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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF ROSIGLITAZONE BY SOLID DISPERSION (KNEADING) TECHNIQUE

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ABSTRACT

Rosiglitazone is a poorly water-soluble (BCS class II) antidiabetic drug. Due to the poor water solubility of this drug, its bioavailability is dissolution rate-limited. The purpose of this study was is to increase the solubility of Rosiglitazone (RG) in aqueous media by solid dispersion (SD) technique with Poloxamer (PXM) 188 and Poloxamer (PXM) 407 by using the kneading method. The RG-PXM solid dispersion system was characterized by Differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) analysis, Fourier transform-infrared spectroscopy (FT-IR) and Scanning electron microscopy (SEM), and in vitro dissolution studies. No chemical interaction was found between RG and PXM 188 or PXM 407. The results from DSC, XRD and SEM studies show that PXM 188 or PXM 407 inhibits the crystallization of RG. The SDs prepared in this study were found to have better dissolution rates in comparison to intact RG and physical mixture of PXM 188 or PXM 407. It was found that the optimum weight ratio for drug: Carrier is 1:5 for PXM 188 and 1:6 for PXM 407.

Key-Words: Solubility, Rosiglitazone, Solid dispersion

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INTRODUCTION:

More than 40 percent of the drug coming from high-throughout screening are poorly soluble in water [1]. The poor solubility and low dissolution rate of poorly water soluble drug in the aqueous gastrointestinal fluid often causes insufficient bioavaibility especially for class II substance according to the biopharmaceutics classification system (BCS) the bioavaibility may be enhance by increasing solubility and dissolution rate of the drug in gastro intestinal fluid [2].

There are number of formulation approaches to resolve the problem of low solubility and low bioavaibility .The approaches include micronization solubilization using Co-solvent, use of permeation enhance, oily solution, surfactant dispersion[3].

Among all technique solid dispersion (SD), is the most efficient technique from the dispersion in carrier more specially[4] define the system has the dispersion of the one or more active ingredient in an inert matrix at solid state perform by melting method, Solvent evaporation method and melting solvent[5].

Rosiglitazone, (RS)-5-{4-(2[methyl(pyridine-2-yl)amino]ethoxy benzyl} thiozolidine-2,4-dione.Oral hypoglycemic agent it is used for treatment of type II diabetes, insoluble in water shows absorption problem and its dissolution rate limiting step.[6]

Generally, poor water soluble compound have solubility and dissolution related bioavaibility problem[7] during the blood glucose level condition, and antidiabetic drug should shows quick and high oral bioavaibility, which can be achieved by high aqueous solubility. Many hydrophilic excipients like PEG 4000, RG 6000, urea, mannitol, PVP and Poloxamer can be used to enhance the dissolution rate[8, 9].

Recentlaly, poloxamer a group of block co-polymer non ionic surfactant have attracted considerable attention for application in preparation of solid dispersion.[10, 11, 12]

So the aim of present study was to enhance the aqueous solubility and oral bioavaibility of RG by solid dispersion using kneading technique, water soluble carrier like PXM-188 and PXM-407 by kneading.

MATERIAL AND METHOD:

Rosiglitazone was obtained from Cipala Pharmaceuticals Ltd.Mumbai as a gift sample, Poloxamer 188 and Poloxamer 407, were obtained from Alembic pharmaceutical Pvt.Ltd.Badodara. All other chemical used were of analytical grade.

Preparation of physical mixture

A physical mixture (PM) of RG with PXM 188 or PXM 407 in 1:1 ratio was prepared by

thoroughly mixing the accurately weighed quantity of drug and carrier in by using glass mortar and pestle for 5 min. This mixture was then subsequently passed through mesh no. 40 and stored in a dessicator for 48 h.

Preparation of Solid dispersions[12]

The Kneading method (KM) was used for the preparation of solid dispersion. Eight different drugs: Carrier ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8) were used. RG 1 to RG 8 corresponds to preparations containing PXM 188 and RG 9 to RG 16 correspond to preparations containing PXM 407. Rosiglitazone and PXM 188 or 407 were weighed according to these weighed ratios. RG and PXM were triturated using a small volume of methanol to give a thick paste, which was kneaded for 30 minutes and then dried at 40° C in an oven. The dried mass was then pulverized, passed through mesh no. 30, stored in vacuum desiccators (48 h) and passed through mesh no. 60 before packaging in an airtight container.

Determination of drug content[13]

The drug content was calculated by dissolving solid dispersion equivalent to 10 mg drug into a 100 ml volumetric flask and dissolved in minimum amount of methanol; and the volume was made up to the mark with using phosphate buffer (pH 7.4) and then filtered through whatmann paper no40 with, filter and assayed for drug content using UV double beam (Shimadzu) spectrophotometer at 228 nm. Three replicates were prepared, and the average drug contents were estimated in the prepared solid dispersion.

Actual drug content was calculated for all batches using the Equation:

$$\text{Drug content (\%)} = \frac{\text{RG act} \times 100}{\text{RG sd}}$$

Where RG_{act} is Actual RG Content in weighed quantity of Solid dispersion and RG_{SD} is theoretical amount of RG in SD.

Determination of Solubility:

Phase solubility was performed as described by Higuchi and Connors. Excess amount of solid dispersion were added to 25 ml phosphate buffer (pH 7.4) taken in a stoppered conical flasks, and mixture were shaken for 24 hrs in a rotary flask shaker. After shaking to achieve attain equilibrium, 2 ml aliquots were withdrawn at 1 hr intervals and filtered through Whatmann filter paper no 40. The filtrate was analyzed spectrophotometrically at 228 nm. Shaking was continued until three consecutive reading were the same.[14]

Fourier transforms infra-red spectroscopy

FT-IR spectra were recorded on the sample prepared in KBr disks (2 mg sample in 200 mg KBr)

using Shimadzu Fourier Transform Infra-Red spectrophotometer. The scanning range was 500-4000/cm with a resolution of 4/cm

Differential scanning calorimetry analysis-

The thermal analyses were carried out with a Mettler Tolado DSC 60 (Japan). All accurately weighed samples were placed in sealed aluminum pans and heated at a rate of 20°C in the temperature range of 20-100°C temperature range under a nitrogen flow rate of 20 ml/min.

Powder X-ray diffraction-

XRD patterns were recorded using BRUKER-axs D8-ADVANCE, model generator Powder X-ray diffraction patterns were traced for RG, various carriers and solid dispersion. The position and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier.

Scanning electron microscopy-

The external morphology of solid dispersion was analyzed by using a scanning Electron Microscope (SEM). The morphology of pure drug, PM and SDs was examined under a scanning electron microscope SEM – JSM 6360 A JEOL JAPAN.

In vitro drug release-

Accurately weighed preparations equivalent to 15 mg of Rosiglitazone were added to 900 ml of dissolution media (7.4 phosphate buffer) contained in USP dissolution apparatus II (Electro lab, TDT-08L) and stirred at a speed of 50 rpm at 37 ± 0.5°C. Five milliliter aliquots were withdrawn at 5, 10, 15, 20, 30 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution at 228 nm using UV-visible spectrophotometer against the blank. The dissolution of pure Rosiglitazone was done similarly. The release profile data was analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency at 5 and 15 minutes.[15]

RESULT AND DISCUSSION

All physical mixtures and solid dispersion (SD) were easy to prepare and reproducible.

Drug content estimation-

The drug content of RG solid dispersion (SD) was found to be in range 97.21 to 99.79 and these values are within the acceptable range. As given in Table 1, indicating uniform drug distribution in all the solid dispersion (SD)

Solubility studies-

The solubility profile of RG was found to be 0.005 mg/ml, and drug release was found to be only

32.15% during in vitro dissolution study, suggesting a strong need to enhance the solubility and dissolution of RG. Therefore, a solid dispersion technique using PXM 188 and PXM 407 was employed for solubility and dissolution enhancement of RG in the present investigation. The improvement in solubility was observed with for all solid dispersion, Increase in weight fraction of surface-active carrier resulted in an increase in the solubility of all dispersions. Maximum solubility enhancement was found in 1:5 ratio of RG: PXM 188 prepared by the kneading method. Enhancement in saturation solubility was found to be in order of PXM 188> PXM 407.

Table 1 : Evaluation of Physical mixtures and solid dispersion SDs of Rosiglitazone

Formulation Code	%Drug content	Solubility mg/ml	DE_5	DE_{15}
RG Pure	--	0.005	17.52±0.09	32.15±0.10
PM 1	98.93	0.013	19.37±0.12	36.23±0.23
PM 2	97.88	0.011	17.65±0.14	32.13±0.10
RG 1	97.60	0.069	40.82±0.08	58.97±0.15
RG 2	97.87	0.123	40.98±0.16	59.28±0.06
RG 3	97.90	0.182	41.38±0.06	59.56±0.05
RG 4	98.30	0.199	41.60±034.	59.70±0.33
RG 5	99.68	0.353	47.19±0.23	63.49±0.25
RG 6	98.89	0.239	45.50±0.16	59.37±0.52
RG 7	99.41	0.304	45.62±0.21	63.57±0.39
RG8	99.60	0.321	45.88±0.34	63.74±0.18
RG9	97.21	0.123	34.45±0.27	55.46±0.18
RG10	97.56	0.164	34.65±0.08	55.64±0.05
RG11	97.93	0.209	34.89±0.10	55.89±0.04
RG12	98.64	0.231	35.15±0.07	56.14±0.08
RG13	98.88	0.178	35.41±0.05	56.31±0.09
RG14	99.79	0.341	41.56±0.07	60.79±0.70
RG15	99.69	0.316	42.78±0.22	58.15±0.28
RG16	99.08	0.312	42.86±0.25	58.46±0.37

FT-IR spectroscopy-

FT-IR spectra of RG, PXM, and SDs (1:5 and 1:6) are illustrated in Figure 1. Characteristic peaks of RG at 1187/cm(C-N stretching aliphatic), 1279/cm (C-N stretching aromatic), 1655/cm (C=O stretching), 1632/cm (N-H Bending amide) and 3418/cm (O-H aliphatic stretching) 3336/cm (N-H stretching) were observed.

Due to similarities in molecular structure, of PXM 188 and PXM 407 showed similar absorption bands, in which characteristic peaks of OH stretching (3443/cm), CH stretching (2880/cm), C-H bending (1477/cm), C-H bending (1452/cm), resp. for PXM-188 and PXM-407 and R-O stretching (1097/cm) were observed. All solid dispersion showed peaks of RG (pure) and carriers. As the carrier concentration was increased, the intensities of carrier peaks also increased while with the decrease in the intensities of the drug peaks decreased. These results indicate that

there is no chemical interaction between drug and carrier when formed as solid dispersion.

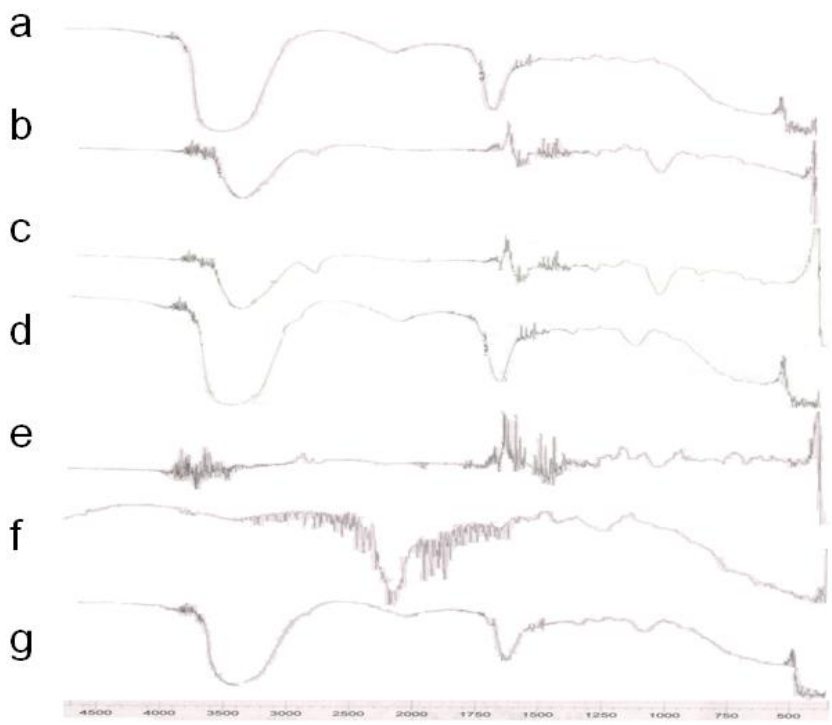

Figure 1:FT-IR of RG, Pure, carriers, physical mixtures and different solid dispersion system(a)RG (b)PXM 188 (c)PXM 407 (d)Physical mixture of RG with PXM188 (e)Physical mixture of RG with PXM 407 (f) Solid dispersion with PXM 188 (g)Solid dispersion with PXM 407

Differential scanning calorimetry -

The DSC thermograms of RG, PXM 188, and PXM 407, and solid dispersion of RG and with polymers, are shown in Figure 2. Pure RG showed the sharp endotherm peak at 125.98°C, corresponding to melting point of RG. Such melting peak with RG-PXM 188 or RG-PXM 407 inclusion complex as well as SDs shifts the melting endotherm to lower temperatures for 118.26°C, 125.47°C, 55.44°C and 56.17°C for RG- PXM 188 physical mixture, RG-PXM 407 physical mixture, solid dispersion with PXM 188, and solid dispersion (SD) with PXM 188, respectively. No melting endotherm of inclusion complexes corresponding to pure RG was observed. It shows the peak at a lower temperature at about approximately 55.44°C; and hence, we can be conclude that RG completely dissolved in the polymer below the melting temperature of crystalline RG. The SD with PXM 188 (RG5) shows the almost disappears, suggesting two possibilities, namely amorphous precipitation of the drug and better solubilization in carrier.

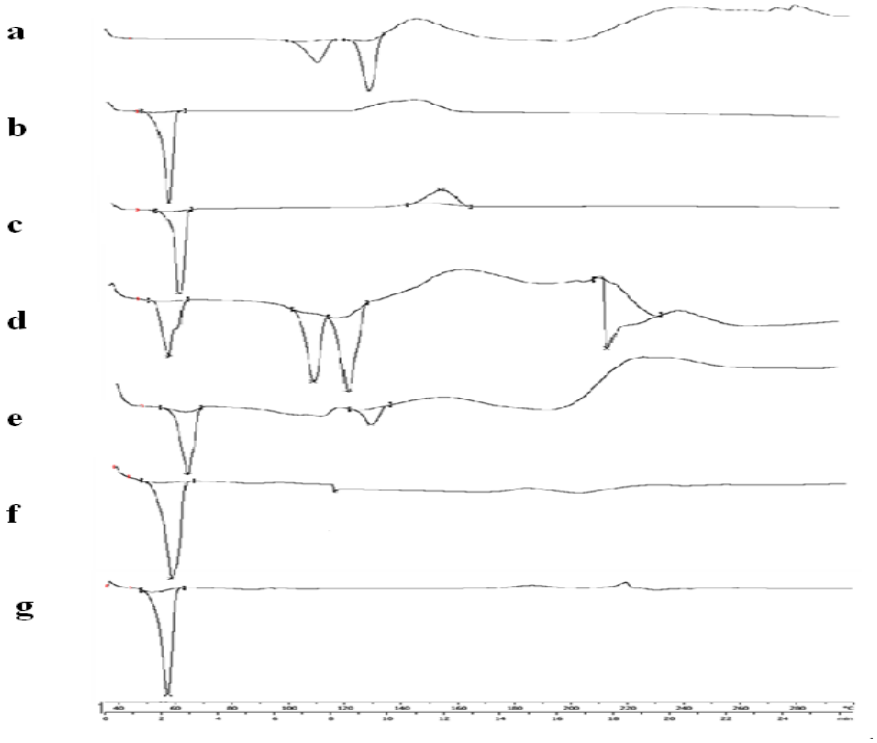

Figure 2: DSC Thermograms of Rosiglitazone and Solid dispersion with different carriers

(a)RG (b)PXM 188 (c)PXM 407 (d)Physical mixture of RG with PXM188 (e)Physical mixture of RG with PXM 407 (f) Solid dispersion with PXM 188 (g)Solid dispersion with PXM 407

X-ray diffraction

The XRD patterns of RG, RG-PXM 188 and RG-PXM 407, and RG-PXM 188 or RG-PXM 407 SDs were shown in Figure 3. In the X-ray differactogram of pure RG, a sharp peak is presented at a diffraction angle (2θ), are presented and it confirms that the drug is in the crystalline form. Typical diffraction peaks of RG in physical mixture indicating indicate the presence of free crystalline drugs, which were revealed by few broad peaks of low intensity which that emerged on the background of PXM as an amorphous carrier. The reduction in intensity and number of typical diffraction peaks of RG in SD X-ray diffractogram suggests the reduction in the crystalline nature of drug.

Scanning electron microscopy

SEM scanning electron micrographs of pure Rosiglitazone, pure poloxamer PXM 188 and SDs (RG5) are shown in Figure 4. Rosiglitazone was present in a crystal form. Poloxamer 188 was present in globular form. The surface morphology of SDs indicates that Rosiglitazone was absorbed into the PXM 188 and homogeneously dispersed into the polymer. SEM pictures images suggested that the individual surface properties of PXM 188 and RG were lost during kneading and the formation of effective SD systems. These findings demonstrated that the drug

was thoroughly mixed in the carriers with a negligible loss of little crystallinity.

In-vitro Dissolution studies

The in vitro release profile of RG from PXM 188 and PXM 407 solid dispersion (prepared by the kneading method) and physical mixture formulations are shown In vitro dissolution studies in Figures 5 and 6, and the graph for the comparison of the cumulative percent release is illustrated in Figure 7. According to observations, drug release was increased with increasing the concentration of both the grades of Poloxamer (i.e., PXM 188 and PXM 407) up to a certain limit, and after that it almost becomes constant. Drug release from SDs and physical mixtures was faster than that from the pure drug. The dissolution of drug from solid dispersion was found to be faster than that from physical mixtures; this may be due to the molecular and colloidal dispersion of drug in hydrophilic carrier matrix of Poloxamer.

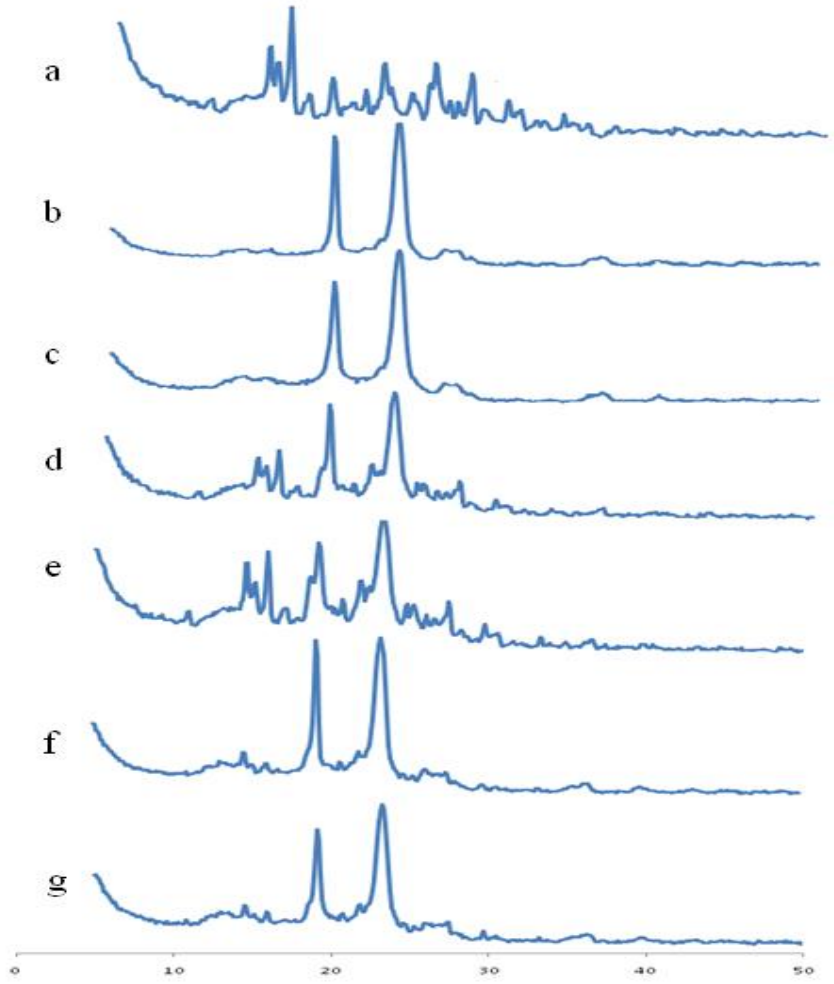

Figure 3:XPRD patterns of RG and Solid dispersion with different carriers (a)RG (b)PXM 188 (c)PXM 407 (d)Physical mixture of RG with PXM188 (e)Physical mixture of RG with PXM 407 (f) Solid dispersion with PXM 188 (g)Solid dispersion with PXM 407

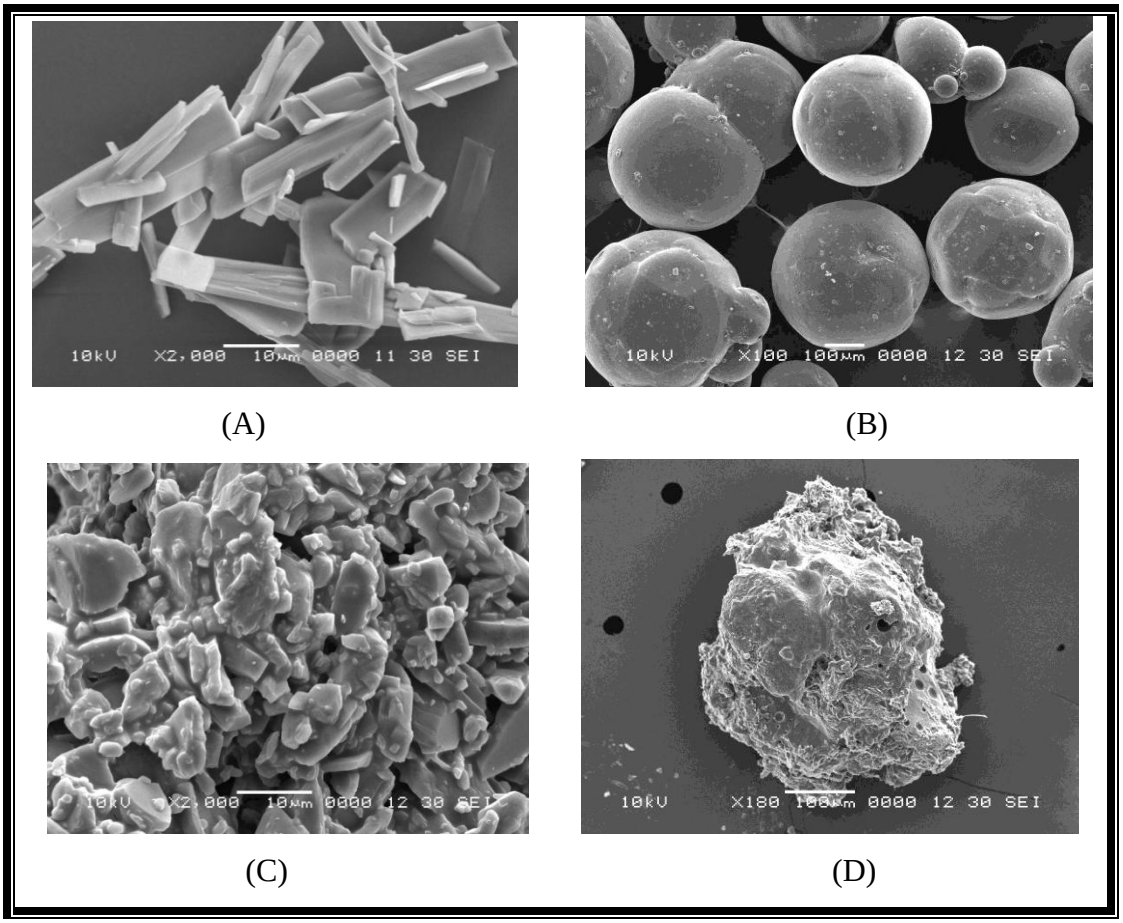

Figure 4: scanning electron micrographs (SEM) (a) RG (b) PXM188 (c) RG5 solid dispersion at 2000x (d) RG5 solid dispersion at100x

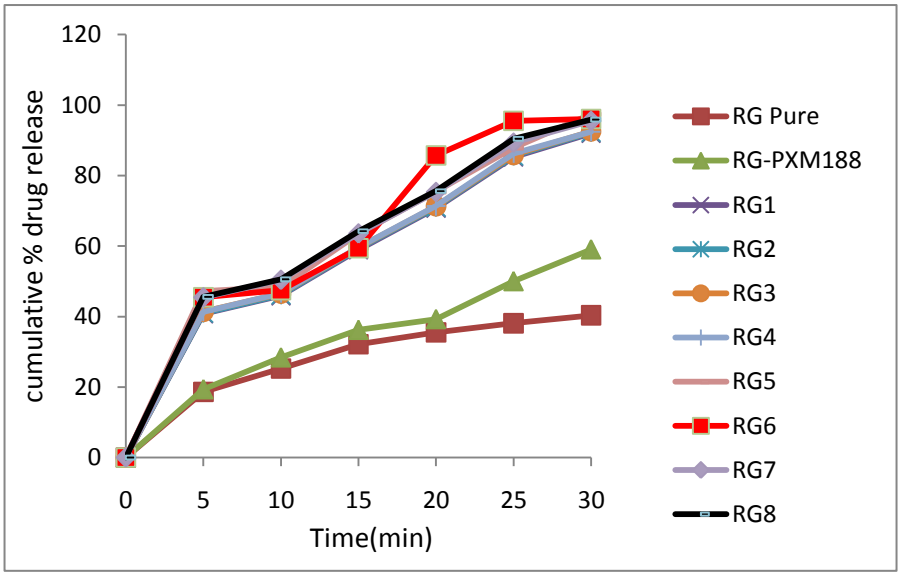

Figure 5 In-vitro drug release of RG in pH 7.4 Phosphate buffer from solid dispersion and physical mixture of RG-PXM 188 systems.

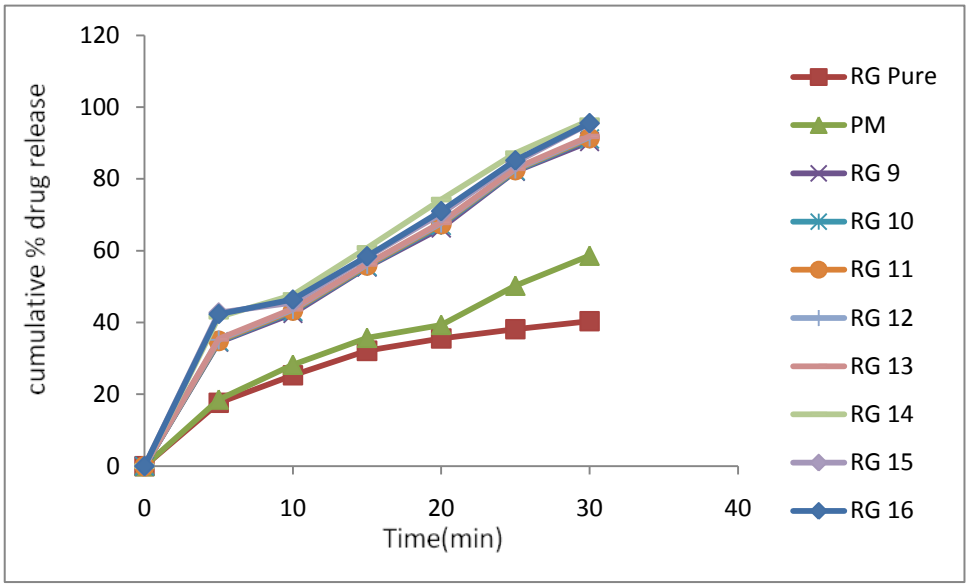

Figure 6 In-vitro drug release of RG in pH 7.4 Phosphate buffer from solid dispersion and physical mixture of RG-PXM 407 systems

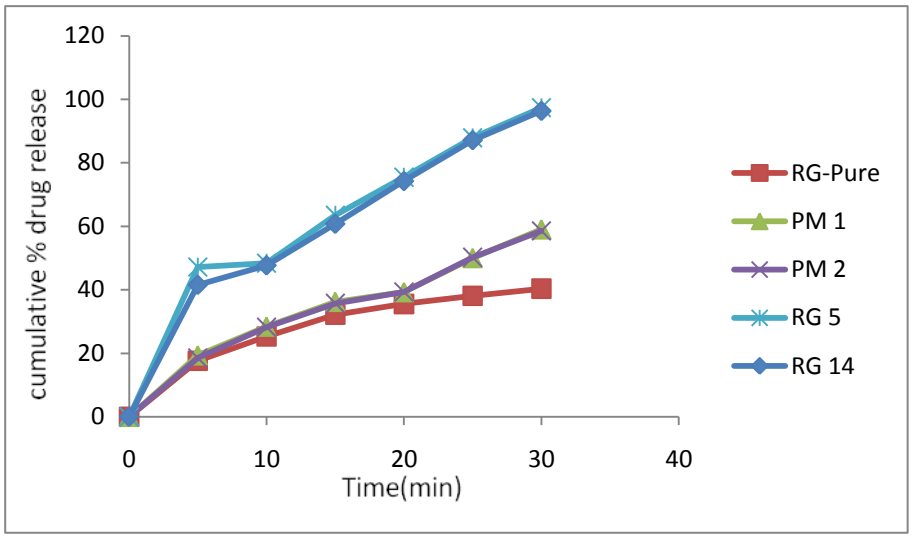

Figure 7 Comparative dissolution profile of RG in pH 7.4 Phosphate buffer from physical mixture and solid dispersions prepared used in PXM188 and PXM407.

Several mechanisms may be possible for might have lead to the enhanced release of RG in the Solid dispersion formulation with the water soluble polymeric surfactants PXM 188 and PXM 407 The reduction of crystallinity of drug resulting in improved release (supported by X-ray diffraction); reduction of particle size to expand the Surface area for dissolution solubilizing effect of PXM is likely to occur through the following mechanism. In the dry state, drug particles were in close contact or adhered to the polymer particles as a result of mixing (supported by SEM). When the mixture comes in contact with water, the polymer particles might have hydrated rapidly into the polymer solution, solubilizing the adjacent drug particles and subsequently

releasing the drug into the medium. Reason for the increase of RG release from solid dispersion SD with the increasing ratio of PXM 188 and PXM 407 is that at low concentrations, approximating those at which more conventional nonionic detergents form micelles, the Poloxamer monomers are thought to form monomolecular micelles by through a change in configuration in solution. At higher concentrations, these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilizing drugs to a larger extent.

Dissolution efficiency of pure RG and all the solid dispersion formulations at 5 minutes and 15 minutes were calculated which is as shown in Table 1. The dissolution efficiency increased in all the formulations as with the increase in the dissolution time was increased from 5 to 15 minutes, the dissolution efficiency was increased in all the formulations. Among the formulations, RG5 has shown maximum dissolution efficiencies of 47.19%±0.23and 63.49%±0.25 at 5 min (DE5) and 15 minutes (DE15) Respectively.

In vitro drug release study indicates that PXM 188 shows better dissolution efficiency than PXM 407. This behavior further could be explained by the physico-chemical properties of these both Poloxamer. PXM 188 is composed of more hydrophilic polyethylene glycol polymers than PXM 407. This composition leads to a higher Hydrophilic lipophilic balance (HLB) value and has a greater tendency to solubilizing into the water then PXM 407.

CONCLUSION

The study shows that the dissolution rate of Rosiglitazone can be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method, without any physical and chemical interaction. Solid dispersion of Rosiglitazone-PXM 188 showed faster release than from that of PXM 407solid dispersion of Rosiglitazone: PXM 188 (1:5) showed the maximum dissolution efficiency among all solid dispersion and physical mixtures.

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