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PREPARATION AND EVALUATION OF PIOGLITAZONE SOLID DISPERSIONS

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ABSTRACT

Pioglitazone HCl (PIO) is a poorly soluble bioactive compound that suffered bioavailability problems after oral administration. Hence, the aim of the proposed research work was to formulate and investigate various solid dispersions (SDs) of PIO in order to enhance its dissolution and bioactivity. PIO-SD were prepared using poloxamer and HPMC at 1:1 and 1:3 ratios by kneading and microwave irradiation methods. The prepared PIO-SD characterized by differential scanning calorimetry (DSC), FTIR and evaluated for in vitro dissolution. The results of FTIR and DSC suggest the formation of PIO-SD. The superior solubility and dissolution properties of PIO-SD over pure PIO and justified by statistically at 95 % confidence through ANOVA. Therefore the SD prepared with poloxamer and HPMC could be a potential technique for enhancing the solubility and in vitro dissolution.

KEYWORDS: Solid dispersion systems, Pioglitazone HCl, HPMC, Poloxamer-407, FTIR, DSC.

INTRODUCTION

Poorly soluble drugs presents challenge to the formulation scientists. Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. Current statistics report showed that about 40% of new chemical entities (NCEs) are known to belong to the Biopharmaceutics classification systems (BCS) class II type of molecules with poor solubility and high permeability properties.[1,2] The term solid dispersion defined as the dispersion of one or more hydrophobic ingredients in an hydrophilic inert carrier or matrixin order to achieve increase the solubility and dissolution rate.[2] Different solubility and dissolution enhancement techniques are applied such as inclusion complexation,[3] drug micronization in to amorphous form,[4] prodrug formation,[5] and solid dispersion,[6-9] among these methods, solid dispersion technique is most frequently used.Pioglitazone is classified as a BCS class II compound exhibit solubility challenge, hence in the present work an attempt was to improve the aqueous solubility and dissolution behavior using solid dispersion techniques such as kneading and Microwave irradiation methods.

MATERIALS AND METHODS

Materials

Pioglitazone HCl (PIO) was a gift sample from Aarti drugs Ltd, Mumbai, India. Poloxamer 407 and HPMC were obtained from Micro Labs Ltd, Bengaluru, India. All other reagents and solvents used were of analytical grade.

Methods

Preparation of solid dispersions

Solid dispersion systems of Poloxamer 407/ HPMC with Pioglitazone HCl at 1:1 and 1:3 w/w ratios were prepared by kneading and microwave irradiation method.

Kneading method (KM): Poloxamer 407/ HPMC with Pioglitazone HCl at mass ratios were triturated in glass mortar with small volume of dichloromethane. The thick slurry was kneaded for 1h and then dried at 45^0C until dryness. The dried mass was powdered and sieved through #120 and stored in a desiccator for further evaluation.

Microwave oven irradiation (MC): The aqueous solution of Poloxamer 407/ HPMC was added slowly into a solution of Pioglitazone HCl dissolved in dried dichloromethane with constant stirring. These solvents containing glass containers subjected for irradiation in microwave oven for 90 sec at 60^0C. After reaction completed, adequate amount of dried dichloromethane added to remove the residuals. The resulting mixture stirred for 1h and evaporated under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in desiccator until further evaluation.

Similarly physical mixture were prepared by trituration mortar and pestle, the different formulae were given in table 1.

Table 1: Formulae of Pioglitazone solid dispersion systems.

Batches	Drug	Polymer	Ratio	Method
FI	PIO	HPMC	1:1	PM
F2	PIO	HPMC	1:3	PM
F3	PIO	HPMC	1:1	Kneading
F4	PIO	HPMC	1:3	Kneading
F5	PIO	HPMC	1:1	Micro wave
F6	PIO	HPMC	1:3	Micro wave
F7	PIO	Poloxamer	1:1	PM
F8	PIO	Poloxamer	1:3	PM
F9	PIO	Poloxamer	1:1	Kneading
F10	PIO	Poloxamer	1:3	Kneading
F11	PIO	Poloxamer	1:1	Micro wave
F12	PIO	Poloxamer	1:3	Micro wave

Detection of solid dispersions in solution state

Drug content uniformity: In each case physical mixture and solid dispersion systems equivalent to 40mg of PIO was accurately weighed and transferred to 25ml volumetric flask. To this add 10 ml of methanol to dissolve the PIO further volume was diluted to 100ml with 0.01N HCl. Filter if necessary further it was subsequently diluted with 0.01N HCl and estimate the drug content by UV at 269nm.

Saturation solubility: In each case excess of PIO, physical mixture and its solid dispersions added in 25ml vials containing 15ml of distilled water. The sealed vials were shaken on rotary shaker for 24 hat room temperature and equilibrated for 48 h. An aliquot was passed through 0.45µ nylon disc filter and the filtrate was suitably diluted and analyzed on UV at 269nm.

FTIR studies: The FTIR spectra were recorded on a Shimadzu FTIR-281-spectrophotometer for PIO, Poloxamer 407, HPMC, physical mixture and solid dispersion systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2Tcm^{-2} for 3 min. The scanning range was 450-4000cm^{-1} and the resolution was 1cm^{-1}.

Differential scanning calorimetry (DSC): DSC measurements were performed for PIO, Poloxamer 407, HPMC, physical mixture and solid dispersion systems on a Shimadzu DSC-50 with a thermal analyser. Accurately weighed samples were placed in sealed aluminium pans, before heating under nitrogen flow (20ml/min) at a scanning rate of 10^{o}C min^{-1}, from 25^{o}C to 300^{o}C.

Dissolution studies: *In vitro* dissolution studies of PIO, physical mixture and solid dispersion systems were carried out in 900ml of 0.01N HCl using a USP type-2 dissolution rate test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 40mg of PIO, speed of 60rpm and a temperature of 37^{0}C were used in each test. A 5ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for PIO content by measuring the absorbance at 269nm.The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

All the solid dispersions subjected for drug content estimation, the low SD and CV values indicates drug content was uniform in all solid dispersion systems. The saturation solubility studies of PIO and its solid dispersion systems were conducted and the results were given in Figure1 and 2. The saturation solubility studies reveals that the solubilizing efficiency of novel polymers are in the order Poloxamer 407 > HPMC > PIO. The solubility of PIO from solid dispersion systems shows concentration and method dependent and were in the rank order 1:3>1:1; MW>KNE>PM.

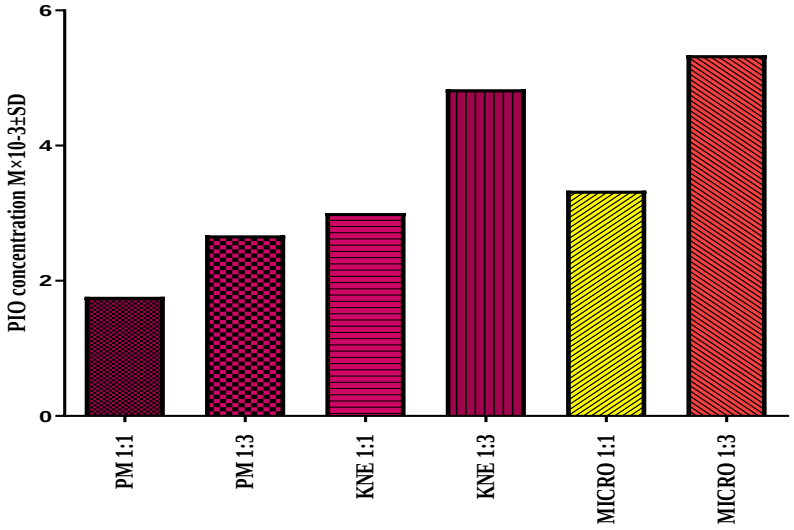

Figure 1: Saturation solubility of PIO-SD and its Physical mixture prepared by Microwave irradiation and kneading methods at 1:1 and 1:3 ratios with HPMC.

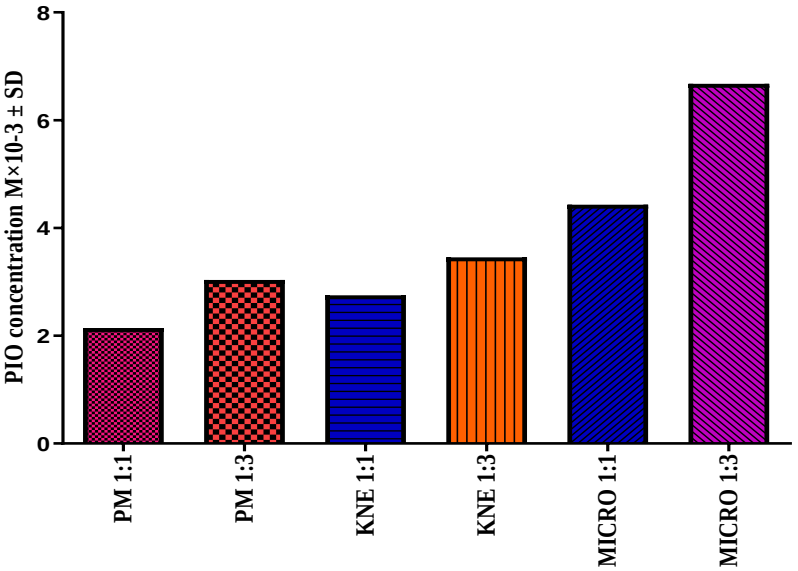

Figure 2: Saturation solubility of PIO-SD and its Physical mixture prepared by Microwave irradiation and kneading methods at 1:1 and 1:3 ratios with Poloxamer-407.

FTIR studies: PIO solid dispersion systems were subjected to FTIR to investigate possible polymer interactions[10], and were shown in figure 3The FTIR data of pure Pioglitazone and its solid dispersions are shown in figure 4. The characteristic functional groups bands of PIO were observed in all solid dispersion systems with slight shifting towards lower wave length or higher wave length suggest mild to no interaction.

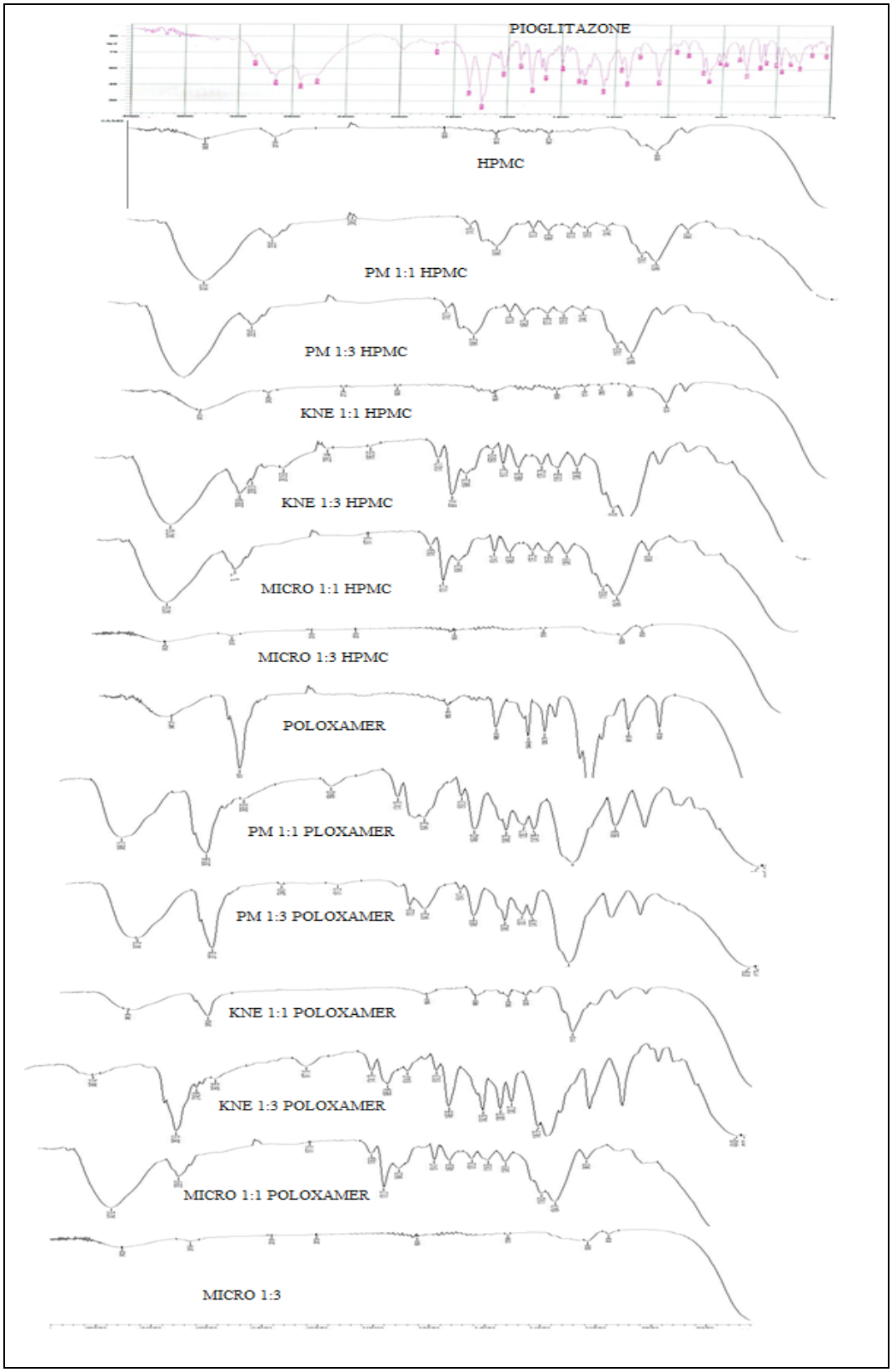

Figure 3: FTIR spectra of PIO, Physical mixture and its solid dispersion systems prepared by Kneading and Microwave irradiation methods at 1:1 and 1:3 ratios with HPMC and Poloxamer-407.

DSC Studies: DSC thermograms of Pioglitazone and its solid dispersion systems were shown in figure 4. The DSC thermogram of Pioglitazone showed an endothermic peak 201.9^0 corresponding to its melting point. DSC studies of solid dispersion systems suggest reduction in Pioglitazone endothermic peak intensity indicating mild or no interaction.

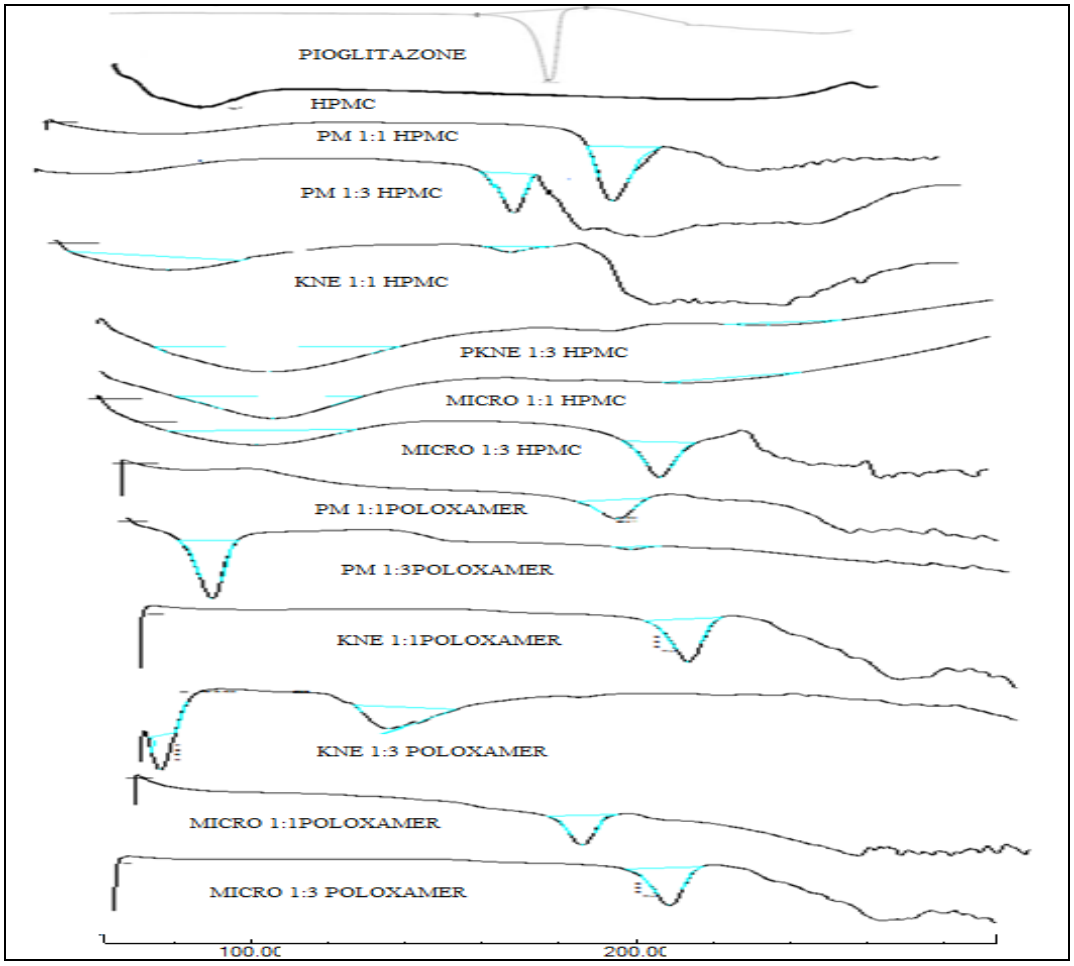

Figure 4: DSC thermogram of PIO, Physical mixture and its solid dispersion systems prepared by Kneading and Microwave irradiation methods at 1:1 and 1:3 ratios with HPMC and Poloxamer-407.

Dissolution studies: In the present investigation, dispersed amount method is used to investigate the various dissolution parameters of PIO and its solid dispersion systems and data were studied using dissolution software PCP DISS0 V.3.0. DP_{30}, DE_{30}, RDR_{30}, t_{50} correlation coefficient (r) of best fit model values were calculated, same were depicted in table 2 and 3, comparative dissolution profiles are shown in figure 5,6. One-way ANOVA was used to test the statistical significant difference between pure drug and prepared solid dispersion systems. Significant differences in the means of DP_{30}, DE_{30}, were tested at 95% confidence. The dissolution enhancement was found to be in the order, 1:3 >1:1; Poloxamer-407 > HPMC; MICRO>KM> PIO

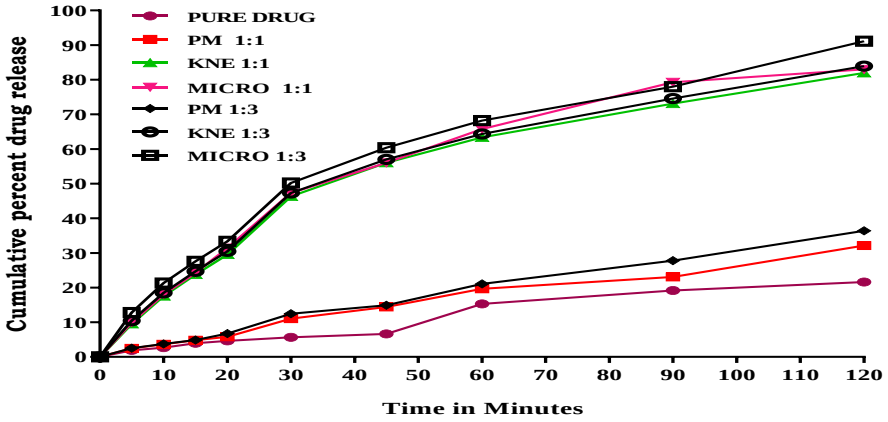

Figure 5: Dissolution profiles of PIO, Physical mixture and its solid dispersion systems prepared with HPMC.

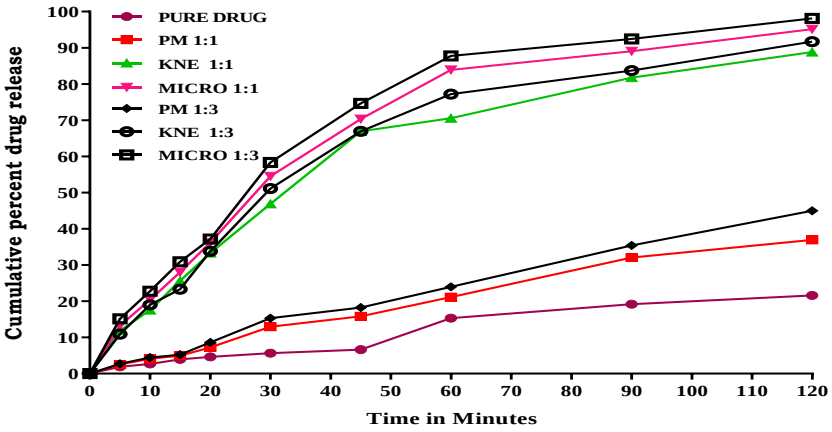

Figure 6: Dissolution profiles of PIO, Physical mixture and its solid dispersion systems prepared with Poloxamer.

Table 2: Dissolution parameter of PIO, Physical mixture and its solid dispersion systems prepared with HPMC.

Dissolution parameter	PIO –HPMC Solid Dispersions						
	Pure drug	Physical Mixture		Kneading		Microwave	
		1:1M	1:3M	1:1M	1:3M	1:1M	1:3M
T_{50}(min)	>120	>120	>120	45.4	43.3	42.1	29.22
D.P_{30} (%)	3.47	5.16	5.62	22.99	23.86	23.86	26.40
RDR_{30}	1	1.96	2.21	8.20	8.37	8.37	8.89
First-order -R	0.9782	0.9923	0.9976	0.9866	0.9895	0.9869	0.9918
Hixson-Crowell-R	0.9774	0.9905	0.9967	0.9608	0.9640	0.9627	0.9767

Table 3: Dissolution parameter of PIO, Physical mixture and its solid dispersion systems prepared with Poloxamer.

Dissolution parameter	PIO-Poloxamer-407 Solid Dispersions						
	Pure drug	Physical Mixture		Kneading		Microwave	
		1:1M	1:3M	1:1M	1:3M	1:1M	1:3M
T_{50}(min)	>120	>120	>120	35.9	43.3	29.5	27.5
D.P_{30} (%)	3.47	5.89	6.85	25.63	25.91	28.40	30.55
RDR_{30}	1	2.29	2.71	8.30	9.05	9.65	10.32
First-order- R	0.9782	0.9963	0.9974	0.9913	0.9932	0.9944	0.9932
Hixson-Crowell's cube root -R	0.9774	0.9952	0.9976	0.9649	0.9692	0.9713	0.9784

CONCLUSIONS

Solid Dispersion systems of Pioglitazone prepared with Poloxamer and HPMC were found to be superior performance in increasing aqueous solubility and dissolution of Pioglitazone. FTIR and DSC study no possible interaction between drug and excipients. The main factors for higher solubility and release rate are due to increased wettability and conversion to amorphous state. The dissolution efficiency for all solid dispersions are greater than pure PIO. Thus the present study provided a way to enhance solubility and understand the release mechanism.

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Conflict of interest-Nil.

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