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(RESEARCH ARTICLE)

Studies on enhancement of solubility and dissolution properties of rosiglitazone hydrochloride by solid dispersion technique

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Abstract

Rosiglitazone HCl, a member of thiazolidinedione class of antidiabetic agent, improves glycemic control by improving insulin sensitivity. The maximum solubility of rosiglitazone was found at pH 1.2 and solubility decreases up to pH 4.0. At a pH 6.0 and higher pH, solubility reduces drastically. Suitable solid dispersion systems of rosiglitazone with maltodextrin and poloxamer were prepared by solvent evaporation and kneading methods at 1:1 and 1:3 drug: carrier. Drug content, saturation solubility, FTIR, XRD, DSC and *In-vitro* dissolution were studied. The drug content was uniform, solubility of the drug increased linearly as a function of the carrier concentration and method. The FTIR studies suggest possible interaction at molecular level further justified by XRD and DSC studies. The dissolution study suggests, the increase in drug release was dependent on type of method of preparation. The DP60 and DE60 values were significantly higher ($P<0.05$) in solid dispersion systems prepared by kneading method when compared to pure rosiglitazone, physical mixture and solvent evaporation method. The dissolution follows first order model and obeyed Hixson-Crowell's cube root law.

Keywords: Solid dispersion systems; Rosiglitazone; Maltodextrin; Poloxamer; *In-vitro* dissolution

1 Introduction

In recent years, the number of poorly soluble drug candidates has increased tremendously. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Most useful methods to overcome the inherent difficulties associated with the formulation and development of a poorly water-soluble drug is to enhance the solubility of the same. Solid dispersions of drugs in different carriers have been employed to increase the dissolution rate and bioavailability of poorly soluble drugs [1-4] This provides a means of reducing particles size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles for quick dissolution and absorption. Rosiglitazone hydrochloride is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. It is a thiazolidinedione which acts as a selective and potent agonist at the peroxisome proliferator activated receptor γ (PPARγ) [5, 6]. The mechanism of action of rosiglitazone is by activation of the intracellular receptor class of the peroxisome proliferator-activated receptors (PPARs), specifically PPARγ. Rosiglitazone is highly pH dependent. The maximum solubility was found at pH 1.2 and solubility decreases up to pH 4.0. At pH 6.0 and higher pH, solubility reduces drastically. Hence suitable solid dispersions [7, 8] are to be prepared to achieve the release of rosiglitazone using hydrophilic polymers [9, 10].

Materials used and the source: The drug Rosiglitazone hydrochloride was obtained as a gift sample from AET Pharmaceuticals, Hyderabad. Maltodextrin was procured from Sigma Aldrich. Poloxamer, Methanol, Hydrochloric acid, Ethanol and Dichloromethane were obtained from sd fine-chem. Limited, Mumbai.

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2 Material and Methods

2.1 Determination of Absorption maxima

10 mg of rosiglitazone was dissolved in 10 ml 0.1N HCl to get stock solution of 1mg/ml. From this 10 ml solution was transferred into a 100 ml volumetric flask, volume was made up to 100 ml with 0.1N HCl which was considered as second stock solution. From this 0.4 ml of solution was transferred into a 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl and subjected for scanning at the UV range using Hitachi-U2000 spectrophotometer. From the spectral data, the absorption maxima obtained was 318 nm with a characteristic peak.

2.2 Preparation of calibration curve

For the preparation of calibration curve 0.2, 0.4, 0.6, 0.8 and 1.0 ml of the second stock solution was transferred into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get 2,4,6,8 and10 µg/ml solutions. The optical density values of resulting solutions which were measured at 318 nm by using Hitachi-U2000 spectrophotometer. Concentration versus optical density values is plotted and displayed. The method obeyed beer-lamberts law and the solution was stable for 48 hours.

2.3 Preparation of physical mixtures (PM)

Physical mixtures of rosiglitazone: maltodextrin and rosiglitazone: poloxamer at 1:1 and 1:3 ratios were obtained by mixing individual components together with a spatula and kept in desiccator for further study.

2.4 Kneaded systems (KNE)

Solid dispersions containing rosiglitazone: maltodextrin and rosiglitazone: poloxamer at 1:1 and 1:3 ratios were prepared by kneading method. The drug and excipient were weighed accordingly to the specified drug: carrier ratio and was taken in a glass mortar. The mixture was triturated slowly with methanol for 1 hour take care that the damp mass was maintained throughout the trituration period. Further mass was dried under vacuum, pulverized and sieved through #80 and stored in desiccator for further study.

2.5 Solvent evaporation systems (SE)

Solid dispersions containing rosiglitazone: maltodextrin and rosiglitazone: poloxamer at 1:1 and 1:3 ratios were prepared by solvent evaporation method. The required amount of rosiglitazone was dissolved in methanol and excipient was dispersed in the drug solution. The solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #80 and stored in desiccator until further evaluation.

2.6 Evaluation of solid dispersion systems

2.6.1 Solubility studies

A little excess amount of rosiglitazone hydrochloride dispersed in 25 ml vials containing different concentrations of maltodextrin and poloxamer solutions. The sealed vials were shaken on rotary shaker for 24 hours at room temperature and equilibrated for 48 hours. An aliquot was passed through 0.45µ nylon disc filter and the filtrate were suitably diluted and analyzed on UV at 318 nm.

2.6.2 Saturation solubility

Weighed amount of rosiglitazone hydrochloride pure drug, physical mixture and all prepared solid dispersions equivalent to 20mg of the drug, dispersed in 25 ml vials containing 20 ml of 0.1N HCl. The sealed vials were shaken on rotary shaker for 24 hours at room temperature and equilibrated for 48 hours. An aliquot was passed through 0.45µ nylon disc filter and the filtrate were suitably diluted with 0.1N HCl and measures the absorbance at 318 nm and estimate the rosiglitazone hydrochloride content using the calibration curve.

2.6.3 Drug content uniformity

In each case physical mixture and solid dispersion systems equivalent to 20 mg of rosiglitazone was accurately weighed and extracted with 100 ml 0.1N HCl and filterd.1ml of the filtrate was serially diluted with 0.1NHCl and absorbance is measured at 318 nm. The drug content of rosiglitazone hydrochloride is measured using the calibration curve.

2.6.4 FTIR studies

Fourier transform infrared (FTIR) spectra were recorded on a Shimadzu FTIR-281-spectrophotometer. The spectrum recorded for rosiglitazone, maltodextrin, poloxamer, physical mixture and all 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 $1cm^{-1}$.

2.6.5 Powder X-ray diffractometry

The powder X-ray diffraction patterns of rosiglitazone hydrochloride, maltodextrin, poloxamer and selected solid dispersion systems were recorded by using Philips X-ray powder diffractometer (model PW 1710) employing Cu-Kα-radiation. The diffractometer was run at 2.4^0/min in terms of 2θ angle.

2.6.6 Differential scanning calorimetry

The thermograms of rosiglitazone hydrochloride, maltodextrin, poloxamer and selected solid dispersion systems were recorded on Seiko, DSC 220C model Differential scanning calorimeter (Tokyo, Japan). About 10 mg of samples were sealed in aluminum pans and heated at a rate of 10^0 C/min from 30^0 C-300^0 C.

2.6.7 Dissolution studies

In vitro dissolution studies of pure rosiglitazone hydrochloride, physical mixture and all solid dispersion systems were carried out in 900 ml of 0.1N HCl using a USPXXI type 2 dissolution test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 20 mg of rosiglitazone, speed of 50 rpm and a temperature of 37^0 C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for rosiglitazone content by measuring the absorbance at 318 nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0.

3 Results

3.1 Solubility studies

The solubility of rosiglitazone was carried out in different molar concentration of excipients selected viz., maltodextrin and poloxamer. The solubility of rosiglitazone hydrochloride in 0.1N HCl was 1.746±0.0025 $Mx10^{-3}$. The solubility data was presented in table 1.

Table 1 Solubility data of rosiglitazone in different concentrations of maltodextrin and poloxamer

Molar concentrations of poloxamer	**Concentration of rosiglitazone in maltodextrin solution $M\times10^{-3}$**	**Concentration of rosiglitazone in poloxamer solution $M\times10^{-3}$**
0.1	2.284 ± 0.001	3.4623 ± 0.002
0.025	2.354 ± 0.0025	3.5646 ± 0.0015
0.5	2.435 ± 0.0025	3.616 ± 0.0025
0.75	2.441 ± 0.0025	3.6976 ± 0.0015
1	2.58 ± 0.0026	3.7113 ± 0.0025
1.25	2.615 ± 0.002	3.733 ± 0.0015
1.5	2.739 ± 0.002	3.7463 ± 0.002
1.75	2.910 ± 0.0025	3.7546 ± 0.00251
2	3.353 ± 0.002	3.7673 ± 0.0015

3.2 Saturation solubility studies

The saturation solubility of rosiglitazone hydrochloride from physical mixture and its solid dispersion systems were carried out in 0.1N HCl. The solubility data was presented in table 2**.** The solubility of rosiglitazone in 0.1N HCl was found to be 1.746±0.0025Mx10^{-3}.

Table 2 Saturation solubility of rosiglitazone in physical mixture and its solid dispersion system prepared with maltodextrin and poloxamer.

Code	Drug	Excipient	Ratio	Method	Concentration M×10^{-3} ± SD
KM-1	Rosiglitazone	maltodextrin	1:1	PM	1.898 ± 0.003606
KM-2	Rosiglitazone	maltodextrin	1:1	SE	3.068 ± 0.002658
KM-3	Rosiglitazone	maltodextrin	1:1	KNE	4.454 ± 0.001893
KM-4	Rosiglitazone	maltodextrin	1:3	PM	1.976 ± 0.004000
KM-5	Rosiglitazone	maltodextrin	1:3	SE	3.132 ± 0.00300
KM-6	Rosiglitazone	maltodextrin	1:3	KNE	4.874 ± 0.003164
KP-1	Rosiglitazone	poloxamer	1:1	PM	1.82 ± 0.0023
KP-2	Rosiglitazone	poloxamer	1:1	SE	2.996 ± 0.0035
KP-3	Rosiglitazone	poloxamer	1:1	KNE	4.502 ± 0.0026
KP-4	Rosiglitazone	poloxamer	1:3	PM	1.874 ± 0.0021
KP-5	Rosiglitazone	poloxamer	1:3	SE	3.036 ± 0.0035
KP-6	Rosiglitazone	poloxamer	1:3	KNE	4.546 ± 0.0045

3.3 Drug content studies

The percentage drug content for all the prepared physical mixture and its solid dispersion systems were calculated with SD and CV values. The obtained data was given in table 3.

Table 3 Rosiglitazone drug content in physical mixture and its solid dispersions prepared with maltodextrin and Poloxamer.

Code	Drug: polymer	Amount of drug taken	Amount of Drug recovered Mean ± SD	% Drug content Mean ± SD	Coefficient of variation (CV)
KM-1	1:1	20mg	19.97±0.0005	99.91±0.0023	0.0013
KM-2	1:1	20mg	19.52±0.0250	98.04±0.0640	0.0371
KM-3	1:1	20mg	19.87±0.0030	99.49±0.0120	0.0069
KM-4	1:3	20mg	19.78±0.0020	99.13±0.0083	0.0048
KM-5	1:3	20mg	19.62±0.1120	98.25±0.0500	0.029
KM-6	1:3	20mg	19.96±0.0010	99.87±0.0040	0.0023
KP-1	1:1	20mg	19.72±0.0026	98.91±0.0105	0.0061
KP-2	1:1	20mg	19.97±0.0005	99.90±0.0023	0.0013
KP-3	1:1	20mg	19.61±0.0116	98.44±0.0400	0.0230
KP-4	1:3	20mg	19.72±0.0025	98.89±0.0100	0.0058

KP-5	1:3	20mg	19.77±0.0020	99.09±0.0080	0.0046
KP-6	1:3	20mg	19.83±0.0025	99.33±0.0100	0.0058

3.4 FTIR studies

The FTIR spectra of solid dispersions prepared by kneading and solvent evaporation methods at 1:1 and 1:3 ratios using maltodextrin and poloxamer were presented in figures 1 and 2.

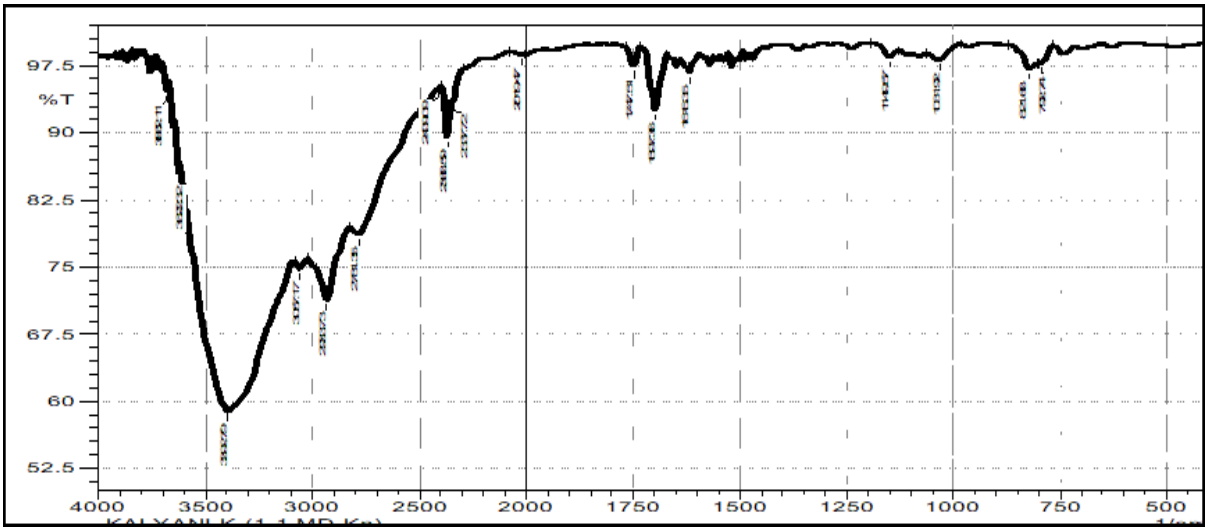

Figure 1 FTIR spectra of solid dispersions prepared by kneading method at 1:3 ratio using maltodextrin.

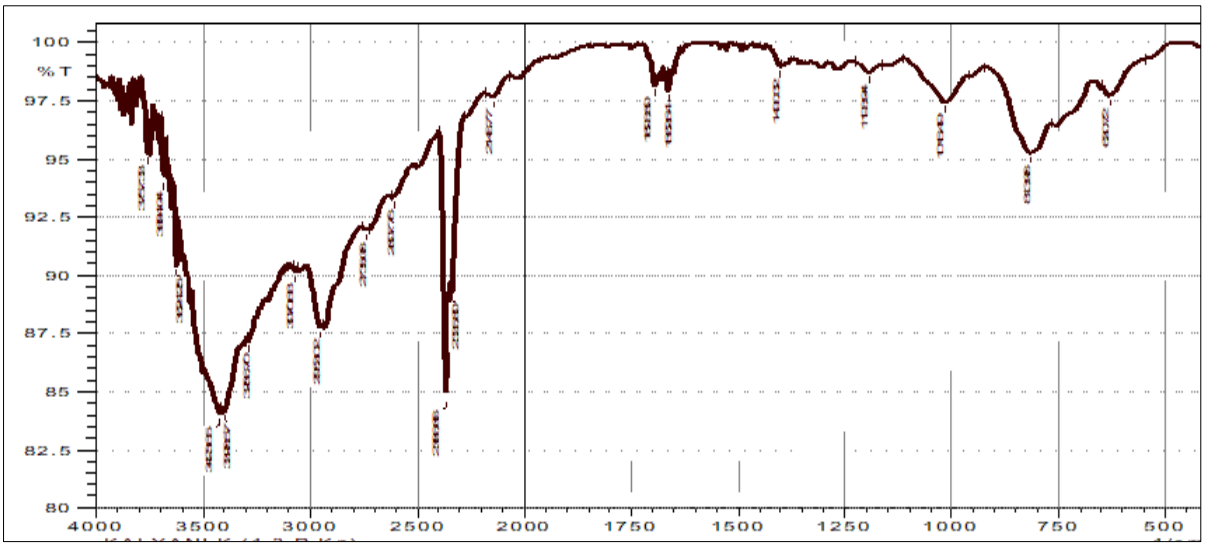

Figure 2 FTIR spectra of solid dispersions prepared by kneading method at 1:3 ratio using poloxamer.

3.5 X-ray diffractometry studies

Powder X-ray diffractometry is a useful tool for the detection of crystallinity in powder and microcrystalline state. Comparative 2θ peak values of rosiglitazone and its solid dispersion systems prepared with maltodextrin and poloxamer by solvent evaporation and kneading method at 1:3 prepared ratios were presented in figures 3 and 4.

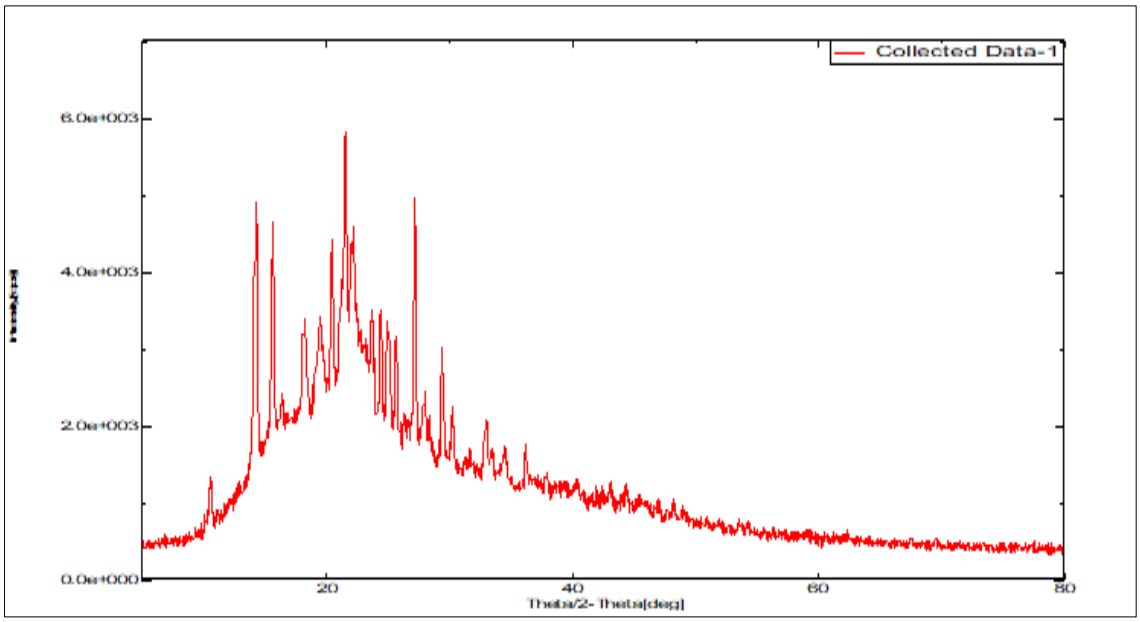

Figure 3 XRD pattern of solid dispersions prepared by kneading method at 1:3 ratio using maltodextrin.

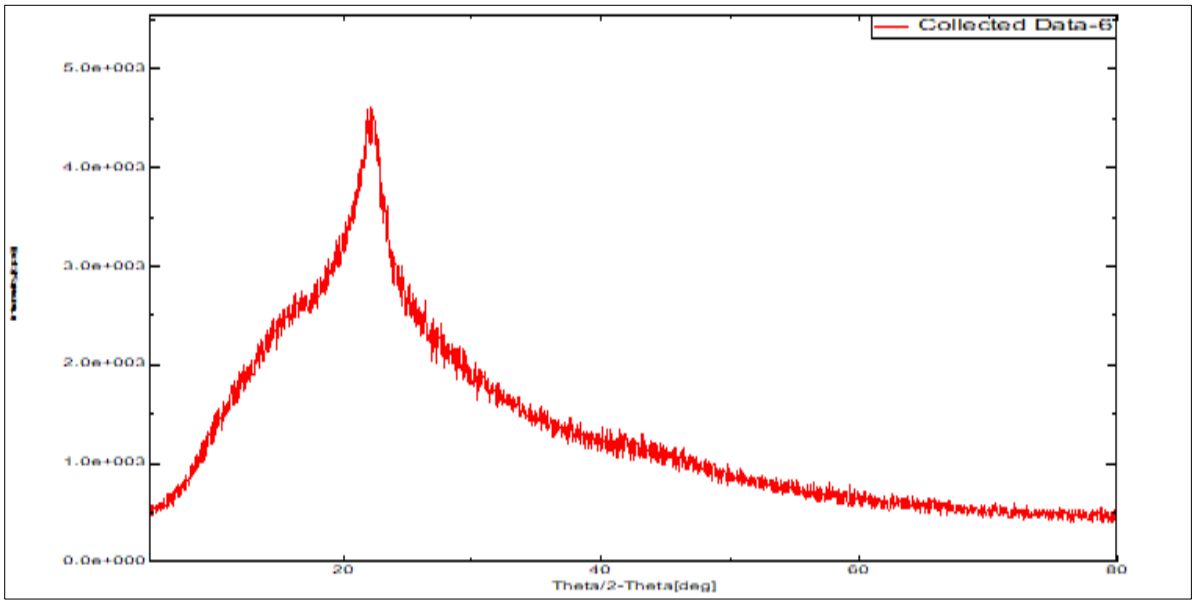

Figure 4 XRD pattern of solid dispersions prepared by kneading method at 1:3 ratio using poloxamer.

Dissolution studies: The dissolution data and profile were studied by using dissolution software PCP Disso V3.0. The dissolution data, profiles with model fitting data were presented in table 4 and 5 and in figures 5 and 6.

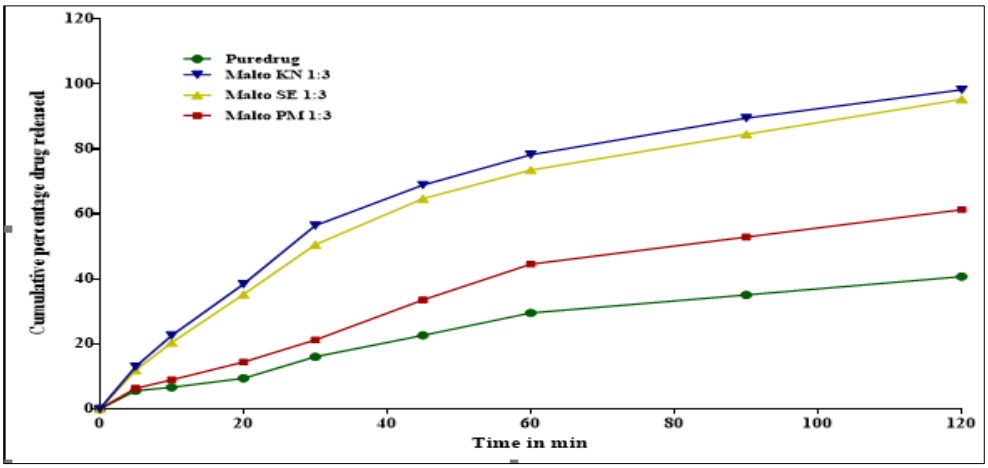

Figure 5 Comparative dissolution profile of pure drug and its solid dispersion systems prepared with maltodextrin by all methods at 1:3 ratios.

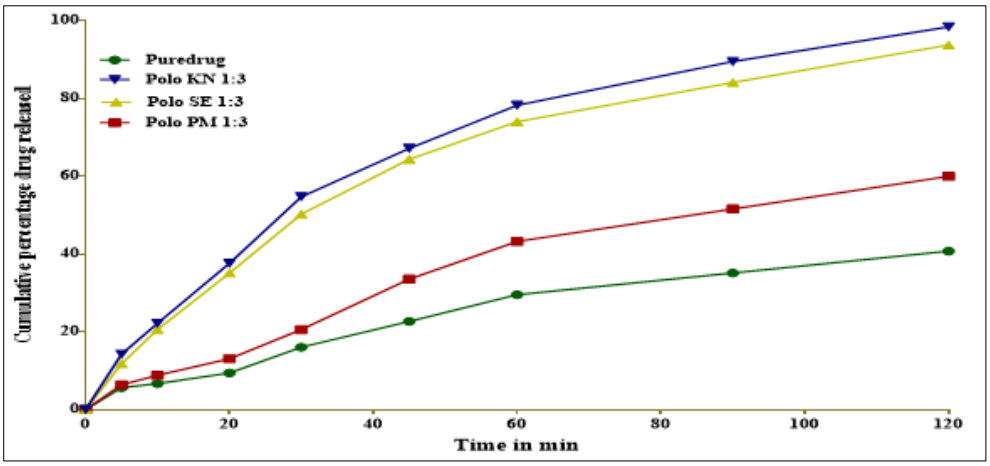

Figure 6 Comparative dissolution profile of pure drug and its solid dispersion systems prepared with poloxamer by all methods at 1:3 ratios.

Table 4 Various dissolution parameters and best model fitting curve values of pure drug, physical mixtures and its solid dispersion systems prepared with maltodextrin at 1:1 and 1:3 ratios.

Batches		DE_{30} (%)	DE_{60} (%)	DP_{30}	DP_{60}	T_{50} (min)	RDR_{30}	RDR_{60}	MDT_{30}	First order rates $K_1 \times 10^2$ (min^{-1})		Hix. Crow $K_{HC} \times 10^2$ ($mg^{1/3}.min^{-1}$)	
										R	K_1	R	K_{HC}
Pure drug		8.52	15.63	13.5	25.1	>120	1	1	14.08	0.9784	-0.0048	0.9714	-0.0015
PM	1:1	9.94	18.02	16.5	30.3	115.1	1.222	1.207	13.92	0.9936	-0.0060	0.9881	-0.0018
PM	1:3	12.34	23.30	22.2	39.5	82.9	1.644	1.573	13.56	0.9920	-0.0084	0.9844	-0.0025
SE	1:1	25.67	42.98	38.3	65.3	41.6	2.837	2.601	13.66	0.9982	-0.0198	0.9814	-0.0050
SE	1:3	27.62	45.77	42.8	70.2	37.3	3.170	2.796	13.81	0.9911	-0.0236	0.9879	-0.0055
KNE	1:1	28.93	47.79	44.2	73.0	35.0	3.266	2.900	13.63	0.9878	-0.0261	0.9881	-0.0059
KNE	1:3	30.06	49.10	47.3	76.0	32.7	3.503	3.027	14.01	0.9977	-0.0297	0.9915	-0.0063

Table 5 Various dissolution parameters and best model fitting curve values of pure drug, physical mixtures and its solid dispersion systems prepared with poloxamer at 1:1 and 1:3 ratios.

Batches		DE_{30} (%)	DE_{60} (%)	DP_{30}	DP_{60}	T_{50} (min)	RDR_{30}	RDR_{60}	MDT_{30}	First order rates $K_1 \times 10^2$ (min^{-1})		Hix. Crow $K_{HC} \times 10^2$ ($mg^{1/3}.min^{-1}$)	
										R	K_1	R	K_{HC}
Pure drug		5.73	11.17	11.14	21.8	>120	1	1	14.03	0.9989	-0.0042	0.9996	-0.0013
PM	1:1	10.16	18.64	17.0	31.1	111.5	1.259	1.239	13.56	0.9921	-0.0062	0.9858	-0.0019
PM	1:3	11.06	21.89	21.6	38.6	86.0	1.600	1.537	13.88	0.9922	-0.0081	0.9862	-0.0024
SE	1:1	26.53	44.18	46.4	71.2	33.4	3.437	2.836	13.90	0.9955	-0.0208	0.9819	-0.0051
SE	1:3	27.20	45.23	48.8	73.8	31.0	3.614	2.940	13.77	0.9964	-0.0223	0.9846	-0.0054
KNE	1:1	27.91	46.63	53.6	78.4	27.1	3.970	3.123	13.83	0.9937	-0.0256	0.9894	-0.0058
KNE	1:3	29.59	48.21	59.5	83.6	23.0	4.407	3.330	13.79	0.9724	-0.0301	0.9935	-0.0063

4 Discussion

Solid dispersion systems of rosiglitazone were conveniently prepared using maltodextrin and poloxamer at 1:1 and 1:3 ratios by solvent evaporation and kneading methods. The solubility of rosiglitazone in 0.1N HCl was found to be 1.746±0.0025 Mx10-3. The solubility of rosiglitazone in maltodextrin and poloxamer solutions was increased linearly with increase in the concentration of excipient. The solubility of rosiglitazone in solid dispersion systems was increased with respect to the concentration of the carrier and method dependent. In both the carriers the saturation solubility was found to be in the order 1:3 > 1:1 and methods KNE > SE > PM > Pure drug. The obtained solid dispersion systems were found to be free flowing. The coefficient of variation (CV) in the percentage drug content was less than 1% in all the batches prepared. With small SD and CV values indicates that method employed resulted solid dispersion systems with uniform drug content. The FTIR spectra of solid dispersions prepared by both methods with both the polymers at 1:1 and 1:3 rations show the presence of characteristic carbonyl stretching (CO) vibration of rosiglitazone with little shifting towards lower to higher wavelength indicate minor to no interaction at molecular level. The X-ray diffraction pattern for solid dispersion systems prepared with maltodextrin, and poloxamer by solvent evaporation and kneading methods at 1:1 & 1:3 ratios show a significant decrease in the degree of crystallinity, as evident by the decrement in the number of sharp distinctive peaks with respect to the excipient. The shearing force applied by the kneading in kneading method, intimate mixing of drug solution with carrier in solvent evaporation method results nucleation and crystal growth phases, leading to formation of crystals/partial amorphization. The results suggest that the crystallinity was modified to great extent indicate there is a possibility of interaction between the rosiglitazone and the excipient, a greater portion of solid dispersion systems was converted into amorphous form. These results were in coordination with by DSC studies a portion of solid dispersion systems was converted into amorphous form. The DSC results suggests that there is shifting of melting temperature to higher region it is mainly due to conversion of crystalline rosiglitazone maleate into of amorphous compound indicating molecular dispersion of rosiglitazone maleate in hydrophilic polymers and the results are justified by XRD studies. The solid dispersions of the water insoluble drug rosiglitazone were successfully prepared by solvent evaporation and kneading method using maltodextrin and poloxamer. The in vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure rosiglitazone. Mechanisms involved are solubilization and improved wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals after dissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with excipients viz., maltodextrin and poloxamer.

5 Conclusion

Finally, it could be concluded that solid dispersion of rosiglitazone using hydrophilic excipients would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. One-way ANOVA was used to test the statistically significant difference between pure and prepared solid dispersion systems. Significant differences in the means of DP60 and DE60 were tested at 95% confidence. The DP60 and DE60 values of solid dispersion systems prepared by solvent evaporation and kneading method are significantly higher ($P<0.05$) when compared to DP60 and DE60 values of physical mixture and pure rosiglitazone.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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