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EFFECT OF HYDROPHILIC POLYMERS ON PIOGLITAZONE COMPLEXATION WITH HYDROXYPROPYL-β-CYCLODEXTRIN

PANKAJ GAJARE [*a], CHANDRASHEKHAR PATIL[a], NAVANATH KALYANE[a], YOGESH PORE[b]
[a]*Department of Pharmaceutics, BLDEA's College of Pharmacy, Bijapur, Karnataka, 586103, India*
[b]*Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad, Maharashtra, 415124, India*

The interactions between pioglitazone hydrochloride, hydroxypropyl-β-cyclodextrin (HPβCD) and the hydrophilic polymers; polyvinylpyrrolidone (PVP K30) and hydroxypropyl methylcellulose (HPMC K4 M) in solution state employing phase solubility method were investigated. Although phase solubility studies indicated A_L-type of solubility curves both in absence or presence of hydrophilic carriers used, the apparent stability constant (*Ks*) of binary complex obtained at room temperature, 1204.88 M^{-1}, was decreased to 788.14 M^{-1} and 576.73 M^{-1} with the addition of PVP and HPMC respectively indicating no positive effect of addition of these substances to promote higher complexation efficiency. Therefore, solid binary systems of pioglitazone-HPβCD were prepared and characterized by FTIR, XRD, DSC and dissolution studies. The dissolution rate of pioglitazone was significantly improved by complexation with HPβCD, as compared with pure drug and physical mixture.

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Keywords: Dissolution, Hydroxypropyl-beta-cyclodextrin, Hydrophilic carriers, Inclusion complex, Phase solubility, Pioglitazone hydrochloride

1. Introduction

Pioglitazone (Fig. 1), chemically, [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]-2, 4-] thiazolidinedione monohydrochloride, is an oral antidiabetic drug effective for reactive hypoglycemia and aggravated glycemic metabolism associated with insulin resistance [1, 2]. It is an activator of the intracellular peroxisome proliferator-activated receptor-γ, and decreases metabolic and vascular insulin resistance causing rise in HDL-cholesterol plasma in humans [3, 4]. However, the poor aqueous solubility of pioglitazone [5] may cause dissolution problems during its formulation. Therefore, it was thought to develop effective methods for dissolution enhancement of pioglitazone using cyclodextrin as a carrier. ^{1}HNMR spectroscopic studies on pioglitazone-β-cyclodextrin inclusion complex have been already reported [1]. In this article, physicochemical investigation of pioglitazone-hydroxypropyl-β-cyclodextrin (HPβCD) system in presence of hydrophilic polymers has been addressed.

Although cyclodextrins have been proved to be effective carriers for solubility and / or dissolution enhancement of poorly soluble drugs, their relatively low water solubility and low

* Corresponding author: gajare_pankaj@rediffmail.com

complexation efficiency limit their use in formulations [6-9]. Due to lower complexation efficiency of cyclodextrins, a large amount of CDs is required to solubilize small amounts of a poorly aqueous-soluble drug. It has been reported that addition of small amount of hydrophilic carriers such as PVP K30 and / or HPMC can improve the complexation efficiency of cyclodextrins and assist to reduce their workable amount in drug delivery systems [10-13]. Thus the enhanced complexation can be achieved with the formation of ternary systems between a drug, cyclodextrin and a suitable ternary substance.

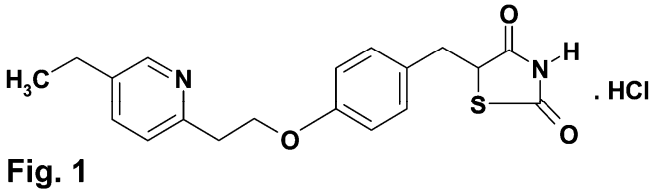

Fig. 1 Structure of Pioglitazone HCl

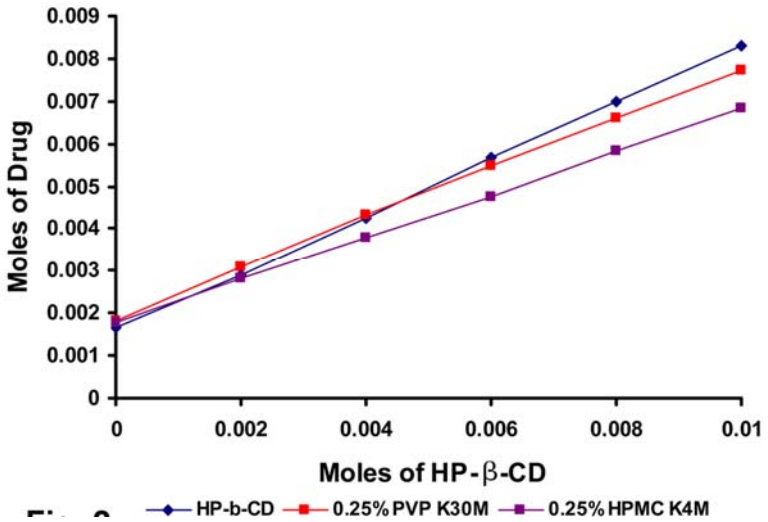

Fig. 2 Phase solubility curves of pioglitazone–HPβCD system with or without hydrophilic polymers.

The purpose of this work was to investigate the effect of water-soluble polymers viz. PVP K30 and HPMC (K4 M) each in the concentration of 0.25% (w/v) separately on stability constant of HPβCD-pioglitazone inclusion complex by phase solubility method. However, the results obtained from the phase solubility studies served as a basis for proper choice of none of the hydrophilic carrier for ternary systems. Therefore, binary systems of pioglitazone-HPβCD were prepared and characterized. The solubility type and the stability constants of the complex were established according to the methods described by Higuchi and Connors. The inclusion complex was prepared by kneading method while physical mixture was prepared by mixing individual components. Fourier transformation-infrared spectroscopy (FTIR), X-ray powder diffractometry (XRD) and Differential scanning calorimetry (DSC) were employed to investigate the solid state properties of binary systems of pioglitazone. The dissolution properties of pure pioglitazone, physical mixture and inclusion complex were further evaluated.

2. Experimental

2.1. Materials

Pioglitazone was provided by Emcure Pvt. Ltd., Pune, India as a gift sample. HPβCD was kindly provided by Panacea Biotech, Chandigad, India. HPMC K4 M was kindly gifted by Colorcon Asia Pvt. Ltd., Goa, India. PVP K30 was purchased from Loba Chemie, Mumbai, India. All the reagents were of analytical grade.

2.2. Phase solubility studies

Phase solubility studies were carried out in distilled water according to the method described by Higuchi and Connors [14]. Excess amount of pioglitazone was added to 20 mL of aqueous solution containing various concentrations of HPβCD (0–0.01 M) with or without fixed concentrations of PVP or HPMC (0.25% w/v) and the suspensions were shaken on rotary shaker at 25 ± 2°C for 72 hrs. Once the equilibrium was achieved, the samples were filtered through 0.45 μm membrane filter and appropriately diluted. The concentration of pioglitazone was determined spectrophotometrically (Shimadzu 1700, Japan) at 268 nm. The apparent 1:1 stability constants were calculated from the phase solubility diagrams, according to the equation (1).

2.3. Preparation of physical mixture of pioglitazone-HPβCD

The physical mixture (PM) of pioglitazone -HPβCD binary system in equimolar quantities was prepared by mixing individual components and sieved through mesh number 60.

2.4. Preparation of inclusion complex by kneading method

The mixture of pioglitazone and HPβCD in equimolar quantities was triturated in a mortar with a small volume of water-ethanol (1:1 v/v) solution till a homogenous paste was formed. The paste was kneaded for 45 min and then dried at 45°C for 24 hrs in an oven. The dried mass was pulverized and sieved through mesh number 60.

2.5. Fourier transformation infrared spectroscopy (FTIR)

Infrared spectra were recorded using a Jasco FTIR spectrometer 5300 (Japan) spectrometer using KBr disks. The scanning range was kept from 4000 to 400 cm^{-1}.

2.6. X-ray powder diffractometry (XRD)

The XRD patterns of all samples were recorded using Philips Analytic X-Ray – PW 3710 (Philips, Almelo, The Netherlands) diffractometer with tube anode Cu over the interval 5-60°/2θ. The generator tension (voltage) and generator current was kept 40 kV and 30 mA respectively with scanning speed of 2°/min.

2.7. Differential scanning calorimetry (DSC)

DSC measurements were carried out on a Mettler DSC 30S (Mettler Toledo Pvt. Ltd. Swizerland) differential scanning. The accurately weighed sample was placed in an aluminum pan. An empty aluminum pan was used as reference. The experiment was carried out in nitrogen atmosphere (flow rate 40 ml/min) at scanning rate of 10°C/min in the range of 30–300°C.

2.8. Dissolution studies

The dissolution rate studies of pure drug and binary systems were performed in 900 ml of distilled water at 75 rpm (37 ± 0.5°C) in a dissolution apparatus (Electrolab DA-3 Model, Mumbai, India) using the paddle method. 30 mg of pioglitazone or its equivalent amount of formulation was added to dissolution medium and the samples were withdrawn at appropriate time intervals. The volume of dissolution medium was adjusted to 900 ml by replacing it with fresh medium. The samples were immediately filtered through 0.45 μm membrane filter, suitably diluted and analysed spectrophotometrically at 268 nm.

3. Results and discussion

3.1. Phase solubility studies

The phase-solubility curves of pioglitazone in aqueous HPβCD solutions in absence and in presence of hydrophilic carriers; PVP or HPMC (0.25% w/v) are displayed in Fig. 2. The figure indicated a linear increase in solubility of pioglitazone as a function of HPβCD concentration, demonstrating A_L-type phase solubility curves in both binary and ternary systems with the formation of a complex. The possible stoichiometry of complex assessed was 1:1 as the slopes of these solubility diagrams were all less than 1. The apparent stability constants (*Ks*) of the binary and ternary complexes were obtained from the equation 1.

$$K_S = \frac{slope}{S_0(1 - slope)} \tag{1}$$

S_0 is the solubility of pioglitazone in absence of CDs.

The calculated values of *So*, slopes of phase-solubility diagrams, r^2 and *Ks* are presented in Table 1 which indicated that the stability constant of pioglitazone in HPβCD aqueous solution was 1204.88 M^{-1} in absence of hydrophilic polymers, but decreased to 788.14 M^{-1} and 576.73 M^{-1}, with the addition of 0.25% (w/v) of PVP and HPMC respectively. From Table 1, it was observed that the slope of phase solubility curve in ternary systems was also decreased with simultaneous little increase in intrinsic solubility of pioglitazone. From these results, it could be concluded that the addition of hydrophilic carriers could not offer any advantage to promote the solubilizing power of HPβCD.

Table 1 Effect of hydrophilic polymers, PVP K30 and / or HPMC K4 M on the intrinsic solubility (S_o), slope of phase-solubility diagrams and stability constant (K_s) for binary and ternary systems of pioglitazone with HPβCD.

System	r^2	Slope	S_0	K_s	K_{TS}/K_{BS}
Drug-HPβCD	0.9996	0.6679	0.001621	1204.88	----
Drug-HPβCD-0.25% PVP	0.9992	0.5899	0.001894	788.14	0.65
Drug-HPβCD-0.25% HPMC	0.9996	0.5056	0.001769	576.73	0.48

K_{TS}/K_{BS} is the ratio of K_s for ternary and binary complexes.

Earlier papers have suggested several mechanisms such as formation of micelles or aggregates with high *Kc* values in ternary systems, hydrogen bond formation, Van der Walls interactions, hydrophobic interactions between drug, cyclodextrin, and the water-soluble polymer

and polymer viscosity which contribute to the improved drug solubility in the presence of water-soluble polymers [15, 12]. It has been also reported that complexation efficiency or *Kc* values can be enhanced by autoclaving the complexing media or heating them at higher temperature conditions [16, 17]. Thus, this might be the reason for significant decrease in the stability constants in case of ternary systems with hydrophilic carriers where all phase solubility studies were performed without certain types of treatment such as autoclaving. Further, lower viscosity and decreased formation of aggregates conferred by the polymer in complexing media might be contributing for negative effect of addition of both the polymers [12, 16, 18]. The obtained results are in full agreement with the reports suggested in earlier papers.

3.2. Fourier transformation-infrared spectroscopy (FTIR)

Fig. 3 displays the FTIR spectra of pioglitazone, HPβCD, physical mixture and pioglitazone-HPβCD inclusion complex. IR spectrum of pure pioglitazone (Fig. 3B) is characterized by 3364 cm^{-1} (N-H stretching amide), 3084 cm^{-1} (aromatic C-H stretching), 2928 cm^{-1} (aliphatic C-H stretching asymmetric), 1743 cm^{-1} (amide C = O stretching), 1616 cm^{-1} (C=C), 1460 cm^{-1} (ring C-N stretching), 1242 cm^{-1} (C-S stretching), 1084 cm^{-1} (aliphatic C-O-C) and 850 cm^{-1} (para disubstituted aromatic ring).

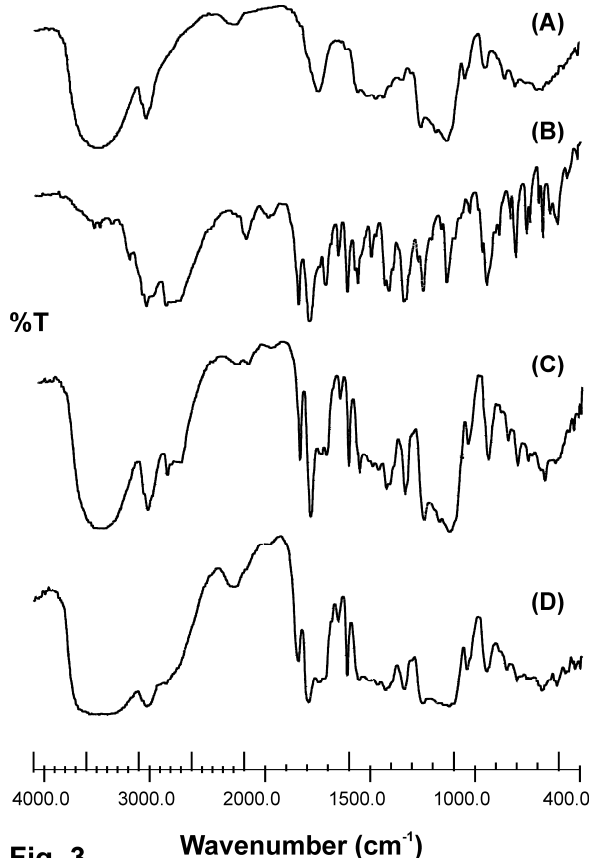

Fig. 3 FTIR spectra of pioglitazone-HPβCD binary systems: (A) HPβCD; (B) pioglitazone; (C) physical mixture; (D) inclusion complex.

The IR spectrum of pure hydroxypropyl-β-cyclodextrin (Fig. 3A) is characterized by prominent peaks at 3412 cm^{-1} (O-H), 2928 cm^{-1} (C-H), 1647 cm^{-1} (H-O-H bending), 1032 cm^{-1} (C-O-C).

No significant alterations in the IR bands of pure were detected in the physical mixture ((Fig. 3C). However, some of the peaks of pioglitazone were slightly shifted and found to be attenuated. The peak of N-H was found to be disappeared or might be overlapped by O-H stretch

of HPβCD. However, IR spectrum of physical mixture could be diagnosed as a superimposition of the bands of pure drug and HPβCD.

Significant changes were recorded in IR spectrum of inclusion complex (Fig. 3D). Almost all peaks of pioglitazone were smoothened indicating strong physical interaction between pure drug and HPβCD. The peak of amide carbonyl was appeared with decreased peak intensity. However, the broad peak of O-H of HPβCD was consistently appeared in both the binary systems. The peak of HPβCD 1647 cm^{-1} due to water of crystallization was disappeared which might be because of the replacement of water molecules by pioglitazone inside the HPβCD cavity indicating formation of inclusion complex in solid state.

All the binary systems of pioglitazone-HPβCD did not show any new peaks, indicating non covalent interaction in inclusion complex [19].

3.3. X-ray powder diffractometry (XRD)

The X-Ray diffraction pattern of pioglitazone (Fig 4B) exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The X-Ray diffraction pattern of physical mixture (Fig 4C) was simply a superimposition of each component with peaks of both pioglitazone and HPβCD, with lower intensity. The kneaded system (Fig 4D) displayed less intense and highly diffused peaks as compared to physical mixture.

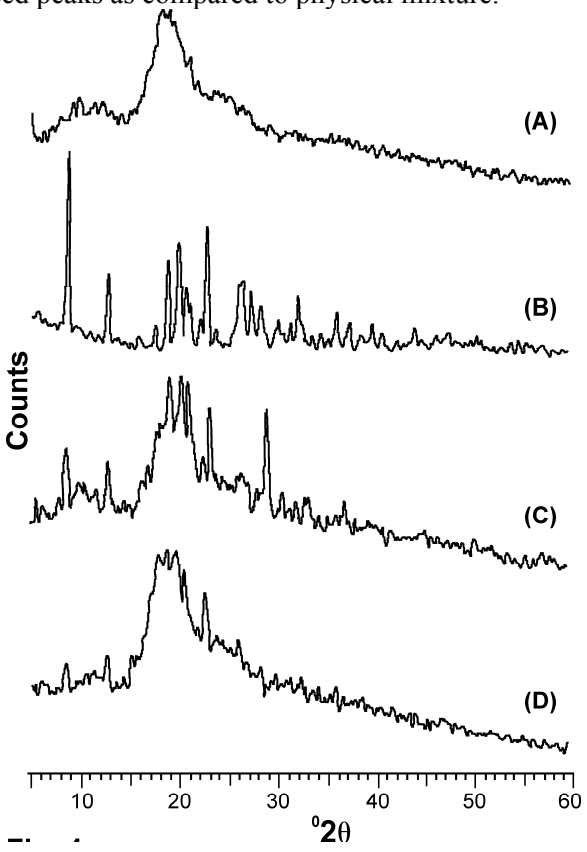

Fig. 4 XRD patterns of pioglitazone-HPβCD binary systems: (A) HPβCD; (B) pioglitazone; (C) physical mixture; (D) inclusion complex.

The peak intensities of pure pioglitazone and its corresponding binary systems are presented in Table 2. The relative decrease in crystallinity of pioglitazone at angle 8.810° (2θ) was found to be 0.1888 and 0.0444 in physical mixture and kneaded system respectively [20]. Thus,

the XRD studies demonstrated a significant reduction in the crystallinity of pioglitazone in inclusion complex indicating a penetration of drug inside the HPβCD cavity.

Table 2 Peak intensities of pioglitazone in the XRD patterns of pioglitazone-HPβCD binary systems.

2θ	Drug	Drug: HPβCD binary system	
		PM	KN
8.81	180	24	8
22.88	59	---	---
19.84	56	30	31
26.45	53	---	---
12.73	50	---	10

PM: Physical mixture; KN: Kneaded product (inclusion complex).

3.4. Differential scanning calorimetry (DSC)

Fig. 5 shows thermal behaviour of pure pioglitazone, HPβCD and their corresponding binary systems. Pure drug exhibited a sharp endothermic peak at 197ºC indicating the melting point of crystalline pioglitazone (Fig. 5B). The DSC thermogram of HPβCD exhibited broad endothermic peak at 86-88ºC attributed to the evaporation of absorbed water (Fig. 5A).

Physical mixture displayed (Fig. 5C) two broad endothermic peaks of drug at 178ºC and 217 ºC which might be attributed to metastable polymorphs of pioglitazone. However the peaks were progressively reduced in the area and appeared with decreased intensity.

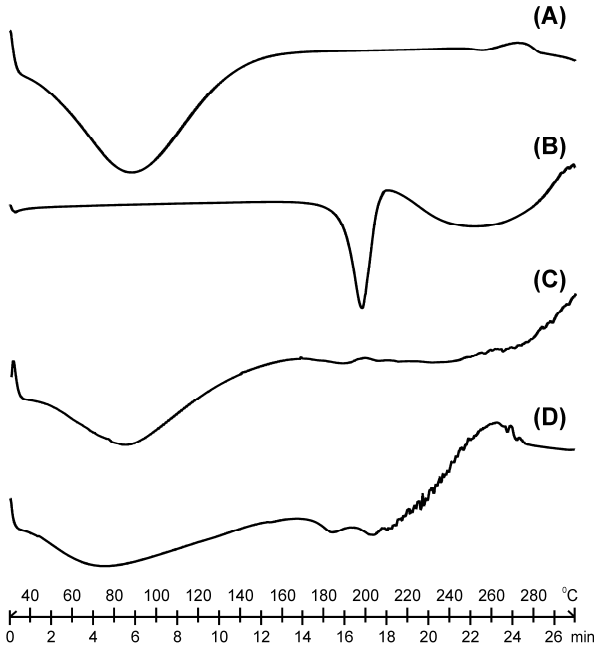

Fig. 5 DSC curves of pioglitazone-HPβCD binary systems: (A) HPβCD; (B) pioglitazone; (C) physical mixture; (D) inclusion complex.

In kneaded system the endotherm of drug was shifted towards lower temperature 183ºC (Fig. 5D). The lower temperature of inclusion complex was because of melting point depression

by the complex [21-23]. The peak was further almost hidden and finally disappeared in the inclusion complex. These thermal studies were indicative of formation of inclusion complex in solid state.

3.5. Dissolution studies

Fig. 6 illustrates dissolution behaviour of pure pioglitazone and its corresponding binary systems with HPβCD. The % release of drug is given in Table 3. It is evident that the inclusion complex has significantly improved the release rate of pioglitazone while physical mixture has shown moderate increase in the dissolution of pioglitazone. This moderate increase in dissolution might be because of local solubilization action and hydrophilic environment of HPβCD. The inclusion complex has released almost 100% drug within 2 min whereas physical mixture has released 62.49% drug in the same time. The dissolution of pure drug displayed burst release (above 50%) in its earlier phase. However, the dissolution of pure drug and physical mixture was incomplete even in 60 min. On the contrary, inclusion complex demonstrated almost complete release of drug in 2 min. The higher dissolution rate from inclusion complex was attributed to reduction in the crystallinity of drug, greater hydrophilicity, higher wetting effect and ability to form stable inclusion complex of HPβCD [24] as evidenced from high K_s value.

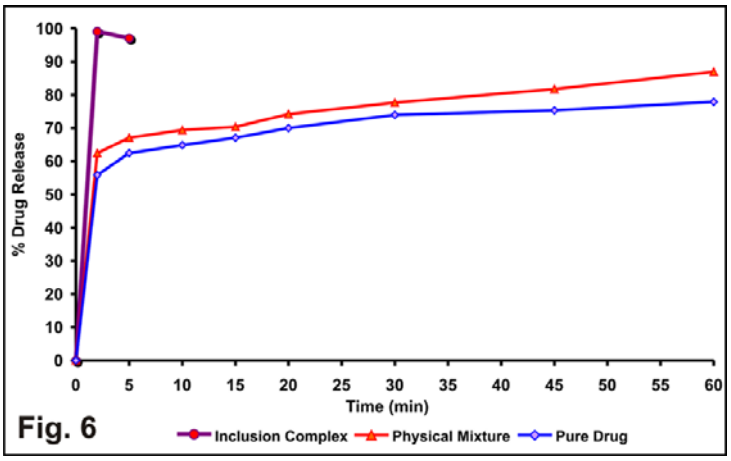

Fig. 6 The dissolution profile of pioglitazone-HPβCD system at 37 ± 0.5 ℃.

Table 3 The dissolution profile of pure pioglitazone and its binary systems with HPβCD in distilled water at 37 ± 0.5 ℃.

Time (min)	% Drug Release		
	Drug	PM	KN
2	55.83 ± 0.36	62.49 ± 0.68	99.839 ± 0.15
5	62.49 ± 0.69	67.09 ± 0.68	97.748 ± 0.61
10	64.87 ± 0.33	68.62 ± 0.07	-
15	67.09 ± 0.69	70.38 ± 0.61	-
20	70.00 ± 0.76	74.21 ± 0.30	-
30	73.98 ±0.24	77.66 ± 0.54	-
45	75.36 ± 0.23	81.72 ± 0.91	-
60	77.89 ± 0.19	86.93 ± 0.30	-

All values are mean ± S.D. (n = 3), S.D.: Standard deviation; PM: Physical mixture; KN: Kneaded product (inclusion complex).

4. Conclusion

The present investigation revealed that pioglitazone could form highly stable inclusion complex with HPβCD even in absence of hydrophilic carriers. Further, physical studies demonstrated the existence of non-covalent interactions and possibly presence of amorphous state of drug in inclusion complex. From these results, it could be concluded that the aqueous solubility and dissolution rate of pioglitazone could be significantly increased by complexation with HPβCD.

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