Evolution of non-covalent derivatives of pioglitazone with salicylic acid and its impact on crystallite characteristics and dissolution

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The bioavailability of a molecule is considerably influenced by its crystalline nature and behaviour, depending on various factors such as internal structure within its crystal lattice. This study aims to develop pioglitazone (PIO) eutectics with co-former salicylic acid (SA). And its effect on crystallite properties as well as drug dissolution has been studied. Pioglitazone-salicylic acid eutectic formulations *i.e.*, PS1, PS2, and PS3 using different molar ratios of 1:1, 2:1, and 1:2 respectively was prepared using the ethanolic solvent evaporation method. Differential scanning colorimetry study showed a broad peak at 117.696°C, which is lower than the melting peaks of PIO (195.61°C) as well as SA (158.69°C) confirming the formation of eutectic. Carbonyl-thiazolidine non-covalent bond or pi-pi attraction might have been involved for the formation of eutectics of PIO-SA having the docking score of -2.5 Kcal/M rather than co-crystals. Having a maximum value of strain (12.69 ± 8.04) in PS2 possibly due to higher deformity within the molecular layer when compared to other formulations and raw PIO. Further, the crystallite size of PS2 (18.57 ± 9.91 nm) was found to be smaller than the others (32.19 to 70.77 nm). All eutectic formulations presented improvement in drug dissolution. PS2 (PIO-SA as 2:1 molar ratio) resulted in drug release more quickly (86.90%) than pure PIO (44.50%) and other formulations (62.76 to 72.15%) at 5 h. Consequently, creating eutectic formulations may be a useful tactic for enhancing PIO solubility.

Keywords: Co-former; Salicylic acid; Pioglitazone; non-covalent derivative; crystal strain; in vitro dissolution.

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1. Introduction

Crystal engineering of multiple systems like hydrates, solvates, polymorphs, solid solutions, cocrystals, eutectics, etc. permits enhancement in therapeutic attributes with no compromise on other physicochemical features. Cocrystal and eutectic mixtures, co-amorphous and salt crystal formation play an important role in enhancing dissolution and consequently absorption of drugs having limited solubility [1-3]. Heteromolecular interaction via bonding between two different compounds can dominate over the bonding within individual compounds, leading to the formation of cocrystals. Conversely, when the bonding within individual components (homo-molecular) is stronger than the interaction between different compounds (hetero-molecular), then it results in the formation of a eutectic mixture [4]. Non-covalent interactions like hydrogen bonding, electrostatic interaction, van der Waals force, halogen bonding, pi-pi interaction as well as pi-sigma interaction between drug compound and the corresponding co-former suggest the structure of cocrystal or eutectic product. Supramolecular synthons (fundamental structural units) are generally considered into two different types *i.e.*, similar functional group (homosynthons) and complementary functional group (heterosynthons) [5]. Formation of eutectic leads to the depression in melting point and the eutectic products are not soluble in the solid state but miscible after turned into liquid [6]. The oral route is known as a non-invasive, easy-to-administer, patient-convenient, painless route to administer any drug. Among all the oral dosage forms, solid dosage forms have more advantages over others due to their chemical and physical stability, less costly, safe, and simple methods of preparation [7]. Pioglitazone (PIO), an oral medication of the thiazolidinedione class, diminishes insulin resistance in individuals with type 2 diabetes [8]. Due to its non-polar nature, water struggles to effectively break down the molecular lattice of PIO. As a result, its ability to dissolve in water is significantly restricted. Insufficient solubility in water and slow dissolution rates of PIO can lead to lower-than-needed levels of the drug in the bloodstream, possibly resulting in ineffective treatment. Salicylic acid (SA) is mono hydroxybenzoic acid having aqueous solubility of 2.24 g/L at 25°C which is higher than the solubility of PIO *i.e.*, 0.02 g/L. SA is considered as Generally Regarded as Safe excipient (GRAS) and the presence of -COOH group makes it a decent co-former for the preparation of eutectic with PIO [9,10]. Here, attempts were made to create PIO eutectics by combining it with salicylic acid in different molar ratios using a straightforward solvent evaporation method. However, the formation of co-crystal was hindered due to the absence of a complementary functional group. Combining PIO with salicylic acid is likely to create a eutectic instead of a co-crystal, characterized by the formation of pi-pi interaction between the PIO molecule and pi-cloud of the benzene ring present in SA. There is another possibility to form a weak thiazolidine-carbonyl bond formation between PIO (having a thiazolidinedione ring) and SA (having a benzene ring). The

impact on distortion of crystallite and deformity due to the induced strain has been examined. These eutectic products are expected to display also an improved dissolution profile as compared to the pure drug.

2. Materials and method

2.1. Materials

PIO was received as a gift sample from Pattanaik Science Supply Syndicate, Bhubaneswar, Odisha, India. Salicylic acid was procured from Merck Specialties Pvt. Ltd., India. Ethanol was procured from Himedia Laboratories Pvt. Ltd., India. All other chemicals and reagents were of analytical grade and commercially available.

2.2. Preparation of Pioglitazone eutectic formulation

PIO eutectic formulations were made using the solvent evaporation process with varying molar ratios of salicylic acid used as a co-former. The solution was dried at 40-50°C for 72 hours after precisely weighed amounts of PIO and SA were combined and dissolved in ethanol. As the solution's solvent evaporated, eutectics were produced (Table I). Figure 2 displays the chemical structure of PIO in a range of potential ratios combined with SA.

2.3. Characterizations

2.3.1. Fourier transform-infrared spectroscopy

IR grade potassium bromide (KBr) was separately mixed with the samples in a 100:1 ratio to create matching pellets, which were then compressed for two minutes using a hydraulic press to apply five tonnes of pressure. With the Fourier transform-infrared (FTIR) spectrophotometer, the pellets were scanned using Spectra Manager software version 2.0 (JASCO FT/IR-4100) within the 400-4000 cm^{-1} frequency range.

2.3.2. Differential scanning calorimetry

To get the thermograms of the samples, the Differential Scanning Calorimetry (DSC) (DSC-1, Mettler Toledo) technique was employed. In a hermetically sealed aluminium pan containing 3-4 mg of test materials, an empty aluminium pan served as a reference. The nitrogen flow rate applied to the samples was 20 ml/min, and the scanning was done at a rate of 10°C/min. All of the samples' temperatures were kept between 30 and 300°C.

TABLE I. Non-covalent derivative of pioglitazone with salicylic acid as co-former by ethanolic solution evaporation technique.

Formulation code	Molar Ratio	PIO (mg)	SA (mg)	Solvent-system
PS1	1:1	1000	387	Ethanol
PS2	1:2	1000	193	Ethanol
PS3	1:3	1000	774	Ethanol

2.3.3. Powder X-ray diffraction

Powder X-ray diffraction (PXRD) was used on a variety of samples to examine their chemical makeup, crystal structure, and physical attributes. A glass slide containing approximately 1 mg of dry powdered sample was treated with a powder X-ray diffractometer (Ultima, IV, Japan). During the experiment, a detection angle of 2-75° 2θ was used with an X-ray power of 40 kV/40 mA for 120 seconds.

2.3.4. Scanning electron microscopy

Using a scanning electron microscope (SEM), the surface morphologies of various samples were noted (Gemini SEM 300). The dehydrated specimens underwent room temperature scanning after being sputtered and coated in gold-palladium.

2.4. In-vitro drug dissolution study

The US Pharmacopoeia XXIII rotating paddle method was followed in the in-vitro dissolving investigation for both pure drug (PIO) and various PIO-SA eutectic formulations. The dissolution apparatus used for the study was Electrolab, India. 50 rpm rotation speed was selected, and 900 ml of 0.5 percent sodium lauryl sulfate (SLS) solution was added to the dissolution vessel along with a predetermined amount of the formulation. Throughout, the temperature was maintained at 37±0.5°C. To keep the sink condition, aliquots of 10 ml of material were taken out of the dissolving media at predetermined intervals and replaced with fresh medium of the same volume. For the measurement of materials in triplicate, the Lamda max of the UV-visible spectrophotometer (Shimadzu) was set at 223 nm.

2.5. In silico binding interaction study

The AutoDock Vina 1.1.2 software has been used to forecast the drug and excipient molecule interaction. Salicylic acid was produced using Marvin Sketch's 3-D representations of the PIO structures. MGL Tools was used to create PDBQT files for additional research because AutoDock Vina can only recognize PDBQT files. The three-dimensional centers and axes were all aligned correctly by enlarging the grid box. Following the successful creation of PDBQT files, the command prompt was used to do the docking. As a ligand against the salicylic acid receptor, PIO was taken. The highest negative score validated the finest binding.

2.6. Statistical analysis

All the measured data are presented as mean ± S.D. (standard deviation).

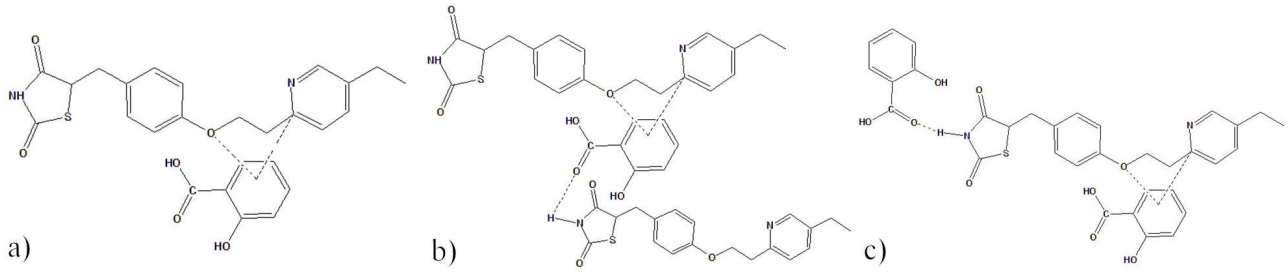

FIGURE 1. Proposed eutectic formation of PIO-SA in various possibilities of a) PS1; b) PS2; c) PS3.

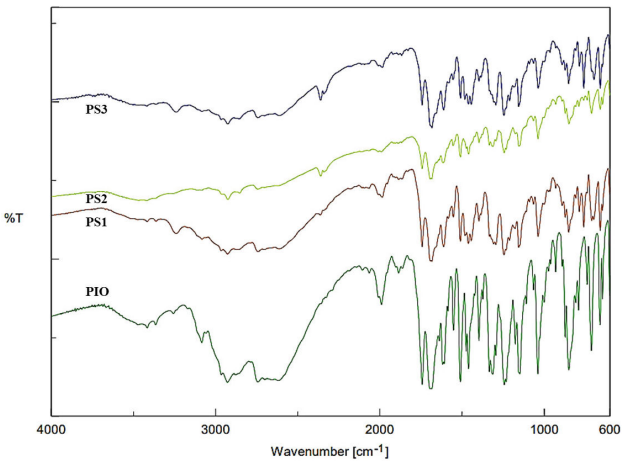

FIGURE 2. FTIR of PIO and PIO-SA eutectic formulations with different ratios for the determination of functional groups.

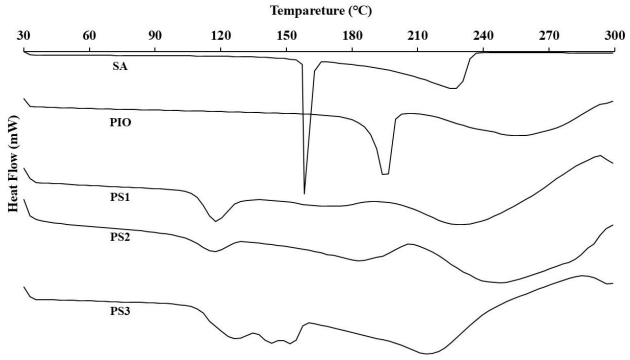

FIGURE 3. DSC thermogram of PIO, raw SA, and PIO-SA eutectic formulation (PS1, PS2, and PS3) to determine the melting endotherm.

3. Result and discussion

3.1. Pioglitazone eutectic products

In this current study, PIO-SA eutectic formulations were produced by using the ethanolic solution evaporation method. The possible structures of PIO-SA eutectics in different ratios are represented in Fig. 1.

3.2. Fourier transform infra-red

The spectrum of FTIR of pure PIO is represented in Fig. 2 Pure PIO exhibited characteristic peaks at 3365.17 cm^{-1} because of N-H stretching. Other peaks were observed at 2965.98 cm^{-1} (asymmetric aliphatic stretching), 1742.37 cm^{-1} (C-H stretching), 1684.52 cm^{-1} (C=O stretching), 1618.95 cm^{-1} (aromatic stretching), 1460.81 cm^{-1} (C-N stretching of the ring), 1242.9 cm^{-1} is because of C-S stretching, 1038.48 cm^{-1} is due to C-H bending. These peaks are confirmed by previously reported studies [11,12]. Spectrum at 1684.52 cm^{-1} and 1460.81 cm^{-1}, in the prepared PIO-SA eutectic formations (PS1,PS2,PS3), are broadened a bit. The C-N stretching at 1460.81 cm^{-1} was divided into three different peaks around 1444.42-1482.99 cm^{-1} in prepared eutectic formations maybe because of the weak attraction (pi- pi interaction) formed between SA's pi-cloud and PIO. Some peaks are merged together maybe due to the formation of weak hydrogen bonding between the drug and co-former SA.

3.3. Differential scanning colorimetry

The presence of a single endothermic curve in the DSC data suggests that the melting point of the resultant system, indicated in the obtained DSC profile, lies either below, between, or above the melting points of the initial components, thereby characterizing it as a cocrystal. Likewise, in the DSC curve of a eutectic mixture, a lower melting depression is observed compared to the individual components involved [13]. Figure 3 displays the DSC thermograms of both raw PIO, pure SA, and its eutectic formations (PS1,PS2,PS3). In the DSC thermogram of PIO, a solitary endotherm at 195.61°C was observed, corresponding to the melting point of PIO [14]. The melting point of co-former salicylic acid was observed at 158.69°C confirmed from the previous literature [15] having an inset melting temperature of 157.84°C and an offset melting temperature of 161.98°C. Eutectic formation (PS2) showed a broad peak at 117.696°C which is lower than the melting temperature of raw PIO as well as SA which is maybe because of the formation of eutectic preparation of PIO in the presence of SA. Other eutectic formations PS1 and PS3 showed melting thermograms at 117.698°C and 125.03°C respectively. The lowest point we get from the thermogram of eutectic formation is 117.696°C which indicates the eutectic temperature.

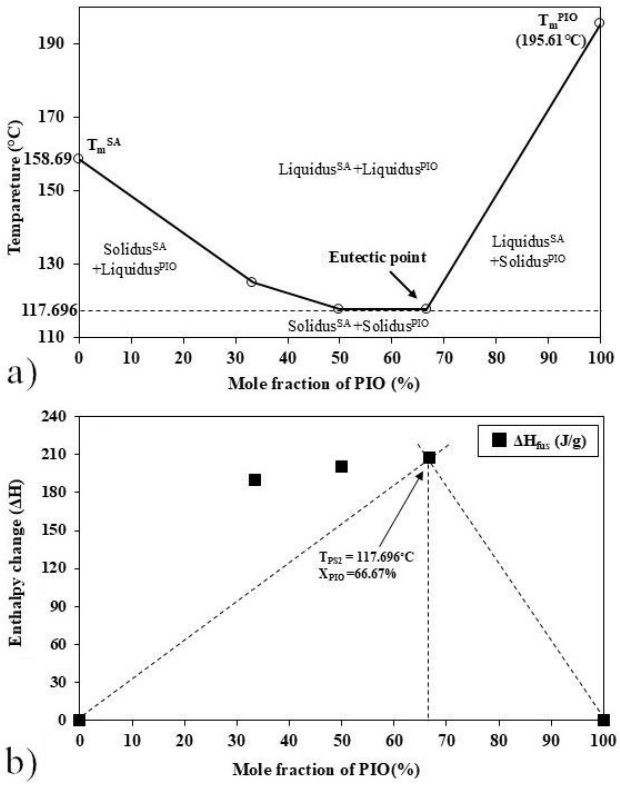

FIGURE 4. a) Binary phase diagram. b) Tammann's triangle graph of prepared eutectic formulation with PIO and SA.

Binary phase diagram [16] of pioglitazone and salicylic acid is used to demonstrate the formation of eutectic and is represented in Fig. 4. T_mPIO represents the melting point of pioglitazone, and T_mSA represents the melting temperature of salicylic acid. The eutectic point is considered at 117.696 which is lower than the melting point of the other two components. Tammann's triangle graph [17,18] was used to further establish the molecular interaction for clarifying precisely the eutectic point [Fig. 4b)]. Tammann's graph revealed the largest ΔHfus value displayed by the mole fraction of PIO at 66.67% which is equivalent to the formulation PS2. This confirms the formation of eutectic of PIO with SA.

3.4. X-Ray diffraction

If the functional groups enable the efficient creation of non-covalent bonds and the size and shape of the original molecule support crystal packing, a co-crystal will result.

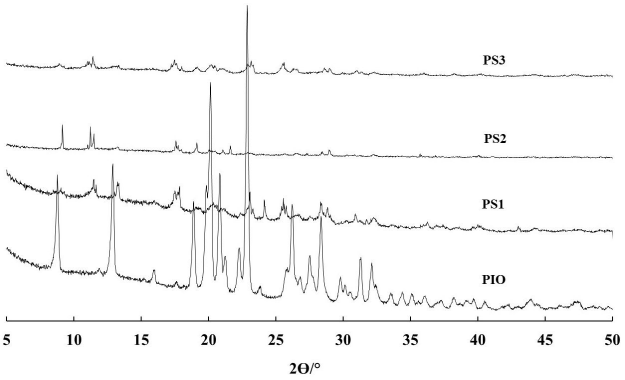

FIGURE 5. XRD pattern of PIO and PIO-SA eutectic formulation to check the crystallinity of raw PIO as well as prepared formulations.

Conversely, if the functional groups are suitable for non-covalent bonding but do not support crystal packing, a eutectic will be produced. The PXRD pattern of pure PIO and prepared eutectic formulations with salicylic acid are demonstrated in Fig. 5. As understood by PXRD analysis, the relative intensity of PIO is much more than PS1, PS2, and PS3. All the diffraction peaks of PS1, PS2, and PS3 are clearly identified with less intensity compared to the pure PIO. Therefore, we may say PS1, PS2, and PS3 are not highly crystalline and seem to have a certain amorphous contribution. From previously reported article by M. A. Elbagerma *et al.*, salicylic acid exhibits characteristic peaks at 2θ values of 11.00 and 17.1. these peaks are observed in prepared eutectic formulations (PS1, PS2, PS3) [19].

Rietveld refinement profile of XRD data of prepared eutectic preparations (PS1-PS3) is displayed in Fig. 6. The red line represents the calculated data and the black line represents observed data for the Rietveld refinement fit [20,21].

Crystallite size is a crucial parameter to determine for a proper understanding of microstructural characteristics. The Scherrer method relies on the broadening of XRD peaks and is the most commonly used approach for calculating crystallite particle size. For the determination of the crystallite size D of the prepared crystal, Scherrer's equation is stated as:

$$D = \frac{k\lambda}{\beta \cos\theta},$$

where D is the crystalline size in nm; k is the shape factor which is taken as 0.9; λ is the wavelength of the X-rays *i.e.*,

TABLE II. Parameters obtained from PXRD of different PIO-salicylic acid eutectic formulations.

Formulation code	Crystallite size (mean ± SD; $n = 3$) (nm)	FWHM	Strain $\times 10^3$	Dislocation density $\times 10^5$	T_{300}
PIO	40.65 ± 10.31	0.209 ± 0.051	4.36 ± 1.04	6.95 ± 3.32	44.50 ± 2.47
PS1	32.19 ± 3.55	0.252 ± 0.026	8.20 ± 0.86	9.92 ± 2.18	72.15 ± 0.33
PS2	18.57 ± 9.91	0.515 ± 0.191	12.69 ± 8.04	45.23 ± 29.53	86.90 ± 1.03
PS3	70.77 ± 10.31	0.115 ± 0.012	2.02 ± 0.22	2.05 ± 0.50	62.76 ± 4.01

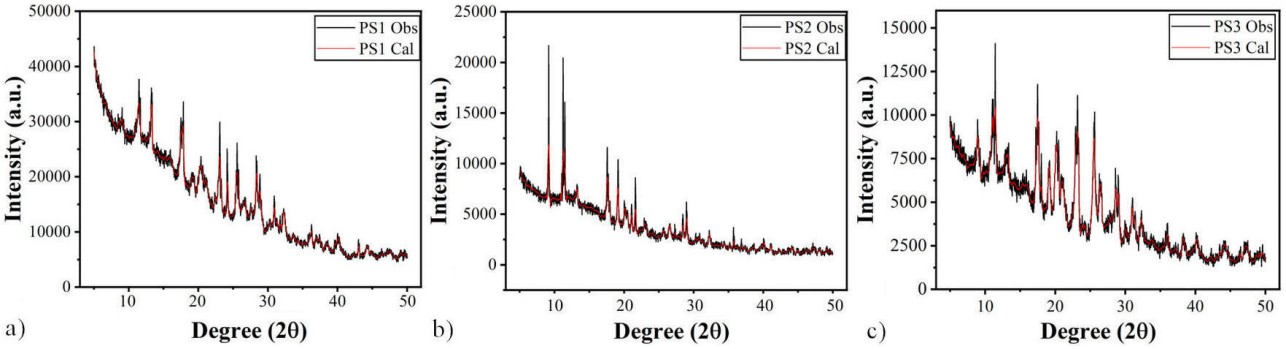

FIGURE 6. Reitvelt analysis of prepared eutectic formulation (PS1-PS3).

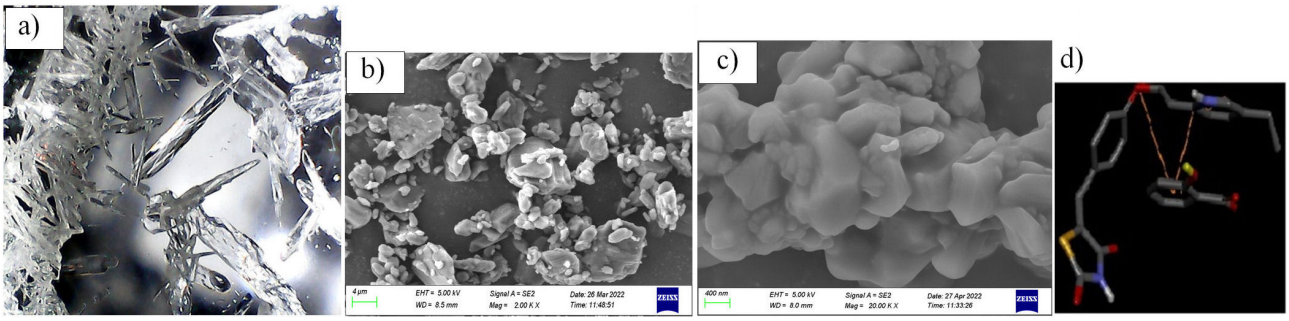

FIGURE 7. a) Pictograph of PIO-SA eutectic formulation (PS2), b) SEM of raw PIO; c) SEM of eutectic PS2. d) Pictographic display of PIO-SA In-silico binding interactions.

0.154056 nm for CuKα 1 radiation; β is the broadening of the peaks and that is also known as peak width at half maxima (FWHM) measured in radians and finally theta is the Bragg's angle of diffraction. Crystal distortion and deformity occurred due to the induced strain and the strain was calculated by using the equation [22]:

$$\epsilon = \frac{\beta}{4\tan\theta}.$$

The dislocation density denoted as delta describes the extent of dislocation or defects in a crystal sample that is defined as length of dislocation lines per unit volume of any crystal can be calculated as:

$$\delta = \frac{1}{D2}.$$

PS2's particle size was determined to be the smallest one when compared to raw PIO and other eutectic formulations. Possibly due to the weak bond formation between PIO and SA, there is a difference in strain value as well as dislocation density between PIO and PIO-SA eutectic. Perhaps as a result of more molecular deformation activity within a material, eutectic PS2 displayed the greatest strain value. From the result, it can be considered that PS2 is produced as a robust eutectic formulation.

3.5. Pictograph and scanning electron microscopy

The prepared eutectics of PIO with salicylic acid were observed as sharp needle-shaped shown in Fig. 7a). Figure 7b) shows SEM image of raw PIO and Fig. 7c) the PIO-SA eutectic formulation (PS2). The micrograph of pure PIO displays its characteristic crystal morphology, whereas the eutectic product exhibits a slightly altered geometry. The eutectic product features a lamellar structure of microstructure with alternating fine layers, indicating partial deformation of the PIO crystal, the formation of the eutectic with salicylic acid as an organic co-former is also confirmed by DSC as well as PXRD analysis.

3.6. In-vitro dissolution study

It is widely recognized that the dissolution procedure often limits the rate at which the drug is absorbed from the gastrointestinal tract from solid dosage forms. Aqueous solubility is a crucial factor that affects both in-vitro as well as in-vivo biopharmaceutical performance. The presence of food interferes with absorption, causing a delay in reaching peak plasma concentration, which is sometimes extended to 5 to 6 hours. Previous studies showed various formulations of PIO such as self-micro emulsifying drug delivery system (SMEDDS) [23], multilayered tablets [24], floating tablets [25], transdermal patches [26], and nano-suspensions [27], come across numerous limitations such as stability (physical or chemical). Inclusion complexes with cyclodextrin [28], using the natural polymer Pullulan [29], application of poloxamer 188 and 407 [30] to enhance the dissolution of PIO and these studies demonstrated an increase in solubility as well as dissolution rate when compared to pure PIO.

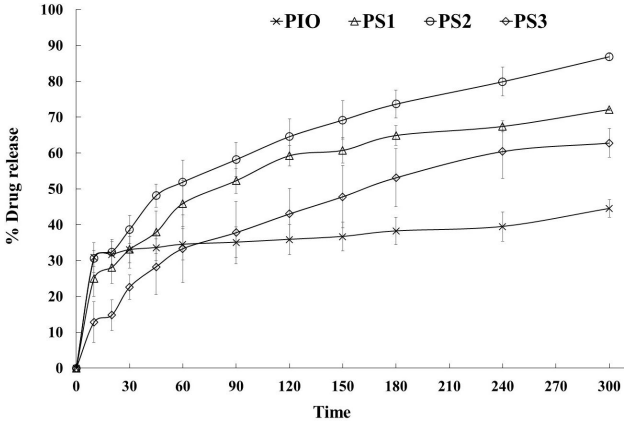

FIGURE 8. In vitro dissolution profile of raw PIO and PIO-SA eutectic formulations: percent drug release was determined by plotting percent drug release against time (min).

One of the vital physicochemical parameters frequently used to evaluate the dissolution profile of any chemical compound is in-vitro drug dissolution. An overall improvement of in-vitro drug dissolution was observed of the eutectic formulation with salicylic acid (86.89 ± 1.03 to 62.76 ± 4.01 percent) compared to pure drug (44.50 ± 2.48 percent) at 5 h (Fig. 8). Dissolution profile of PS2 (molar ratio of PIO: SA= 2:1) profile demonstrated the highest value rather than PS1 and PS3 (molar ratio of PIO: SA = 1:1 and 1:2 respectively). The maximum drug release associated with PS2 might be due to the most effective intermolecular interaction at molar ratio of PIO: SA= 2:1 compared to others.

3.7. In-silico docking study

To uncover the information about the interaction type and interaction affinity between the drug and the excipient, an in-silico molecular docking study has been performed [31,32]. Here, PIO was taken as a ligand molecule while SA was taken as a receptor. The highest negative score confirms the finest binding between the drug and the excipient. A stable binding interaction between PIO and organic acid molecule (*i.e.*, SA) was exposed by the molecular docking study. Possible binding interaction is represented in Fig. 6d) revealed by in-silico binding interaction. The docking score observed was -2.5 Kcal/M along with a bond distance of 1.07 Angstrom. The bond types observed were pi-sigma interactions and pi-pi interactions.

4. Conclusion

The pioglitazone-salicylic acid eutectic systems were prepared using a simple evaporation method. The formation of the eutectic system is due to the weak hydrogen bond between the thiazolidine-carbonyl bond as well as pi-pi stacking between the thiazolidine ring of raw PIO and the benzene ring of salicylic acid. DSC analysis exhibited a low melting point of the prepared formulation which is lower than the melting temperature of SA (158.69°C) and raw PIO (195.61°C) confirming the formation of eutectic. The in-vitro drug dissolution was observed highest in the case of PS2 (86.90 ± 1.03 percent at 5 hours) as compared to other ratios as well as raw API. Therefore, as a conclusion we conclude that the preparation of eutectic formulations can be a potential approach for the upgrading of dissolution profile of PIO.

Abbreviation

DSC:	Differential scanning colorimetry;
FTIR:	Fourier Transform Infra-red spectroscopy;
FWHM:	Full Width at Half Maxima;
GRAS:	Generally Regarded as Safe;
PIO:	Pioglitazone;
PXRD:	Powder X-Ray Diffraction;
SA:	Salicylic Acid;
SEM:	Scanning Electron Microscopy;
SLS:	Sodium Lauryl Sulphate;
SMEDDS:	Self-Micro emulsifying Drug Delivery System.

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Authors contribution

S.P.: methodology, investigation. M.D.: writing original draft, formal analysis, data curation. R.D.: software. S.H.: data curation, T.D.: data curation and S.M.: Conceptualization, investigation, supervision, writing-review, and editing.

Disclosure statement

All the authors declare there is no known competing interest to declare.

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