Research Article

International Journal of Pharmacy and Industrial Research

ISSN	Print	2231 – 3648
	Online	2231 – 3656

DISSOLUTION ENHANCEMENT OF PIOGLITAZONE HYDROCHLORIDE USING β- CYCLODEXTRIN

*Sowmya C, Suryaprakash Reddy C, Bharath kumar G, Siva Prasad N
Raghavendra Institute of Pharmaceutical Education and Research,
Anantapur, Andhra Pradesh, India – 515 721.

Abstract

Pioglitazone hydrochloride is an oral anti diabetic drug. It is poorly soluble in water. In the present investigation an attempt was made to increase the solubility and dissolution of Pioglitazone by preparing β-cyclodextrin complexes in different ratios. Prepared inclusion complexes were evaluated for angle of repose, Carr's index, Hausner's ratio and in *vitro* dissolution studies. The *in vitro* dissolution studies had shown that the complexes containing pioglitazone hydrochloride: β cyclodextrin in 1:10 ratio had shown better enhancement in dissolution rate when compared with other ratios.

Key words: Pioglitazone hydrochloride, β–cyclodextrin, Inclusion complex, Angle of repose, Invitro dissolution.

Introduction

Solubility and dissolution of drug substance is prerequisite for absorption which are rate limiting steps in the bioavailability of poorly soluble drugs like Pioglitazone which belongs to BCS class II[1, 2]. There are various techniques to improve the solubility of hydrophobic drugs. Some traditional and novel approaches to improve the solubility and dissolution are Particle Size Reduction, Solid Dispersion, Nano suspension, Supercritical Fluid Technology, Cryogenic Technology, Inclusion Complex formation and Floating Granules[3] etc. Solid dispersions are one of the most successful strategies to improve the drug release of poorly soluble drugs. The beta and gamma cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility[4]. The molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. β-cyclodextrins are cyclic oligosaccharides, whose molecule structure is like a cylinder compound from 7 glucose groups[5]. The function of β-Cyclodextrin depends on its cylinder molecule structure which can be easy to integrate other materials. That feature is applied widely in industry. The

Author for Correspondence:
Sowmya C,
Raghavendra Institute of Pharmaceutical Education and Research,
Saigram, KR Pally cross, Chiyyedu, Anantapur, Andhra Pradesh, India– 515721.
Email: drsowmyariper@rediffmail.com

solubility degree of β-Cyclodextrin in water is 1.85%w/w[6]. β cyclodextrins have many applications in the field of pharmacy as drug delivery vehicles, solubilizers, stabilizers[7] etc.

Experimental

Materials

Pioglitazone HCl, β-cyclodextrins were obtained as gift samples from Matrix laboratories Ltd Hyderabad. Methanol was procured from Loba Chem. All chemicals were of analytical grade.

Methods

Preparation of inclusion complexes

β-cyclodextrin complexes of Pioglitazone were prepared by using solvent evaporation technique[8]. The drug was accurately weighed and taken in a mortar. The drug was properly triturated to remove any lumps. The polymer beta cyclodextrin was added in geometrical ratio, mixed and triturated well and about 20 ml of methanol was added such that the drug and polymer both were dissolved. Then slowly the solvent was allowed to evaporate and the complex was obtained.

Table 01: Formulation of Pioglitazone HCl β cyclodextrin Inclusion complexes

Ingredients(mg)	F1	F2	F3
Drug	100	100	100
β cyclodextrin	500	750	1000
Methanol	q.s	q.s	q.s

Evaluation[9, 10]

1. **Angle of repose (θ)**

These are the simple and related techniques for measuring the resistance to particle moment. Angle of repose is defined as the maximum angle possible between the surface of a pile of powder and horizontal plane,

$$\text{Tan } \theta = h/r$$

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

Where,

h =height of pile

r =radius of base of pile

θ =angle of repose

Method: A glass funnel is held in place with a clamp on a ring support over a tile. Approximately 100gms of powder is transferred into funnel through a mesh size number 20 keeping the orifice of the funnel blocked by the thumb.

When the powder is emptied from the funnel, the angle of the heap to the horizontal plane is measured with a scale. The height of the pile (h) and the radius at the base is measured with a ruler. The angle of repose is thus estimated.

2. **Bulk density**

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is of great importance when considers the size of high dose capsule product or homogenicity of allow dose formulation in which these are large differences in drug and excipient densities.

Bulk density is determined by graduated cylinder containing a known mass of powder whose initial volume is noted. Cylinder is fixed on the mechanical tapper apparatus. Then the final volume is noted, and this bulk

volume. Then bulk density is calculated is using

$$\text{Bulk density } (\rho) = \frac{\text{Mass of the powder } (W)}{\text{Bulk volume}}$$

3. **Compressibility index**

It is defined as

$$\text{compressibility index} = \frac{\text{tapped density} - \text{fluff density}}{\text{tapped density}} \times 100$$

Method: Using a suitable adhesive, the base of a 10 ml tarred measuring cylinder is fixed to the standard rubber bung at the top of the 250 ml cylinder. A powder sample (about 5.0 g) is transferred into the tarred 10 ml cylinder with the help of a funnel. The 250 ml measuring cylinder is placed on the tapping apparatus. The initial volume occupied by the powder is denoted as V_0.

The contents are tapped in the following order, 2, 4, 6, 8, 10, 20, 30 and 50 taps. After completing the tappings, the volume is denoted as V_2, V_4 .....V_{50}.

The powder is carefully collected from the cylinder and weighed (W).

Fluff density (ρ_b, minimum) = w/v_o g/cc

Tapped density (ρ_b, maximum) = w/v_{50} g/cc

Consolidation index can be calculated using the equation

The nature of flow is inferred by comparing the data with the index given in the below table

4. **Hausner ratio**

It is defined as the ratio of the tapped density to bulk density it can also be calculated by using the formula by using Carr's consolidation index.

$$\text{Hausner ratio} = \frac{\rho\text{tapped}}{\rho\text{bulk}}$$

$$\text{Hausner ratio} = \frac{100}{100 - C}$$

Where, C is compressibility index value.

5. ***Invitro* dissolution test method development**

Preparation of standard stock solution

Standard stock solution of Pioglitazone Hcl is prepared by dissolving 10mg of drug in methanol and making up the volume to 10ml in three different 10ml volumetric flasks to get 1mg/ml

Determination of λ_{max}

From the stock solutions, a working standard was prepared. The absorption spectrum forpioglitazone Hcl was recorded using the concentration of 10 µg/mL and it was found to show absorption maxima at , 270 nm. The Calibration curve was prepared in the concentration range of 1-10 µg/mL, at selected wave length.

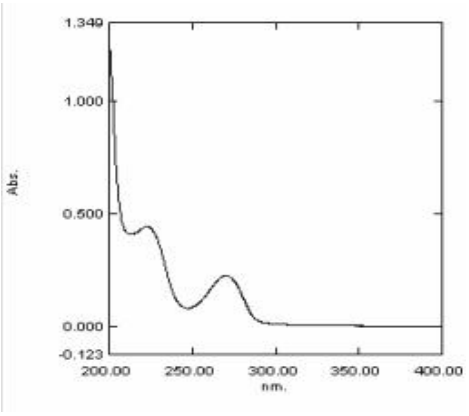

Figure 01: UV spectra of Pioglitazone HCl standard

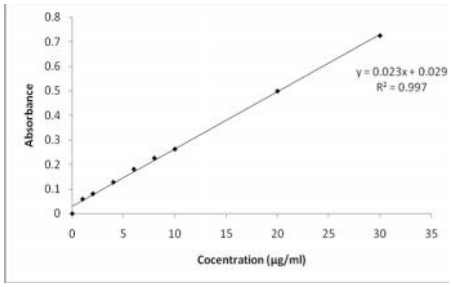

Figure 02: standard graph of Pioglitazone HCl

The Pioglitazone HCl obeys Beer lamberts law in the range of 1-34µg/ml and it had shown a slope, intercept and R^2 of 0.0234, 0.0297, 0.9972 respectively. The complexation mixtures equivalent to 10 mg of Pioglitazone HCl was added directly in to the dissolution jars then dissolution was performed by using USP apparatus II (paddle type).Temperature was maintained at 37.5°C[11].

Dissolution parameters

The dissolution testing was performed using USP type II (paddle) dissolution apparatus using water as the medium, temperature of 37.5±0.5°c, and RPM of 50±2. Equal amounts of dissolution medium was collected and replaced with the fresh dissolution medium. The samples were analysed using Systronics UV Visible double beam Spectrophotometer 2202.

Results and discussion

Table 02: flow properties of prepared complex mixtures

Formulation code	Angle of Repose ± SD	Density(g/cm^3)		Hausner Ratio±SD	Carr's index±SD
		Bulk Density ± SD	Tap Density ± SD		
F1	23.54±0.032	0.456±0.0047	0.555±0.0093	1.13±0.044	14.51±0.086
F2	23.47±0.044	0.465±0.0035	0.553±0.02	1.14±0.043	10.39±0.055
F3	25.22±0.042	0.453±0.0046	0.500±0.008	1.12±0.032	13.51±0.086

The angle of repose was found to be 23.54 to 25.22, which show good flow property.

The Density, Carr's index and Hausner Ratio showed satisfactory results.

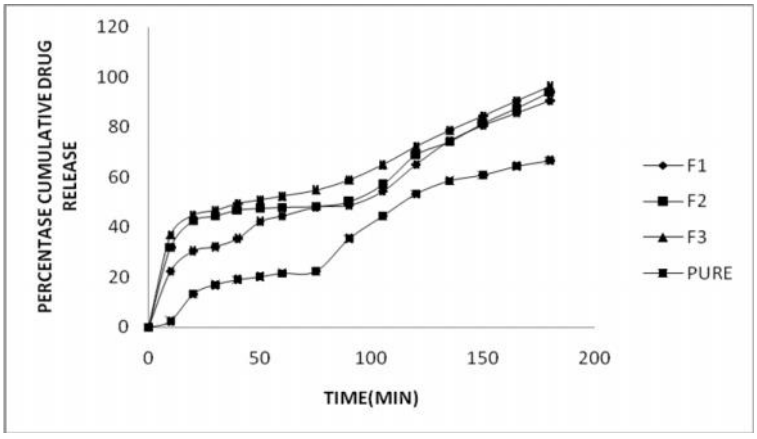

Figure 03: Release profile of Pioglitazone HCl from β cyclodextrin inclusion complexes

From the graph it is clear that F3 (drug: β cyclodextrin, 1:10) had shown better release than the F2 (1:5), F1 (1:7.5) and pure. At 180th min the F1, F2,F3, pure had released 90.42, 94.09, 96.4, 66.66 mg of Pioglitazone HCl respectively.

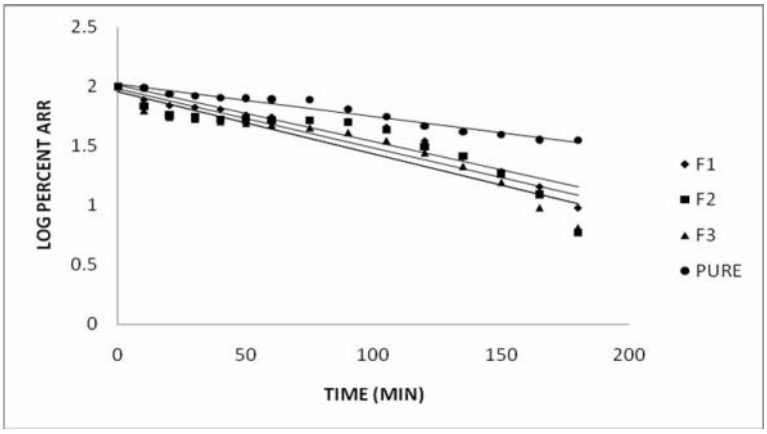

Figure 04: First order plots

Table 03: Release profiles of Pioglitazone HCl

Time (min)	Cumulative percent release ± sd*			
	F1	F2	F3	PURE
0	0	0	0	0
10	22.46±0.01	31.92±0.25	36.89±0.01	2.36±0.01
20	30.50±0.23	42.49±0.26	44.66±0.14	13.28±0.11
30	32.09±0.26	44.52±0.24	46.54±0.14	16.89±0.01
40	35.46±0.29	46.89±0.12	49.28±0.17	19.07±0.12
50	42.3±0.01	47.53±0.15	50.76±0.13	20.24±0.17
60	44.37±0.01	47.98±0.21	52.29±0.11	21.50±0.15
75	47.97±0.21	48.29±0.11	54.86±0.13	22.31±0.15
90	48.77±0.11	49.98±0.14	58.83±0.21	35.45±0.13
105	54.45±0.14	56.83±0.13	64.82±0.13	44.49±0.14
120	65.07±0.15	68.85±0.11	72.09±0.14	53.27±0.10
135	74.36±0.13	74.20±0.12	78.64±0.13	58.42±0.01
150	80.63±0.12	81.52±0.19	84.32±0.12	60.82±0.19
165	85.56±0.21	87.63±0.17	90.42±0.14	64.42±0.17
180	90.42±0.13	94.09±0.24	96.40±0.11	66.66±0.14

* mean of three replicates

Table 04: Release characteristics

S.No	First order Equation	First order R^2	K1(hr^{-1})	t_{50} (min)	t_{90} (min)
F1	Y=-0.0048x+2.022	0.9138	0.011	87	186
F2	Y=-0.005x+1.9804	0.8354	0.0115	70	168
F3	Y=-0.0058x+1.983	0.8393	0.013	42	164
PURE	Y=-0.0027x+2.022	0.9653	0.006	116	_

The F3 had shown K1 of 0.013 hr^{-1} which is more than F2 (0.0115 hr^{-1}), F1 (0.011 hr^{-1}) and pure (0.006 hr^{-1}) and t_{50}, t_{90} of F3 was found to be (42min, 164min); which is less than F2(70min, 168min); F1(87min, 186min); and pure(116min). Hence F3 has better than the F2, F1, and pure.

Conclusion

The prepared formulations had shown good Angle of repose, Compressibility Index and Hausner Ratio. Among them F3 had shown better than F2, F1 and Pure. The F3 has shown better dissolution rate than the F2, F1, and pure. As the concentration of β cyclodextrin increases, the dissolution rate is also increased. So β cyclodextrins can be employed to improve the dissolution of poorly water soluble drug Pioglitazone HCl.

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