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Solid Dispersion of Pioglitazone: A Solubility Enhancement Approach

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ABSTRACT
Pioglitazone, a member of the thiazolidinedione group of drugs used for the management of type 2 diabetes mellitus. It belongs to BCS Class-II drug. Poor solubility of any drug may have negative influence on its dissolution rate, leading to subtherapeutic plasma drug level affecting therapeutic action. In present study, an effort was primed to design solid dispersion incorporated to enhance dissolution rate and ½ life of drug by using solvent evaporation technique for sold dispersion. Prepared formulations of SD were characterized for drug content, % yield, solubility, and Fourier Transform Infrared (FTIR) studies. Characterization was done with the motive to select the suitable method for SD preparation. The dissolution study performed showed that dissolution rate of API enhanced to greater extent by solid dispersion technique using kneading method and microwave technique. The kneading technique for preparation of SDs was much simpler and also feasible industrially. PVP K30 showed most important result indicating usage as a carrier for solid dispersion. Significant outcomes like drug content and solubility were obtained for SDs having the drug: poloxamer188 ratio of 1:1.5 and hence the same SDs have been considered for the further investigations.
Keywords: *Solid Dispersion, Pioglitazone, Fourier Transform Infrared*

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INTRODUCTION

Diabetes mellitus is one amid long-lasting diseases. Diabetes is metabolic disorder occurring when pancreas doesn't yield enough insulin or when the formed insulin can't be efficiently used by body leading to serious damage to the body's systems [1, 2, 3]. The prevalence of it is increasing continuously and may be due to changing lifestyle in nearly all countries. The global prevalence of diabetes millitus in 2010 was 6.3 %, and affecting 287 million adults. Prevalence may be around 7.6 % by 2030 affecting 438 million adults. There may be a 68% surge in number of diabetes in developing countries and nearby 21% increase in developed countries in 2030 [4,5,6]. Thiazolidinedione (TZDs) is class of oral hypoglycemic agent reverses few metabolic processes which were responsible for growth of insulin resistance leading to type II diabetes mellitus [7, 8, 9]. TZD act through nuclear hormone, peroxisome proliferator activated receptorγ (PPARγ) [10,11,12] which upsurges insulin sensitivity by enhancing an expression of proteins accountable for modulating glucose and lipid metabolism leading to enhanced insulin sensitivity in liver, muscle and adipose tissues. Members of class TZDs include troglitazone, pioglitazone, darglitazone and rosiglitazone [13, 14].

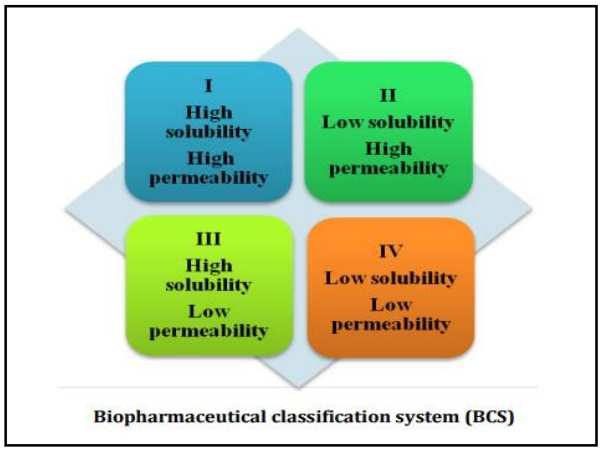

Fig. 1. Biopharmaceutical Classification System

Pioglitazone, a member of the thiazolidinedione group of drugs used for the management of type 2 diabetes mellitus [15,16]. The solubility of its hydrochloride salt is small and classified as BCS class II drug. Other classes of BCS are shown in above figure. Poor solubility of any drug may have negative influence on its dissolution rate, leading to subtherapeutic plasma drug level affecting therapeutic action. techniques for increasing water solubility of poor soluble drugs include: Complexation, addition of surface active agents, soluble prodrug, cosolvency, salt formation, hydrotropism, crystal engineering and addition of ionic liquid [17,18]. Few core techniques are shown in following fig. 2

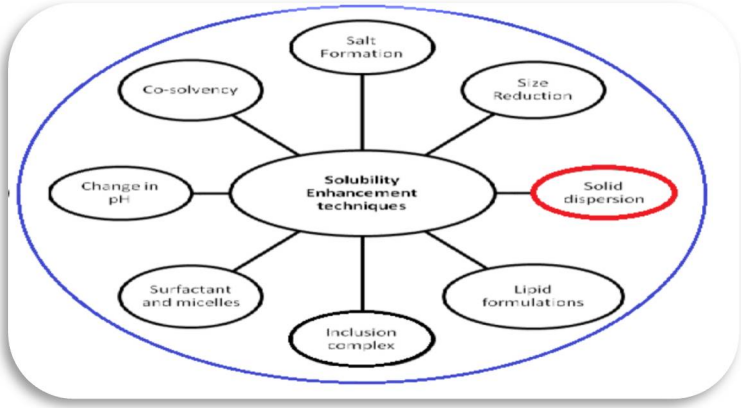

Fig. 2. Techniques of Solubility Enhancement

Amongst these approaches, solid dispersion of drug has proven efficient in enhancing solubility of poorly water-soluble drug [19,20]. Pioglitazone has biological half-life of 4 – 7hrs with outstanding oral bioavailability (84%) [21].Although at steady state, maximum plasma drug concentrations (C_{max}) were reported as 0.8 (for 15mg/day dose) and 1.2 mg/l (for30 mg/day dose), the T_{max} was reported to be 4.7hrs. This delayed T_{max} may be owing to poor aqueous solubility of Pioglitazone (solubility of 0.014mg/ml). Consequently, this may result in the delayed onset of action. Moreover, because of subtherapeutic plasma drug level; may also lead to therapeutic failure. Said problem may be sorted out by successfully enhancing the solubility of the drug. Solid dispersion refers a system in which hydrophobic drug is usually dispersed in hydrophilic matrix, to improve its dissolution properties and bioavailability [22,23].In solid dispersion, drug can exist in an amorphous or crystalline form in hydrophilic polymeric surroundings. This surrounding is usually called as carrier. Hydrophilic polymers like poly vinyl pyrrolidine K30(PVPK 30), polyethylene glycols, urea, cyclodextrins etc. are commonly used carriers in the processing of solid dispersion [24,25,26]. These hydrophilic polymers may result in improved solubility and dissolution rate. Solid dispersion can subsequently processed in microparticulate drug delivery system like microencapsulation. Microparticulate approaches like nanoparticles or microencapsulation have been widely established process to accomplish controlled release as well as drug targeting [29, 30].

MATERIALS AND METHODS

Table 1: List of Materials

Sr. no	Materials	Source
1	API (Pioglitazone)	Sample procured from Sun Pharmaceutical Industries Ltd
2	PEG 4000	Dr. Reddy's Laboratories Ltd(Hyderabad, India).
3	PEG 6000	Dr. Reddy's Laboratories Ltd(Hyderabad, India).
4	Poloxomer 188	Glenmark Pharmaceuticals
5	PVP K30	Dr. Reddy's Laboratories Ltd(Hyderabad, India).
6	(PEG 20 K)	Dr. Reddy's Laboratories Ltd(Hyderabad, India).
7	Reagents and solvents	Analytical grade

Methods (Experimental)

Determination of Absorption Maxima

Before the analysis of solution containing Pioglitazone, the spectrophotometry was adjusted with phosphate buffer pH 7.4. The spectrum was recorded from 200 nm to 400 nm. Standard solutions (10mcg/ml) was scanned against a solvent (phosphate buffer pH 7.4) as blank between 200-400nm. Spectrum was recorded and the suitable absorption maximum (λmax) was selected.

Standard curve of API

Stock solution of API was prepared to obtain final solution of 100µg of pioglitazone per ml. From this, 1ml stock was pipetted out in 10 ml volumetric flask and diluted with standard buffer to give working standard solution. From this working standard, suitable dilutions were prepared to give 10, 20, 30, 40, 50µg/ml. All solutions were prepared in triplicate using stock and absorbance was measured using UV-Visible spectrophotometer (Shimadzu UV-1800) against the standard buffer 7.4 as a blank at 238 nm wavelength. Same procedure was followed using phosphate buffer having pH 7.4. All experiments were performed in triplicate.

Solubility study

Solubility studies were conducted out by the method proposed by Higuchi and Connors. A surplus quantity of pioglitazone was separately added to distilled water, pH 1.2 and pH7.4 buffer respectively, in different screw-capped bottle. Each bottle was placed on holder of orbital shaker and shaken at room temperature (26±2°C)for 24hours. The sample was collected from each bottle and filtered through membrane filter (0.21µm). The filtrate was diluted appropriately and analyzed using UV spectrophotometer (Shimadzu 1700 UV- visible spectrophotometer) at 270 nm.

Screening

Screening of carrier for solid dispersion

The physical mixture of pure drug and different water-soluble polymers like PEG 4000, PEG 6000, Poloxomer188, PEG 20 K and PVP K30 were used for the screening of polymer. Solubility of each physical mixture was tested and compared with the solubility of pure drug. PEG20K and PVPK30 were considered in a ratio of 1: 1 based on the outcomes obtained during screening.

Preparation of solid dispersion

3 methods were used for the preparation of solid dispersions, which were kneading, hotmelt, and microwave.

Preparation of SD by kneading

API and polymer, both were mixed smoothly with each other to get uniform mixture. Water: methanol in ratio of1:1 was added with small increments to obtain a smooth paste. The paste was kept as it was for 45minutes and subsequently dried at 40°Cin hot air oven. Product obtained was milled and passed through mesh 60. Drug polymer proportions were shown in following table 2.

Table 2: Drug polymer proportions (kneading)

Formulation code	API:PEG	API:PVPK30
PIO	-	-
K1	1:0.5	-
K2	1:1	-
K3	1:1.5	-
K4	-	1:0.5
K5	-	1:1
K6	-	1:1.5

Preparation of SD by Hot Melt Technique

Polymers were melted in porcelain dish. API was dispersed in molten mass of polymer to get uniform dispersion. The dispersion was cooled to RT. The product obtained was dried at room temperature and was passed through mesh 60.Drug polymer proportions were shown in following table 3.

Table 3: Drug polymer proportions (hot-melt)

Formulation code	API:PEG	API:PVPK30
PIO	-	-
H1	1:0.5	-
H2	1:1	-
H3	1:1.5	-
H4	-	1:0.5
H5	-	1:1
H6	-	1:1.5

Preparation of SD using microwave

At first, API and polymer, both were mixed gently to get uniform mixture. Fixed quantity of obtained mixture was kept in microwave oven at the power of 800 to 1500W in a domestic microwave oven (Bajaj 17 L Solo Microwave Oven). The duration of microwave irradiation was kept for 2 mins. The products were kept at room temperature subsequently pulverized. Passed through mesh 60 sieve. Drug polymer proportions were shown in following table 4.

Prepared formulations of SD were characterized for drug content, % yield, solubility, and Fourier Transform Infrared (FTIR) studies. Characterization was done with the motive to select the suitable method for SD preparation.

Table 4: Drug polymer proportions (microwave)

Formulation code	API:PEG	API:PVPK30
PIO	-	-
M1	1:0.5	-
M2	1:1	-
M3	1:1.5	-
M4	-	1:0.5
M5	-	1:1
M6	-	1:1.5

Characterization of SDS

Percentage yield

Yield was determined by considering theoretical and practical weights. It was calculated with respect to SD dry product. %yield was calculated based on practical yield (P.Y) acquired and calculated theoretical yield (T.Y). Formula used was,

$$\% \, yield = \frac{PY \times 100}{TY}$$

Drug content

Weight of SD equivalent to 15mg of API was taken and solubilizes in volumetric flask (100ml) in 0.2M HCl. Absorbance was measured at 270nm in triplicate.

Solubility of Solid Dispersions

Surplus of pure API and prepared solid dispersions were added to tightly sealed bottles containing distilled water. Bottles were shaken mechanically at 26°C for 24h using orbital shaker at 95 RPM for 24h. All dispersions were allowed to settle for ½ hr and supernatant from each system was assayed for API content at 270nm spectrophotometrically.

FTIR Spectroscopy

FTIR spectra were recorded by potassium bromide (KBr) disc method. Shimazdu model FTIR 700 spectrophotometer was used. The scanning range was between 400and4000/cm and resolution was 4/cm.

Differential Scanning Calorimetry

DSC analysis was performed using Perkin-Elmer 7 calorimeter on 4 to 8 mg sample. Pure API, selected formulations were analysed. Samples were heated in an open aluminum pan (rate of heating was 10°C/min). Temperature was gradually raised from 0 to 250°C under nitrogen flow of 40 ml/min as a purging gas.

***In vitro* drug dissolution**

In vitro dissolution for selected SDs (equivalentwt15mgofAPI) was carried out. Dissolution test apparatus used was Paddle USP type 2. The dissolution medium was distilled water (900ml) which was previously maintained at 37°C. Rotational speed maintained was75rpm. Samples were withdrawn at an interval of 15 min, filtered through filter paper (0.22µm) and were analyzed spectrophotometrically at270nm.

Similarly, the 15 mg of API was subjected for in-vitro drug release study and the release profile was compared with selected formulations.

Mathematical analysis of *In vitro* dissolution study

The data gained from in-vitro release study was analyzed by curve fitting to several models like Zero order, 1st order kinetics, Higuchi and Korsmeyer-Peppas model etc. using PCP dissolution v2. 08 software. Dissolution efficacy (DE) is area under dissolution curve up to a certain time 't' which is expressed as percentage of area of the rectangle described by hundred % dissolution in same time.

Mean dissolution time was calculated by using the equation

$$MDT=(n/n+1).\ k-1/\ n$$

Where, n= release exponent and k = release rate constant.

Dissolution data of pure API, and selected formulations and Marketed formulation (MF) were further statistically analyzed by one way ANOVA technique where $P \leq 0.05$ considered significant.

RESULT AND DISCUSSIONS

Absorption maxima

An absorption maximum was found to be 238nm when scanned between 200 to 400 nm.

Standard curve of API

Standard calibration curve of API at 238nm was plotted as concentration versus absorbance. Beer-Lamberts law was followed through standard curve for API in phosphate buffer 7.4.

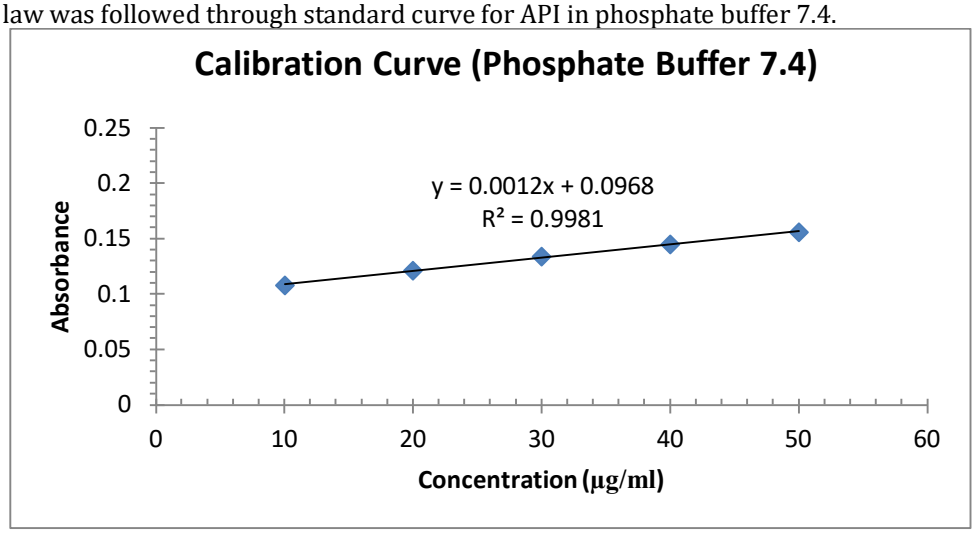

Fig. 3: Standard calibration curve of Pioglitazone in phosphate buffer 7.4

Table 5: Absorbance of Pioglitazone in phosphate buffer 7.4

Concentration (µg/ml)	Absorbance
10	0.108
20	0.121
30	0.134
40	0.145
50	0.156

Solubility investigations of Pure API:

Solubility of pure API in water, pH1.2 and pH 7.4 was found to be 0.014±0.003mg/ml, 0.021±0.002mg/ml and 0.019±0.001mg/ml, respectively.

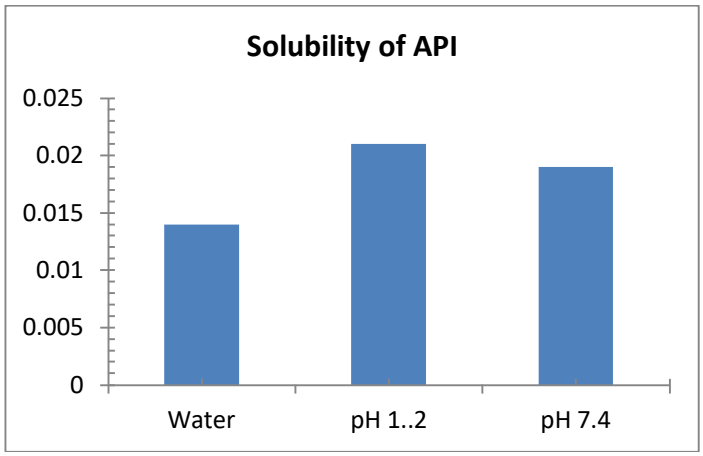

Fig. 4: Solubility of Pioglitazone in water, pH1.2 and pH7.4

Screening:

Following Figure demonstrate that PEG 6K, PVP K30, PEG 20K, ploxamer 188, PEG 4K were used to prepare SD of API. All the polymers successfully enhances the solubility of API however, PVP 30 K and Poloxamer 188 enhances significantly the solubility of pure API. This may be owing to the hydrophilic environment provided by the polymers. The solid dispersions of prepared using Poloxamer 188 and PVP K30 were selected as carrier for preparation of solid dispersions of API, Pioglitazone for the further investigations.

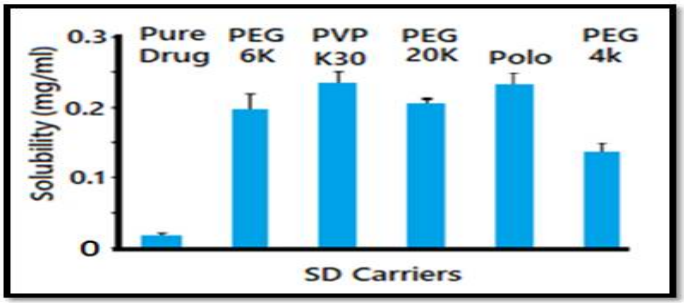

Fig. 5: Screening of polymer for the SDs

Preparation and Evaluation of Solid Dispersions:

Solid dispersions were successfully made by 3differenttechniques, which were kneading, hot-melt and microwave. Polymers, Poloxamer 188 andPVPK30 were used based on the study carried out during screening step of present investigation. Procedural steps followed for each technique were explained in the experimental. The SDs acquired by kneading were found to be free flowing when evaluated by the performing angle of repose for each set of powder obtained by 3 different techniques. SDs formed by hot-melt and microwave technique were observed to be sticky.

% yield and % drug content of SDs were depicted in following Table. The highest % yield (88.17±0.003% to 93.28±0.004%) and drug content (>98%) were observed in case of kneading technique. Drug content was found to be decreased significantly in hot melt technique and may be because of utilization of heat for the processing of said technique. However, microwave technique also gave significant results following to kneading technique and may be because of electromagnetic radiation utilized in the microwave oven. Electromagnetic radiations could cause less degradation of the API compared to the direct heating method. The data of preliminary evaluations like % yields, %drug content and solubility were shown in following table.

Table 6: Preparation and preliminary evaluation of SD by kneading

Formulation code	API: Poloxamer 188	API:PVPK30	%Yield	%API content	Solubility(mg/ml)
PIO	-	-	-	-	0.014±0.003
K1	1:0.5	-	90.56±0.008	93.56±0.001	0.321±0.035
K2	1:1	-	88.23±0.004	92.16±0.021	0.334±0.001
K3	**1:1.5**	**-**	**92.81±0.003**	**96.18±0.006**	**0.414±0.002**
K4	-	1:0.5	94.21±0.008	96.15±0.005	0.378±0.003
K5	-	1:1	88.17±0.003	95.10±0.005	0.361±0.000
K6	-	1:1.5	93.28±0.004	96.21±0.003	0.350±0.003

Table 7: Preparation and preliminary evaluation of SD by hotmelt

Formulation code	API: Poloxamer 188	Drug:PVPK30	%Yield	%API content	Solubility(mg/ml)
PIO	-	-	-	-	0.014±0.003
H1	1:0.5	-	77.92±0.003	84.95±0.001	0.283±0.002
H2	1:1	-	73.08±0.003	69.78±0.002	0.238±0.008
H3	1:1.5	-	82.10±0.004	40.76±0.002	0.319±0.001
H4	-	1:0.5	85.03±0.002	77.97±0.003	0.229±0.005
H5	-	1:1	85.91±0.003	72.86±0.003	0.210±0.002
H6	-	1:1.5	80.89±0.004	52.14±0.004	0.281±0.001

Table 8: Preparation and preliminary evaluation of SD using microwave

Formulation code	API: Poloxamer 188	API:PVP K30	%Yield	%API content	Solubility(mg/ml)
PIO	-	-	-	-	0.014±0.004
M1	1:0.5	-	88.87±0.004	92.09±0.004	0.321±0.003
M2	1:1	-	90.43±0.004	93.36±0.003	0.381±0.001
M3	**1:1.5**	**-**	**88.80±0.003**	**93.89±0.004**	**0.389±0.002**
M4	-	1:0.5	81.69±0.003	92.91±0.002	0.361±0.003
M5	-	1:1	80.19±0.002	93.03±0.003	0.358±0.004
M6	-	1:1.5	79.71±0.003	91.29±0.004	0.388±0.003

FTIR studies

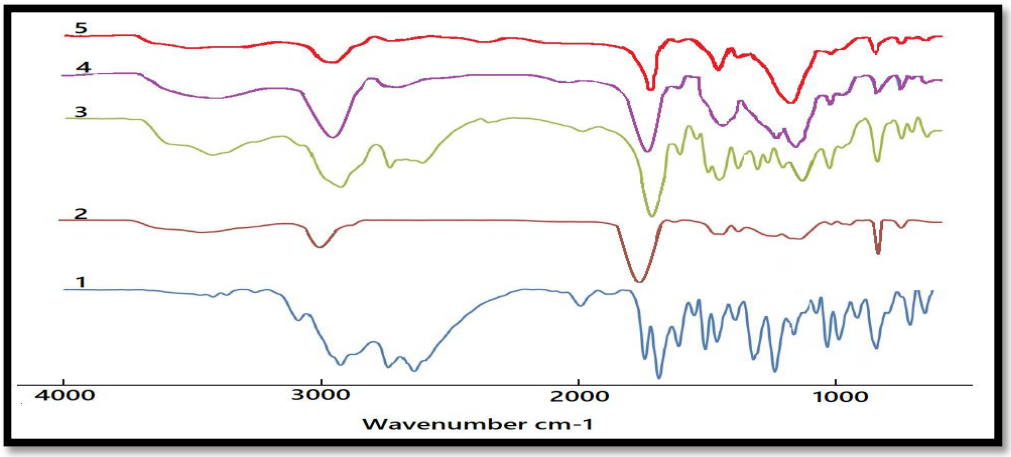

Fig. 6: FTIR: 1: Pioglitazone, 2: Poloxamer 188, 3: SD with PVP 30 K (Formulation K3), 4: SD with Poloxamer 188 (Formulation M3), 5: PM

Drug–polymer possible interactions in physical mixtures prepared for the SDs were investigated by FTIR analysis. Above figure depicts the FTIR spectra of API, their corresponding physical mixtures. FTIR designated as 1, 2, 3, 4, and 5 were of Pioglitazone, Poloxamer 188, SD with PVP 30 K (Formulation K3), SD with Poloxamer 188(Formulation M3) and PM respectively. FTIR spectrum of API with the molecular formula of C19H20N2O3S was characterized by 2933 (C–H asymmetric stretching, aliphatic), 3108 (C–H stretching, aromatic), 3281 (amide N–H stretching), 1698 (amide C=O stretching), 1322 (ring C–N stretching), 1245 (C–S stretching), 1471and 1618 (C=C), 1753 (C=N), 1039 (aliphatic C–O– C), and 852 cm–1 (para-substituted aromatic ring). All the PMs of API–polymer didn't show any additional peak during the physical mixture interaction study, verifying absence of any chemical reaction between the API and polymers. However, the intensity of the spectrum was observed to be minimized, suggesting the dilution effect of the polymer. Dilution with polymer may also cause physical entrapment of the API within the polymer matrix. Solubility study for the formulation K3 and M3 was found to be 0.414±0.002 and 0.389±0.002 respectively and hence both formulations were considered for the FTIR studies.

Differential Scanning Calorimetry

Thermal curve of API and SDs (Formulation K3 and M3)along with PM were shown in following Figure. The thermal curve of API showed an initial flat followed by sharp endothermic peak, with a T peak at 200.12°C indicating state of anhydrous crystalline (abbreviated as API in figure).The thermal curve of PM was practically the sum of those of pure components, showing endothermic effect due to polymer dehydration followed by sharp end other mic peak at 200°C corresponding to melting point of the drug (abbreviated as PM) in figure. There was a disappearance of the peak in solid dispersion of formulation

K3 and M3 indicating the change in crystalline nature of API in solid dispersion. Further investigation was done on DSC of Poloxamer 188 and PVP K30 which was typical of amorphous substance, showing a huge dehydration peak inthe50° to 100°C. Solitary peak for both polymers was shown in following figure.

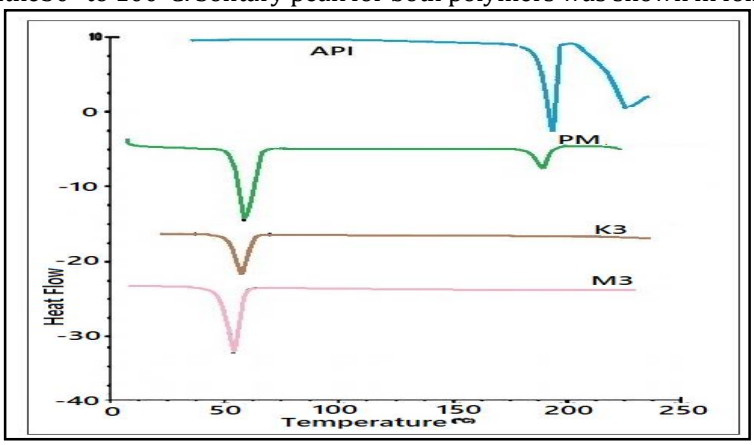

Fig. 7: DSC of API, PM, formulation K3 and M3

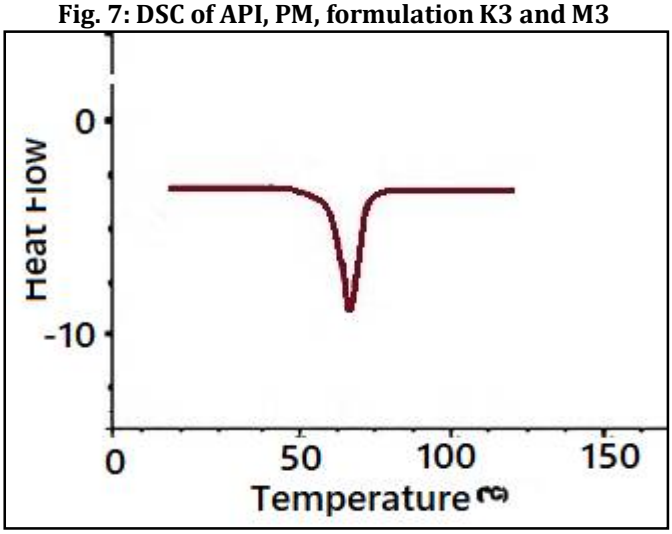

Fig.8: DSC of polymers

Mathematical Analysis of *In vitro* dissolution study

The release data of pure drug (PIO), PM, and selected SDs (K3 and M3)were examined according to the Zero-order, 1st-order, and Higuchi's, Hixson Crowell, and Korsmeyer-Peppasusing PCP Dissov 2.08 software. It was observed that the HixsonCrowell was best suitable mathematical model for describing experimental data for solid dispersions. Data obtained for mathematical expressions are shown in following table 9.

Table 9: Mathematical Analysis of *In vitro* dissolution study

Mathematical model		Pure API	Physical mixture	K3	M3
Zero-order	R_1	0.9971	0.9761	0.8632	0.8800
1st-order	R_2	0.9941	0.9930	0.9561	0.9888
Higuchi-matrix model	R_3	0.9381	0.9682	0.9653	0.9709
Korsmeyer-peppas	R_4	0.9972	0.9591	0.9551	0.9505
Hixsoncrowell Bestfit	R_5	0.9962 Zero order	0.9889 1st-order	0.9682 Hixson Crowell	0.9901 Hixson Crowell
Korsmeyer-Peppas	N	1.2611	1.3178	0.5173	0.5969
	K	0.0432	0.0639	8.2536	5.6152
%DE	15min	0.66	0.70	13.92	11.11
	30min	1.35	2.02	27.58	23.02
	180min	13.92	27.21	80.38	76.19
MDT	180min	94.45	76.21	37.01	42.41

CONCLUSION

Solubility study was conducted successfully in acid and alkaline medium. Major focus was given to prepare solid dispersions of Pioglitazone to enhance the solubility and bioavailability. Various polymers were screened during the study. Out of all polymers, PVP K30 and poloxamer 188 were found to enhance the solubility significantly. Selected polymers were processed successfully to prepare SDs by three different methods. Kneading followed by microwave technique was found to be effective. Calibration curve was plotted using phosphate buffer. Phosphate buffer was considered with the forthcoming view to prepare sustained release microparticles of Pioglitazone to release the drug at alkaline pH. Evaluation of prepared SDs were done by SEM, FTIR etc. FTIR showed that there was not any significant interaction between the drug and polymer used for the SD preparation. SEM was also performed successfully which revealed that the crystalline form of pure API was partially converted in to amorphous form. This could be the probable reason for the betterment of solubility when API is converted in to SD.

The dissolution study performed showed that dissolution rate of API enhanced to greater extent by solid dispersion technique using kneading method and microwave technique. The kneading technique for preparation of SDs was much simpler and also feasible industrially. PVP K30 showed most important result indicating usage as a carrier for solid dispersion. Significant outcomes like drug content and solubility were obtained for SDs having the drug: poloxamer188 ratio of 1:1.5 and hence the same SDs has been considered for the further investigations.

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