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ORIGINAL RESEARCH PAPER

Preparation and Evaluation of Pioglitazone HCl Solid Dispersions

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Abstract
In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, pioglitazone HCl by solid dispersion method using crospovidone. Solid dispersion systems were prepared with varying drug: carrier ratios viz.1:1 and 1:9 by kneading and solvent evaporation method and the corresponding physical mixtures were also prepared and compared. The formulations were characterized for solubility by phase solubility studies and drug-polymer interactions by XRD and FTIR studies and in vitro drug dissolution studies. All the formulations showed marked improvement in the solubility behaviour and improved drug release. The interaction studies showed no interaction between the drug and the carrier. Formulation containing drug: polymer ratio of 1:9 and prepared by solvent evaporation method showed the best release as compared to physical mixture and the pure drug. It was concluded that crospovidone as a carrier can be very well utilized to improve the solubility of poorly soluble drug pioglitazone HCl.

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INTRODUCTION

The formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industry[1-4]. Various formulation parameters that play a crucial role for successful formulation are aqueous solubility, stability at ambient temperature and humidity, photo stability, compatibility with solvents and excipients etc. of these, solubility is the most important property for developing formulations. Compounds exhibiting dissolution rate limited bioavailability are considered class II according to BCS classification[5]. As per recent report[6], 46% of the total NDAs were BCS class IV, while only 9% were BCS class I drugs, revealing that a majority of approved new drugs were water insoluble.

There are drug candidates that have poor solubility in water but can be dissolved by suitable conventional formulation strategies which include cosolvents[7], milling techniques[8], super critical processing[9] and solid dispersions[10]. Solid dispersion technique has often proved to be the most commonly used in improving dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic and advantageous. In solid dispersion technique, water soluble carriers are used to improve dissolution characteristics of poorly water-soluble drugs. Pioglitazone HCl is having poor aqueous solubility and belongs to class II drug where the solubility is the rate limiting step for the dissolution. The present study is an attempt to overcome the poor aqueous solubility of pioglitazone HCl by solid dispersion technique using cross povidone.

EXPERIMENTAL

Materials

Pioglitazone HCl was procured from the alembic drugs. Mumbai as gift sample and all other polymers and ingredients were used of analytical grade. Double distilled water was used for throughout the studies.

Preparation of Solid Dispersion Systems

The solid dispersion systems of Pioglitazone HCl were prepared with crospovidone at 1:1, 1:9 ratios by kneading and solvent evaporation methods. The different formulae are given in Table 1.

Preparation of Physical mixtures (PM)

The drug and carrier were weighed accordingly to the specified drug: carrier ratio. Physical mixtures of pioglitazone HCl and crospovidone in 1:1, 1:9 were obtained by mixing individual components together with a spatula.

Kneading Method (KNE)

The drug and carrier were weighed accordingly to the specified drug: carrier ratio. Pioglitazone HCl was dissolved in methanol and carrier was taken in a mortar. The carrier was triturated slowly with methanol for 1 hr. Further mass was dried in vacuum oven, pulverized and sieved through #120 and stored in desiccator until further evaluation.[11]

Solvent Evaporation Method (SE)

The required amount of pioglitazone HCl was dissolved in methanol. The carrier was dispersed in the drug solution. The solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in desiccator until further evaluation.

Table 1. Formulae of physical mixture and solid dispersion systems

Code	Method	Drug	Polymer	Ratio
F1	PM	Pioglitazone HCl	Cross Povidone	1:1
F2	PM	Pioglitazone HCl	Cross Povidone	1:9
F3	KNE	Pioglitazone HCl	Cross Povidone	1:1
F4	KNE	Pioglitazone HCl	Cross Povidone	1:9
F5	SE	Pioglitazone HCl	Cross Povidone	1:1
F6	SE	Pioglitazone HCl	Cross Povidone	1:9

Evaluation

Detection of solid dispersion systems were evaluated for of drug content, solubility, FTIR spectroscopy, powder XRD and *in vitro* dissolution studies.

Drug Content Uniformity

In each case physical mixture and solid dispersion systems equivalent to 40 mg of pioglitazone HCl was accurately weighed and transferred to 25 mL volumetric flask. To this add 10 mL of methanol to dissolve the pioglitazone HCl further volume was diluted to 100 mL with acetate buffer pH 2. Filter if necessary further it was subsequently diluted with acetate buffer pH 2 and measure the absorbance at 269 nm, and estimate the pioglitazone HCl content using calibration curve.

Saturation Solubility

The saturation solubility studies were performed for pure drug, physical mixture and solid dispersion systems[12]. Pure pioglitazone HCl, physical mixture and solid dispersion systems equivalent to 40 mg of the pioglitazone HCl, dispersed in 25 mL vials containing 15 mL of distilled water. The sealed vials were shaken on rotary shaker for 24 h at room temperature and equilibrated for 48 h. An aliquot was passed through 0.45 µ nylon disc filter and the filtrate was suitably diluted and analyzed on UV at 269 nm.

FTIR Studies

Fourier transform infrared (FTIR) spectra were recorded on Shimadzu FTIR-281-spectrophotometer. The spectra recorded for pioglitazone HCl, crospovidone, physical mixture and solid dispersion systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2 T cm^{-2} for 3 min. The scanning range was 450-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Powder X-ray Diffractometry

The powder X-ray diffraction patterns of pioglitazone HCl, crospovidone, physical mixture and solid dispersion systems were recorded by using Philips X-ray powder diffractometer (model PW 1710) employing Cu-Kα-radiation. The diffractometer was run at 2.40/min in terms of 2θ angle.

In vitro Dissolution Studies

In vitro dissolution studies of pure Pioglitazone HCl, physical mixtures and solid dispersion systems were carried out in 900 mL of acetate buffer pH 2.0 using a USP XXI Type 2 (paddle) dissolution test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 40 mg of pioglitazone HCl, speed of 60 rpm and a temperature of 37 °C were used in each test. A 5 mL aliquot was withdrawn at different time intervals, filtered using a 0.45 µm nylon disc filter and replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted and assayed for Pioglitazone HCl content by measuring the absorbance at 269 nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0.

RESULTS AND DISCUSSION

Drug Content

The percent drug content of the physical mixture and solid dispersion systems are found to be in the range of 97.08±0.520 to 99.86±1.015. The coefficient of variation (CV) and standard deviation (SD) in the percent drug content was found to be less than 0.2% in all the batches prepared. Small SD and CV values indicate that the method employed gave solid dispersions with uniform drug content. There was no significant loss of drug during the preparation of solid dispersion systems and proportion of drug and carrier remained the content in all batches prepared. The results are given in Table 2.

Solubility

The solubility studies of pioglitazone HCl and their solid dispersion systems are studied in distilled water. The results were shown in Table 2 and Fig 1**.** The solubility of pioglitazone HCl from solid dispersion systems prepared by all methods showed method dependent solubility and were in the rank order SE > KNE > PM in all the ratios.

Table 2. Drug content and solubility data of physical mixture and solid dispersion systems

Code	Percent Drug Content*	Coeff of Variation (CV)	Solubility (mg/mL)*
F1	97.08±0.520	0.536	0.23±0.13
F2	99.40±0.655	0.634	0.63±0.32
F3	98.46±1.662	1.662	2.25±0.25
F4	98.42±0.854	0.893	6.25±0.23
F5	99.86±1.015	1.016	2.66±0.19
F6	98.81±1.643	1.682	10.0±0.21

* Mean ± SD, n = 3

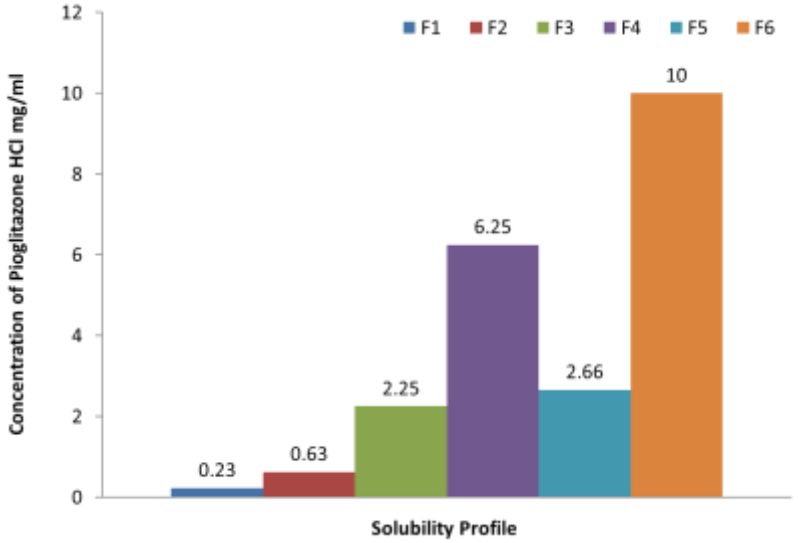

Fig 1. Solubility profile of developed solid dispersions

FTIR Studies

FTIR spectrum of pioglitazone HCl, crospovidone, physical mixtures and comparative FTIR spectrums of solid dispersion systems were given in Fig 2, 3. FTIR spectrum of pioglitazone HCl is characterized by 3082.35 cm^{-1} for N-H stretching amide, 2929.27 cm^{-1} for C-H stretching asymmetric, 2876.96 cm^{-1} for CH_2-stretching absorption bands, 1745.64 cm^{-1} for amide C=O stretching, 1612.14 cm^{-1} for C=C, 1465.95 cm^{-1} for ring C-N stretching, 1240.27 cm^{-1} for C-S stretching, 1084 cm^{-1} for aliphatic C-O-C and 844.95 cm^{-1} for para disubstituted aromatic ring. The characteristic C=O absorption band of pioglitazone HCl at 1745 cm^{-1} was observed in solid dispersions at 1:1 ratios showed C=O absorption band in the region of 1732-1749cm^{-1} and at 1:9 ratio showed C=O absorption band in the region of 1649-1653 cm^{-1} with lower to higher shifting of the absorption bands indicates there is an interaction at molecular level.

XRD Studies

Powder X-ray diffractometry is a useful tool for the detection of microcrystalline states. The diffraction pattern of the solid dispersion should be distinct from the superimposition of each of the components if a true dispersion were to form. X-ray diffraction pattern of pioglitazone hydrochloride, physical mixture, and its solid dispersion systems prepare by kneading and solvent evaporation methods at 1:1, 1:9 ratios are shown in Fig 4, 5. Pioglitazone HCl is having an X-ray diffraction pattern characterized by major peaks at about 12.91, 19.06, 26.10, and 28.08 at 2oθ confirming that existing compound was found to be form I compound[13]. The X-ray diffraction patterns of physical mixtures at 1:1, 1:9 ratios showed all the characteristic peaks of pioglitazone HCl. However, the peak intensities of the physical mixtures at 1:9 were lower than the corresponding 1:1 physical mixtures.

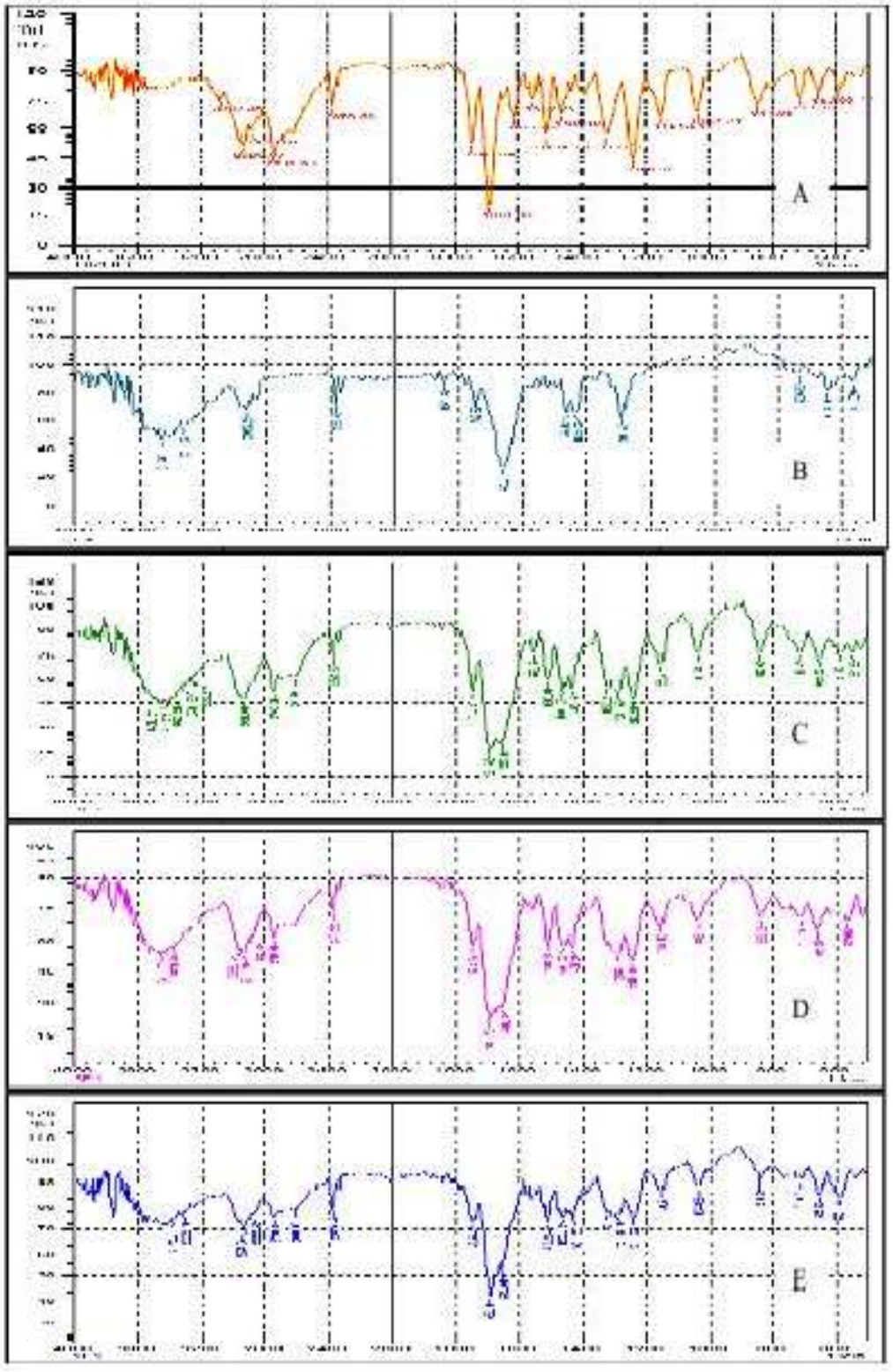

Fig 2. Comparative FTIR spectra of pioglitazone HCl, physical mixture and solid dispersion systems prepared with crospovidone at 1:1 ratios

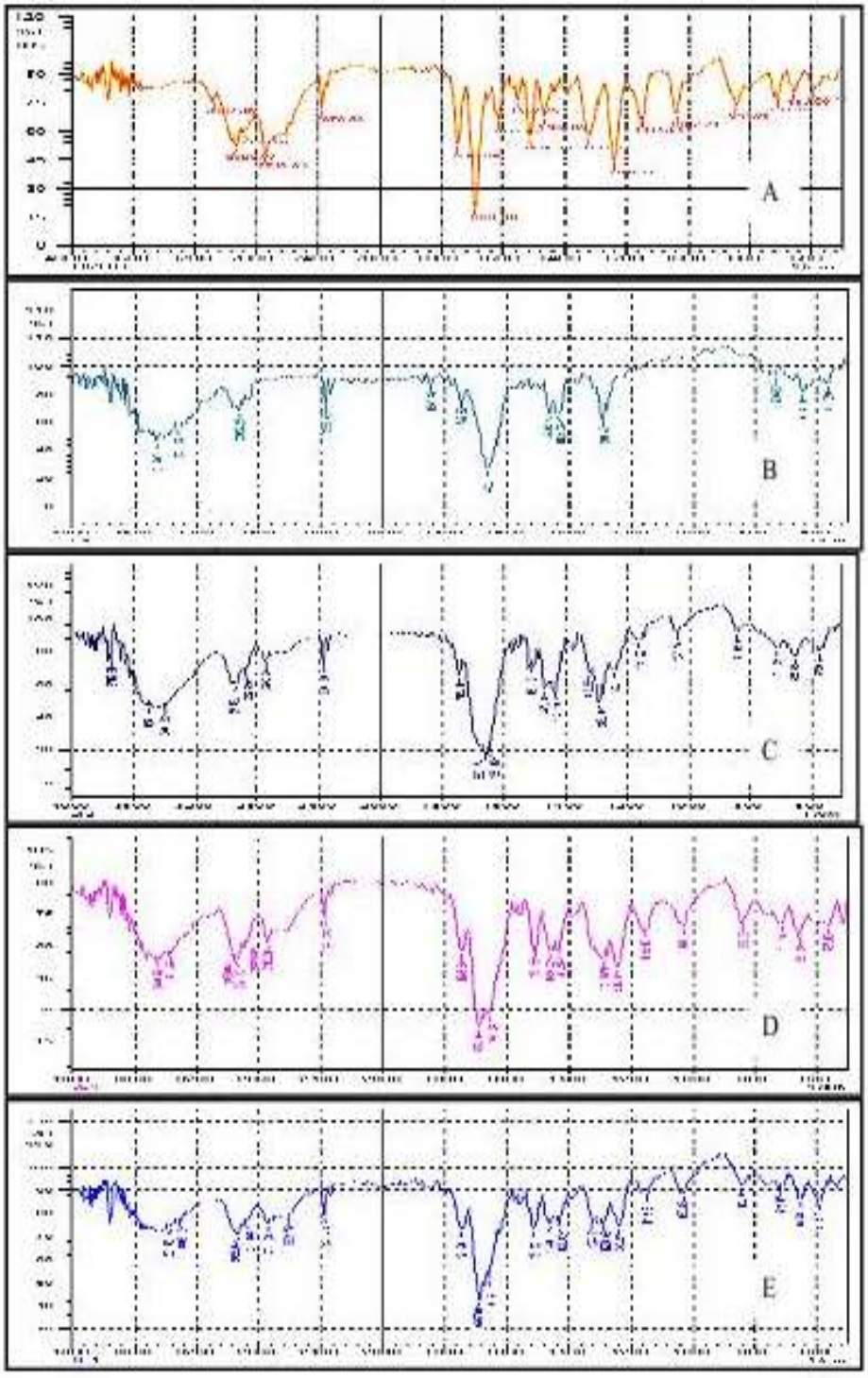

Fig 3. Comparative FTIR spectra of pioglitazone HCl, physical mixture and solid dispersion systems prepared with crospovidone at 1:9 ratios

In case of solid dispersion systems prepared with kneading and solvent evaporation methods at 1:1 ratio principle peaks of pioglitazone HCl were present but at 1:9 ratios these principle peaks were disappeared with minimum number of peaks indicating the drug is in amorphous form. The diffraction patterns are the sum of each component, indicating the presence of pioglitazone HCl in crystalline state. These results suggest that no alteration in the crystal structure of pioglitazone HCl, but the crystallinity being modified,

since the peak position (angle of diffraction) is an indication of crystal structure and the peak heights are a measure of the sample crystallinity.

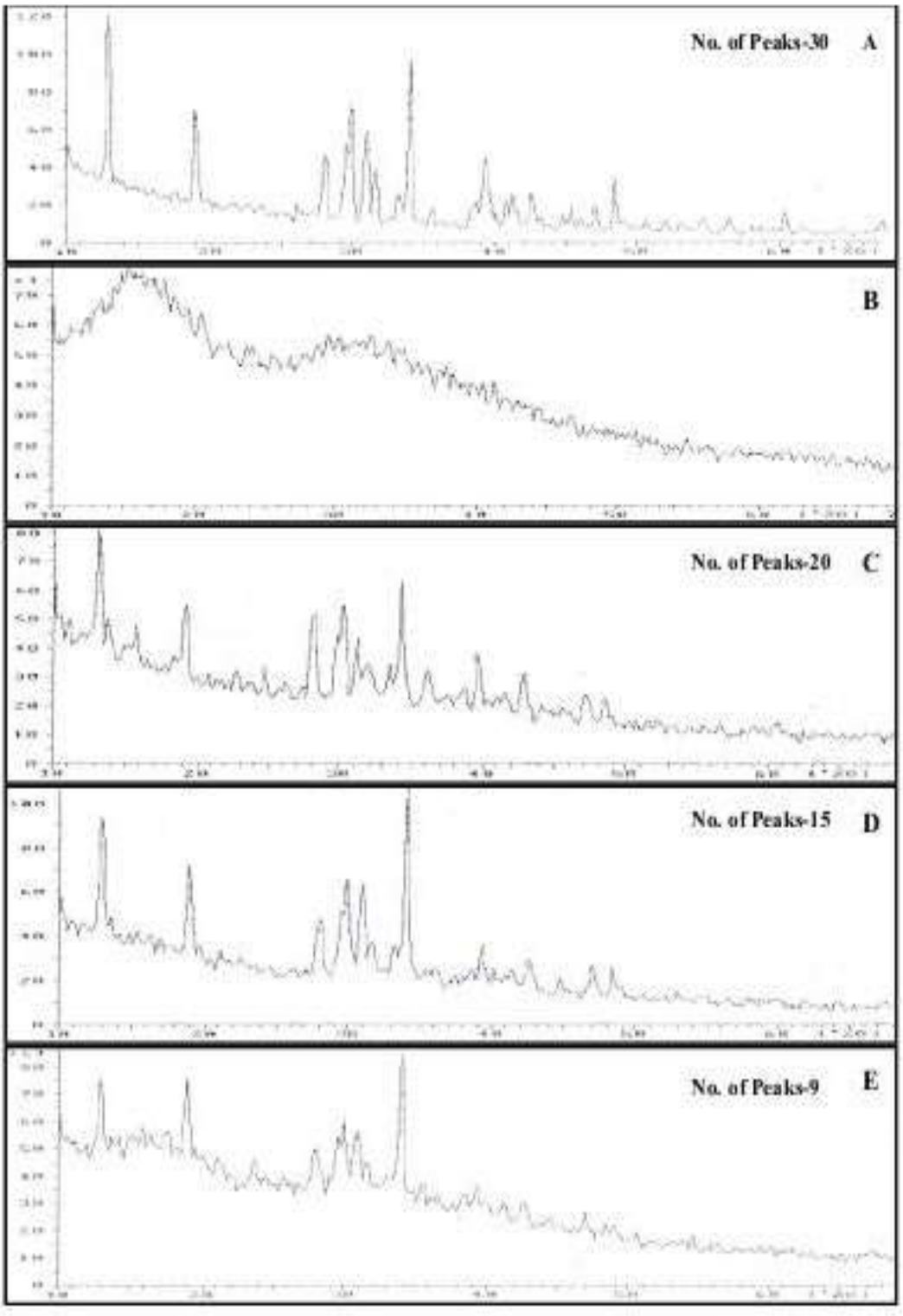

Fig 4. Comparative XRD spectra of pioglitazone HCl, physical mixture and solid dispersion systems prepared with crospovidone at 1:1 ratios

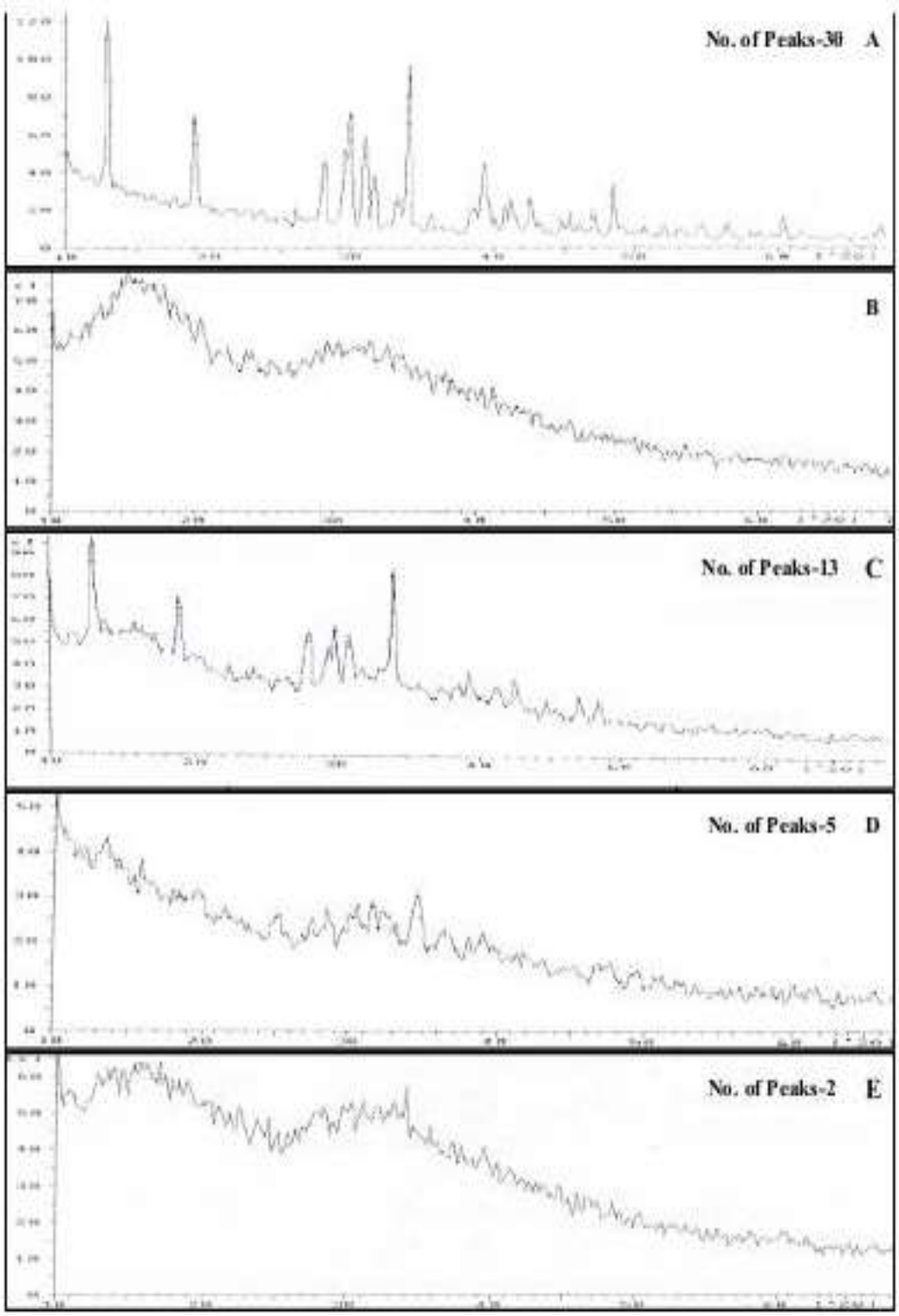

Fig 5. Comparative XRD spectra of pioglitazone HCl, physical mixture and solid dispersion systems prepared with crospovidone at 1:9 ratios

In vitro Dissolution Studies

In the present investigation, dispersed amount method is used to investigate the various dissolution parameters of pioglitazone HCl and its solid dispersion systems. The usual method of evaluation of *in vitro* dissolution testing is the comparison of time taken for given proportions of active drug to be released into

solution and parameters such RDR_{30} (relative dissolution rate), t_{50} values are often used. Another parameter suitable for the evaluation of *in vitro* dissolution has been suggested by Khan[14] who introduced the idea of 'Dissolution Efficiency' (D.E.). Dissolution Efficiency is defined as the area under the dissolution curve up to a certain time 't', expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$D.E = \frac{\int_o^t ydt}{y100^t} \times 100$$

The dissolution data of pioglitazone HCl and its solid dispersions were studied by using dissolution software PCP DISS0 V.3.0 and comparative dissolution profiles are depicted in Fig 6. The results of the dissolution rate studies indicated higher dissolution rate of pioglitazone HCl from solid dispersion systems when compared to pioglitazone hydrochloride itself and the corresponding physical mixtures.

The dissolution data obtained were subjected to model fitting and the model which fits the observed dissolution data was evaluated by correlation coefficient (r) between the variables involved. The dissolution of pioglitazone HCl from various solid dispersions obeyed both Hixson-Crowell's cube root law and first-order dissolution models. T_{50}, RDR_{30}, DE_{30}, DE_{60}, values were calculated from the dissolution software and are given in Table 3.

One-way ANOVA was used to test the statistical significance of difference between pure and prepared solid dispersions. Significant differences in the means were tested at 95% confidence. The DE_{30} and t_{50} values were significantly higher ($P<0.05$) in solid dispersion systems prepared by solvent evaporation method when compared to pure pioglitazone hydrochloride, physical mixture and kneaded solid dispersion systems.

Overall the rank order of improvement in dissolution properties of pioglitazone hydrochloride with different concentration 1:9 >1:1ratios and with methods SE>KNE> PM. The enhancement of dissolution rate from the solid dispersion prepared with solvent evaporation method may be due to decrement in the crystallinity of the dispersion when compare to the solid dispersions prepared by kneaded systems and physical mixtures.

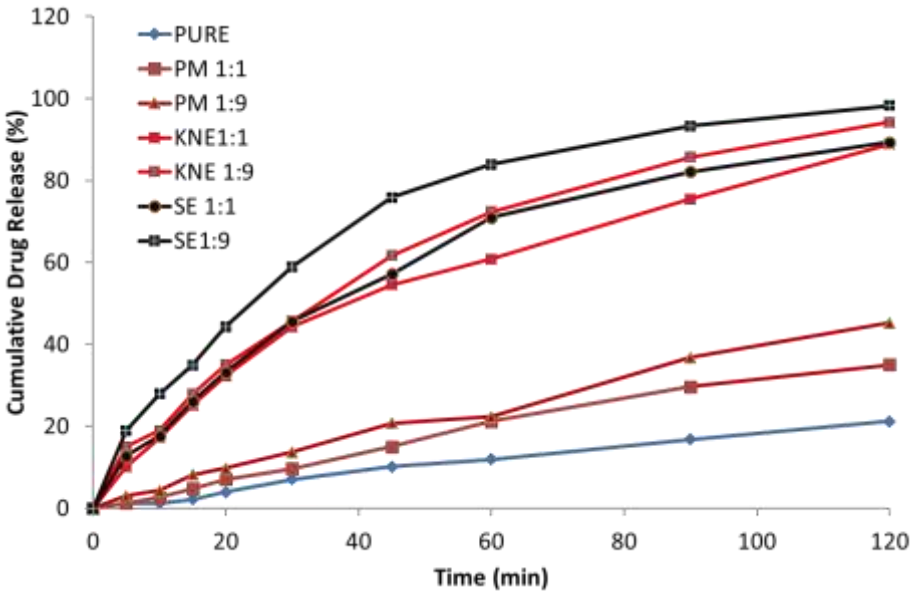

Fig 6. Comparative *in vitro* dissolution profiles of solid dispersions, physical mixtures and pure drug

Table 3. Comparative dissolution parameter data of pure drug, physical mixture and solid dispersions

Method	Batches	DE_{30}	DE_{60}	T_{50}	RDR_{30}
Pure drug	-	2.92	6.36	>120	1.00
PM	1:1	4.81	10.02	>120	1.38
	1:9	14.83	12.96	138.8	1.95
KNE	1:1	24.21	38.87	40.2	6.31
	1:9	24.36	43.44	30.7	6.52
SE	1:1	25.32	41.54	36.3	6.50
	1:9	26.36	54.08	21.7	8.40

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DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

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