, Eudragit L100, Xanthan gum as rate controlling polymers in four different ratios like 1:0.5,1:1, 1:1.5 and 1:2 to achieve desired drug release in CR layer. Evaluation was performed according to the pharmacopoeia standards including drug excipient compatibility, percentage yield, particle size distribution, drug content analysis and *in-vitro* drug release study. The best results were shown in F11 Pioglitzone and Eudragit L100 in1:1.5 ratios. A broad variety of drug release pattern could be achieved by variation of polymer ratios which was optimized to match the target release profile. In comparision of *in-vitro* release studies for all developed controlled release formulations, F11 relelases 97.50% of drug at the end of 12th hour and was considered as best formulation.

Keywords: controlled release; Eudragit L100; Immediate release; Pioglitazone; Xanthan Gum.

INTRODUCTION

Pelletization

Pelletization can be defined as the process of compressing or molding a material into the shape of a pellet. The main thing in that pelletization technique conversion of a bulk drugs with excipient in to a small or fine particle in nature. Pellets are multi-unit dosage forms have both therapeutic and other pharmaceutical advantages. Therapeutic advantages include modification of drug release, division of dose strength, and free dispersion in the gastro intestinal tract when administered orally. Pharmaceutical advantages include a high degree of flexibility in design and development during delivery of incompatible bioactive agents due to the low surface area to volume ratio compared to powders and granules. The main mechanism involved in this drug is released from pellets depends on the type of coating, pH dependent coating and slowly erodible coating. (Palmieri F.G., Grifantini R 2000).

Pioglitazone is an oral drug that reduces the amount of glucose (sugar) in the blood. It is a class of anti-diabetic drug called thiazolidinediones that are used in the treatment of type-2 diabetes. This is mainly depending on the presence of insulin for its mechanism of action. Pioglitazone is decreases the insulin resistance in the periphery and in the liver which will leads to the increased insulin dependent glucose disposal and leads to the decreased hepatic glucose output. Pioglitazone hydrochloride have the chemical name of [[±]-5-[[4-[2-[5-ethyl-2-pyridinyl] ethoxy] phenyl] methyl]-2,4] thiazolidine–dione monohydrochloride. Emperical formula is $C_{19}H_{20}N_2O_3S.HCL$, Molecular weight of this is 356.44g/mol. Physical properties of Pioglitazone is white to off white crystalline powder in nature, Solubility is in soluble in water & slightly soluble in ethanol.

The aim of the present study was to formulate and evaluate Pioglitazone hydrochloride pellets. The Pioglitazone hydrochloride immediate and controlled release pellets were prepared by solution/suspension layering technique by using croscarmellose in IR layer and three different polymers such as Ethyl cellulose, Eudragit L100, Xanthan gum as rate controlling polymers in four different ratios like 1:0.5,1:1, 1:1.5 and 1:2 to achieve desired drug release in CR layer. (Ghebresellasie I.2002).

MATERIALS AND METHODS

Materials

Pioglitazone hydrochloride was obtained as a gift sample from Thorab Pharmaceuticals Pvt. Ltd., Chennai, Non-Pariel seeds having sieve size #22/#24 obtained from Aadhya Biotech pvt. Ltd., Hyderabad, Ethyl cellulose, Eudragit L100, Xanthan Gum and croscarmellose sodium were procured from Loba chemicals pvt. Ltd., Mumbai, HPMC KE5 received from Himedia Laboratories Pvt. Ltd. Mumbai. Some of the solvents used for this formulation such as acetone, ethanol, dichloromethane and isopropyl alcohol are obtained from Lab India Pvt. Ltd., Hyderabad. For this formulation using

* Corresponding Author
Email: nelloremahesh22@gmail.com
Contact: +91-9490073583
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all reagents are in analytical grade. (Ghebre-sellasie I.2002).

Methods

Drug and excipient compatibility study

The drug and excipient compatibility study was performed by using FTIR.

Drug and excipient compatibility study performed by FTIR

Physicochemical characterization was performed by using Fourier-transform infrared (FTIR). The spectra were obtained using an FTIR spectrometer (Bruker Pvt.Ltd ., Germany). The compatibility study performed by the pure drug mixed with polymers to prepare a binary mixture. This drug and polymers mixed thoroughly with potassium bromide, an infrared transparent matrix, KBr pellets were prepared so as to contain approximately2% (2:100) of drug and excipient mixture at a pressure of 30.7 Mpa and a dwell time of 3minutes. The spectrum for drug was recorded over the range of 4000 to 400 cm-1.

Formulation of pellets by solution/suspension layer technique

The Pioglitazone pellets prepared by solution/suspension layering technique of pelletization, For this pelletization here we are using Non-pariel seeds (sugar pellets) (#22/#24) having the high solubility, and which is immediately get dissolved in aqueous media without buildup of sufficient osmotic pressure in the core. Increasing this dissolution rate by coated with 2%w/w HPMC E5 as a seal coat. (Palmieri F.G., Grifantini R 2000).

Pioglitazone immediate release pellets Preparation and coating procedure

Slurry of Pioglitazone hydrochloride with 6% croscarmellose sodium, 1% povidone k30 (w/w) and add 0.01% tween 80 were dissolved in 100ml acetone. The seal coated sugar pellets preheat up to 35ºc with gentle movement in a pan coater, and then sprayed prepared slurry coating % weight build up 30% w/w on sugar pellets while spraying the drug solution pan were allowed to rotate for about 10 min until uniform drug loading occurs. Spray rate inlet air temperature maintain at 35ºc should avoid agglomeration during the formulation time. (Venkates B. 2013)

Preparation of a coating solution

The Pioglitazone hydrochloride drug and Ethyl cellulose, Eudragit L100 and Xanthan Gum here taken in 4 different ratios those are 1:0.5, 1:1, 1:1.5 and 1:2 dissolved in 1:1 ratio of methanol and dichloromethane, ethanol and acetone respectively. And then finally we have to add the 0.1% of tween 80 and 0.5% PEG 400. Composition of coating solution is coated with all formulations. The above solutions filtered with nylon cloth and then taken into spray gun (Venkates B. 2013)

Coating procedure

Often the seal coating pellets are taken and then preheated up to 35ºc with gentle movement in a pan coater, and then sprayed prepared Pioglitazone hydrochloride, Ethyl cellulose, Eudragit L100 and Xanthan Gum in four different ratios. After the seal coated sugar pellets coating % weight build up for 30%, 31%, 32%, and 33% respectively, should maintain uniform drug and polymer coating or loading into the sugar pellets. During this process high inlet temperature will causes the agglomeration of beads why because of excessive drying or softening and sticking of the coating so should avoid this. Inlet air temperature should maintain at 35ºc. the pellets were then dried in a tray drier at about 45ºc to moisture content of this pellets maintain at ≤2%. The dried pellets sized by using a sifter to remove the agglomerates, broken pellets and fine powder. After coating the formulations are named with F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12. (Venkates B. 2013)

EVALUATION STUDIES

Percentage yield

All the 12 formulations of immediate and controlled release Pioglitazone hydrochloride pellets prepared by pan coating were evaluated for percentage yield of the pellets. The actual percentage yield of pellets calculated by using this formula

$$Percentage\ yield = \frac{practical\ yield\ of\ pellet}{theoretical\ yield\ of\ pellets}$$

Drug content analysis

This is mainly determined by using U.V spectrometry, pellets containing of 30 mg equivalent of drug taken into 100ml volumetric flask which is containing of pH 7.4 phosphate buffers. Which is mainly help full for complete solubility sonication was done for 30 min which is filtered through watmann filter paper. Ofter that the filtrate was analyzed by using U.V spectrophotometer at the wavelength range of 286nm (Venkates B. 2013)

Particle size distribution by sieve analysis

Sieve analysis is done by using electromagnetic sieve shaker. Four sieves such as #18, #20, #22, #44 and a collector plate were taken, cleaned and dried in an oven for free of moisture. (Venkates B. 2013)

***In-vitro* drug release study**

Pioglitazone hydrochloride 30mg equivalent weight of both immediate 10mg and controlled release 20mg pellets were filled in '0' size transparent hard gelatin capsule by hand filling capsule machine and the drug release studies were carried out for each formulation by using Dissolution test apparatus Type-1. The basket rotation speed adjusted to 100 rpm, 900ml of 0.1N HCL for 2hours having the pH 7.4 phosphate buffer

Table 1: composition of coating solution

	Drug : Polymer ratio	Percentage of coating	Polymers used
S1	1;0.5	30	
S2	1;1	31	Eudragit L100
S3	1;1.5	32	
S4	1;2	33	
S5	1;0.5	30	
S6	1;1	31	Ethyl cellulose
S7	1;1.5	32	
S8	1;2	33	
S9	1;0.5	30	
S10	1;1	31	Xanthan Gum
S11	1;1.5	32	
S12	1;2	33	

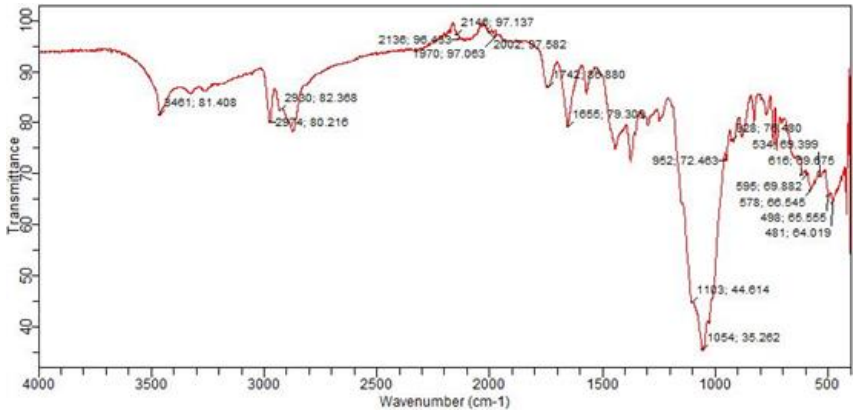

Figure 1: FTIR spectra of Pioglitazone hydrochloride

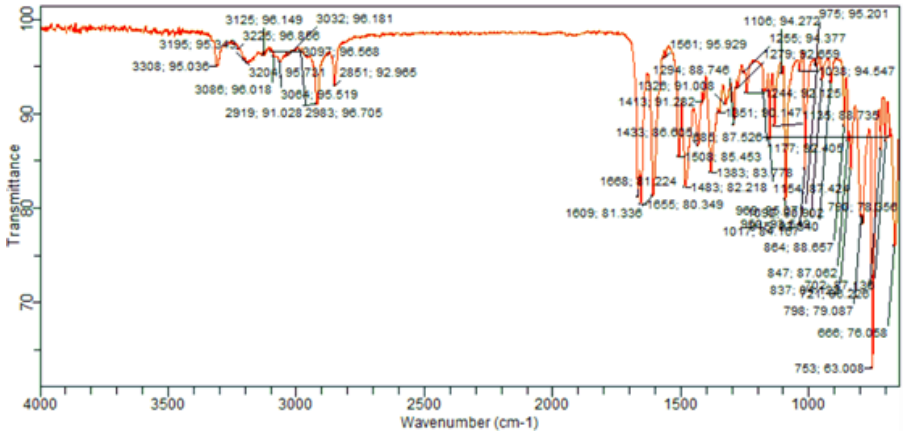

Figure 2: FTIR spectra of Pioglitazone + Eudragit L100

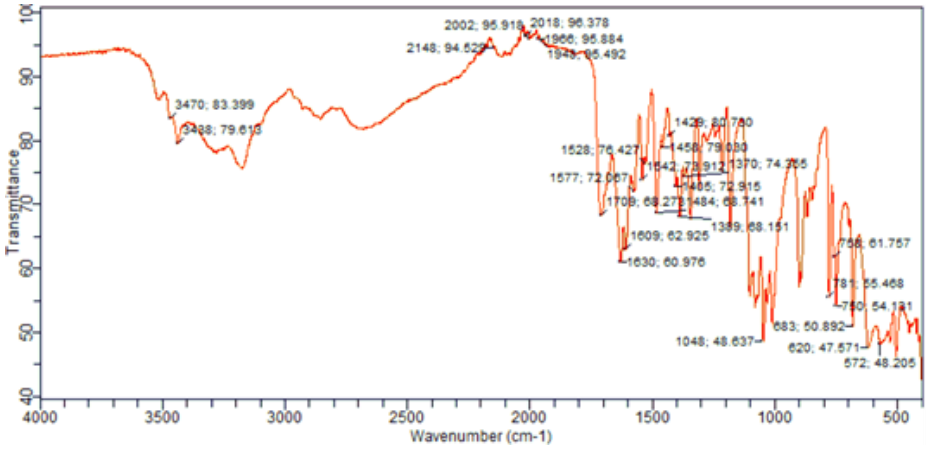

Figure 3: FTIR spectra of Pioglitazone + Ethyl cellulose

Table 2: %Yield of pellets and % Drug content Analysis data of prepared pellets

Formulation code	%yield of pellets	%drug content analysis
Immediate release	94.3	96.2 ± 0.5
F1	86.1	95.1 ±0.6
F2	88.1	96.2 ±0.8
F3	90.2	90.4 ±0.4
F4	91.5	95.6 ±0.9
F5	89.4	95.7 ±0.5
F6	92.4	95.9 ±0.4
F7	85.1	93.4 ±0.8
F8	87.5	92.4 ±0.1
F9	92.5	93.6 ±0.9
F10	93.8	96.1 ±0.9
F11	96.5	98.5 ±0.9
F12	93.1	97.4 ±0.8

Table 3: In-vitro drug release data from formulation F1-F6

pH	Time(H)	Cumulative%drug release					
		F1	F2	F3	F4	F5	F6
1.2	1	36.56	35.45	32.52	33.45	33.13	33.99
	2	36.99	37.33	35.54	40.15	34.98	39.45
	3	43.32	39.99	39.54	49.21	43.21	41.79
	4	49.30	45.95	42.84	56.14	49.99	53.79
	5	50.36	49.65	49.65	59.78	56.79	59.79
	6	53.36	56.35	52.45	65.14	69.72	61.95
	7	59.12	59.36	59.64	71.78	76.76	69.85
	8	68.65	65.21	63.45	73.12	82.94	72.52
7.4	9	72.33	76.34	69.14	86.45	89.74	79.31
	10	85.99	85.45	76.65	90.12	90.12	85.95
	11	93.66	92.32	89.21	91.42	90.99	90.14
	12	91.33	90.21	92.14	90.47	92.14	91.51

Table 4: In-vitro Drug release data from Formulation F7-F12

pH	Time	Cumulative % drug release					
		F7	F8	F9	F10	F11	F12
1.2	1	35.68	36.54	35.98	36.22	38.69	37.55
	2	39.54	41.22	39.25	40.44	45.65	40.32
	3	42.65	49.36	44.44	42.55	49.69	45.32
	4	56.45	45.98	49.55	49.33	59.98	49.36
	5	69.65	52.36	55.32	55.22	68.99	.55.35
	6	75.88	59.74	59.25	56.89	78.98	56.15
	7	82.22	69.78	69.54	65.89	85.99	62.45
	8	89.78	72.64	77.54	64.21	89.88	69.54
7.4	9	92.65	79.54	75.66	78.24	90.99	71.54
	10	93.45	89.21	7932	89.99	95.89	75.54
	11	92.22	90.41	89.55	90.99	96.65	83.54
	12	93.55	93.24	90.21	92.89	97.50	92.35

Table 5: Particle size distribution of Pioglitazone hydrochloride

Formulation code	Nominal mesh Aperture size	% weight of pellets re-tained	Cumulative % of pellets Re-tained
	1000	**0**	**0**
Immediate release	850	8	8
	710	84	89
	355	6	89
	1000	0	0
	850	9	6
F1	710	86	98
	355	6	89
	1000	0	0
	850	7	9
F2	710	88	95
	355	8	88
	1000	0	0
	850	8	8
F3	710	83	88
	355	7	95
	1000	0	0
	850	6	7
F4	710	82	88
	355	8	87
	1000	0	0
	850	8	7
F5	710	88	85
	355	9	89
	1000	0	0
	850	9	8
F6	710	84	89
	355	7	85
	1000	0	0
	850	7	9
F7	710	86	85
	355	8	88
	1000	0	0
	850	8	9
F8	710	81	87
	355	6	85
	1000	0	0
	850	7	8
F9	710	87	88
	355	9	85
	1000	0	0
	850	8	8
F10	710	89	86
	355	8	83
	1000	0	0

	850	7	8
F11	710	88	87
	355	9	81
	1000	0	0
	850	8	9
F12	710	87	82
	355	8	80

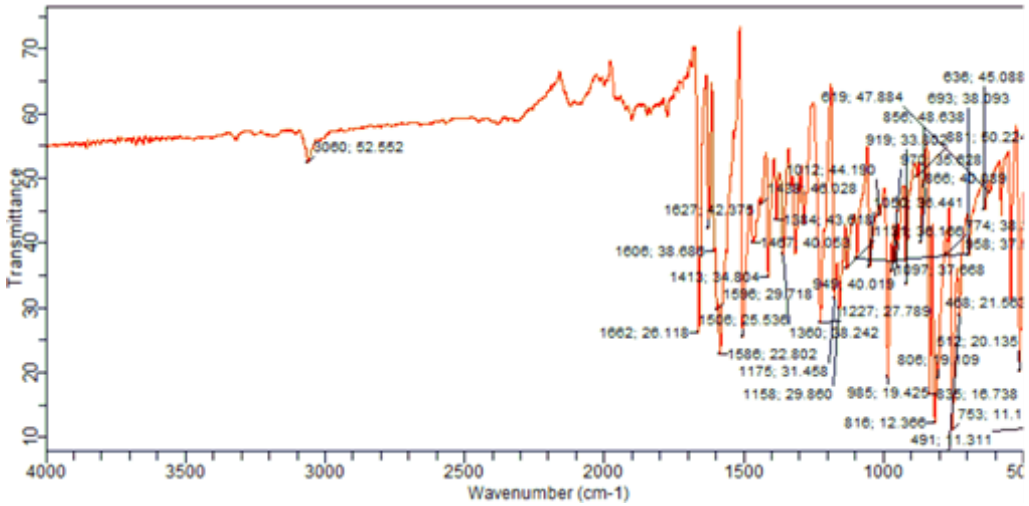

Figure 4: FTIR spectra of Pioglitazone + Xanthan Gum

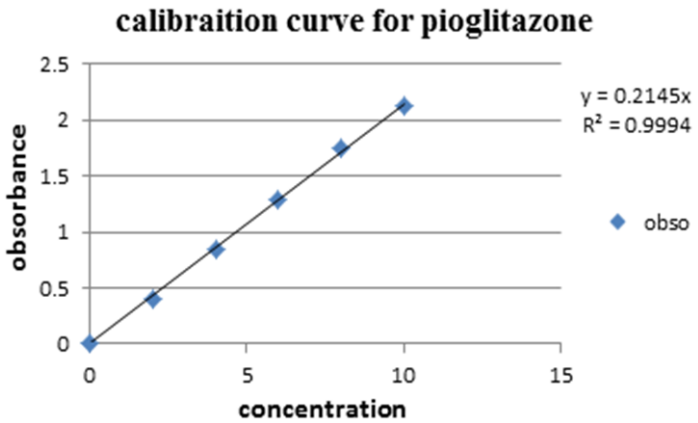

Figure 5: Standard calibration curve for Pioglitazone hydrochloride

solution for 10 hours here taken as a dissolution media, temperature maintained at 37ºc up to completion of this dissolution study. 1ml sample with drawn at predetermined time interval of 1hour to12hours and replace with fresh dissolution medium. The above collected sample filtered and analyzed by UV spectrophotometer at286nm. Those results helpful for understand kinetic treatment and obtain best fit model.

RESULTS AND DISCUSSION

Drug and excipient compatibility study

Compatibility study of Pioglitazone and polymers was determined by FTIR Spectroscopy and the results shown that the Pioglitazone is compatible with Eudragit L100, Ethyl cellulose and Xanthan Gum polymers.

Percent Yield

The percent yield of Pioglitazone hydrochloride pellets was calculated. The % Yield of immediate release pellets was found to be 94.3% and the controlled release pellets formulations F1 to F12 was found to be in the range of 86.1% to 93.1%. (Krishnamoorthy V2011)

Drug content analysis

Percent drug content of Pioglitazone hydrochloride pellets of immediate release F1-F12 of all formulations determined by UV spectrophotometric method. Three trails analyzed from each formulation. The mean value and standard deviation of all formulations are calculated. The drug content analysis of immediate release pellets was found to be in the range of 96.2% and controlled release formulations F1-F12 was found to be

90.4 to 98.5 this result within the range of IP. (Ghebre-sellasie I.2002).

Sieve analysis method

This was carried out for both immediate and controlled release formulations F1-F12 formulations indicates that the majority of the pellets 85-89% falls in the size range of 852-710µm that is #20/22 mesh fraction that is 20 pass and 22 is retained. The yield of #20/22 mesh fraction was found to be good. 5-1% shown in 1000-850µm that is #18/20 mess and 4-8% shown in 710-355µm that is #22/44 mess. (Krishnamoorthy V.2011)

***In-vitro* Dissolution study**

The dissolution study of Pioglitazone hydrochloride pellets was carried out in acid buffer of pH 1.2 that is 0.1 N HCL for 12 hours by using XXIII dissolution apparatus. In that the sample was withdrawn at different intervals and analyzed at286nm. The burst effect shown in first one hour because presence of croscarmellose sodium which is having super dis-integrant property. Those 12 formulations was coated by 3 different polymers at 4 different ratios by increasing coating percentage weight such as 30%, 31%, 32% and 33% which is shows the release range from 90.99-97.55%. If the polymer coating percentage increase means release rate also increased. All the 12 formulations was compared among those formulation F11 shows the best release that is 97.50%. In that having Pioglitazone drug and Eudragit L100. (Ghebre-sellasie I.2002).

CONCLUSION

It is concluded that the Formulate and Evaluate Pioglitazone pellets by using Eudragit L100, Ethyl cellulose, Xanthan gum those are in different ratios as a release regarding nature polymers by solution/suspension method or layer technique, this technique have the main advantage of prolong the drug release leading to minimize the peak and valley effect in the plasma and provide the patient convenience.

1. Compatibility or physicochemical characteristics of the Pioglitazone hydrochloride with Polymers was determined by using the FTIR Spectroscopy results showed that the Pioglitazone is compatible with all the 3 polymers such as Eudragit L100, Ethyl cellulose and Xanthan Gum.
2. All twelve formulations from F1 to F12 containing the Eudragit L100, Ethyl cellulose &Xanthan gum in four different ratios that is (drug:polymer) 1:0.5,1:1, 1:1.5& 1:2 ratios were prepared.
3. Finally the best results was obtained *in-vitro* Dissolution study among the all twelve formulations from F1 to F12, combination of Pioglitazone with Eudragit L100 shows the 97.50% drug release at 12 hour.

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Drug profile is available at http/www.drug bank.com./Pioglitazone hydrochloride. accessed on 20-01-2015

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