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Scientific paper

Development of Eutectics of Pioglitazone with Citric Acid and its Effect on Crystallite Properties and Dissolution

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Abstract

Eutectics of pioglitazone were developed using citric acid (CA) as the co-former, and the effect on crystallite properties and dissolution has correspondingly been studied. Pioglitazone-citric acid eutectics (PC1, PC2, PC3, and PC4) in different molar ratios (3:1, 3:2, 1:1, and 3:4 respectively) were prepared by simple solvent evaporation method. Difference in dislocation density and strain value of the eutectics were observed, and the maximum strain value of PC1 might be due to the highest deformation activity compared to PC2, PC3, and PC4. Carbonyl-thiazolidine or carboxyl-pyridine weak bond formation might be the reason of producing eutectics of PGZ-CA rather than cocrystal with a docking score of −2.2 kcal/mol. Likewise, lowest particle size was found with PC1 rather than that of pure PGZ and other eutectics. PC1 demonstrated highest dissolution of drug (68%) rather than other eutectics (54 to 61%) and PGZ (44%) after 360 min.

Keywords: Eutectics; pioglitazone; citric acid; *In vitro* dissolution; strain and dislocation density

1. Introduction

Currently, crystal engineering approach focuses on the formation of various systems like hydrate, solvate, polymorphs, solid solution, cocrystal, eutectic, etc. facilitating advancements in improving the pharmaceutical properties without compromising other physicochemical properties.[1,2] Among all these rising systems, cocrystal and eutectic mixtures are playing a pivotal role in efficiently enhancing dissolution and consequently absorption particularly of drugs with limited solubility. Heteromolecular (adhesive) interaction between two compounds can overshadow a homo-molecular (cohesive) interaction of distinct components creating co-crystals whereas, stronger homo-molecular interaction compared to heteromolecular interaction leads to the formation of eutectic mixture.[3,4] Non-covalent interactions such as van der Waals force, electrostatic interaction, halogen bonding, and hydrogen bonding between the drug molecule and the co-former suggest the structure of the cocrystal formation. Supramolecular synthons are the usual name used to describe these fundamental structural units found in supermolecules. Homosynthons (similar functional group) and heterosynthons (complementary but unlike functional group) are the two divided groups of supramolecular synthons.[5] Hydrogen bond formation between the acid group and the amide group or the amine or alcohol is required to create a supramolecular synthon.[6] For instance, when a molecule possesses a carboxylic acid group, one can select a complementary partner molecule, often referred to as a cocrystal former or co-former, containing functionalities like acid, amide, or pyridyl groups, to form a cocrystal. Nevertheless, not every molecule possessing complementary functional groups is suitable for cocrystal formation. In addition to producing a cocrystal, the outcome of co-crystallization may result in a solid solution, a eutectic, or even a basic physical mixture of unreacted compounds. Eutectics have been suggested as transitional states leading to specific cocrystals, and it was observed that solution eutectic constants play a vital role in the formation and stabilization of cocrystals in solution.[3] Eutectics are the formulations having low melting points as a result of combining two or more compounds in a certain molar ratio. It has been noted in many literatures that organic acids like benzoic acid,[7] citric acid (CA), salicylic acid,[8] and malic acid,[9] among others, can produce eutectics. In a eutectic system, the different components are present in specific proportions that lead to a eutectic composition, and when this composition is heated or cooled, it undergoes a

phase transition at a single, well-defined temperature, forming a eutectic mixture. In a standard co-crystallization experiment, the development of multi-component adducts, such as salts, cocrystals, solid solutions, or eutectics, is contingent upon the characteristics of the components involved and the specific interactions that emerge between them.[4] Generally, if a molecule contains a carboxylic acid group it can choose a co-former or a partner containing a complementary functional group like amide, acid, or pyridine to make a co-crystal. However, it is very rare to have a complementary functional group to prepare a cocrystal.

The molecule and the co-former are exploited to make a eutectic or a solid solution when cocrystal formation is hampered.[3] In the case of eutectic formation, adhesive interaction is heteromolecular which is generally weaker because of the lack of lattice arrangement of any long-range order.[10] A study demonstrated that the soluble carrier quickly dissolves, leaving the insoluble drug in an absolutely fine state of subdivision when the eutectic mixture is in contact with digestive fluids.[11] In a study solubility of itraconazole, griseofulvin, danazol, and benzoic acid in urea- and malonic acid-choline chloride deep eutectic solvent has been increased by many folds.[12]

Pioglitazone (PGZ), an ethylpyridin-thiazolidinedione-type oral drug, reduces insulin resistance in "type 2 diabetes mellitus". It exhibits non-polar characteristics, rendering water incapable of efficiently disrupting the lattice structure of the molecules. Consequently, its solubility in aqueous medium is notably limited.[13] Inadequate aqueous solubility and slow dissolution of PGZ contribute to sub-therapeutic plasma levels, potentially lacking in therapeutic success. Eutectics of pioglitazone were attempted to prepare using CA as the co-former in different molar ratios by simple solvent evaporation method as the cocrystal formation is hampered due to lack of complementary functional group. The combination of PGZ-CA could form eutectic rather than cocrystal via weak carbonyl-thiazolidinedione or carboxyl-pyridine bond development and may lack a long-range order arrangement. The eutectic products are supposed to exhibit enhanced drug dissolution.

2. Material and Methods

2. 1. Materials

PGZ was received as a gift sample from Pattanaik Science Supply Syndicate, Bhubaneswar, Odisha, India. Citric 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 PGZ Eutectic Formulation

Eutectic formulations of PGZ were prepared by solvent evaporation method employing CA as a co-former in different molar ratios. Accurately weighed amounts of CA were mixed with precisely weighed amounts of PGZ before being dissolved in ethanol followed by drying the solution at 40–50 °C for 72 h. Eutectics were obtained as the solvent of the solution evaporated (Table 1). The chemical structure of PGZ with CA is presented in Fig. 2 in various possible ratios.

Table 1: Eutectic formulation of PGZ using CA as co-former from ethanolic solution by solvent evaporation technique

Eutectic code	Molar ratio	PGZ (mg)	CA (mg)	Solvent
PC1	3:1	1000	180	Ethanol
PC2	3:2	1000	360	Ethanol
PC3	1:1	1000	537	Ethanol
PC4	3:4	1000	716	Ethanol

2. 2. Characterizations

2. 3. 1. Fourier Transform-infrared (FTIR) Spectroscopy

IR grade potassium bromide (KBr) was mixed with the samples separately in the ratio of 100:1in order to obtain corresponding pellets with the help of applied 5 tons pressure for 2 min using a hydraulic press. The pellets were scanned between the range of 400–4000 cm^{-1} frequency in FTIR spectrophotometer using *Spectra Manager* software version 2.0 (JASCO FT/IR-4100).

2. 3. 2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry technique (DSC-1, Mettler Toledo) was used to obtain the thermograms of samples. 3 to 4 mg of test samples were placed in a hermetically sealed aluminum pan and another empty aluminum pan was used as a reference. Samples were subjected to a nitrogen flow with a flow rate of 20 ml/min and the scanning was carried out at a rate of 10 °C/min. The temperature of all the samples were maintained within the range of 30–300 °C.[14]

2. 3. 3. Powder X-ray Diffraction (PXRD)

PXRD was carried out for different samples to study their crystal structure, chemical composition followed by their physical characteristics. About 1 mg of dry powdered sample was placed on the glass slide and was subjected to powder X-ray diffractometer (Ultima, IV, Japan)[15] Throughout the testing, an X-ray power of 40kV/40mA at a detection angle (2–75° 2θ) was employed for 120 sec.

2. 3. 3. Scanning Electron Microscopy (SEM)

The surface morphologies of different samples were recorded with a scanning electron microscope (Gemini

SEM 300). The dried samples were sputtered coated with gold-palladium and scanned at room temperature.

2. 4. *In vitro* Drug Dissolution Study

The *in vitro* dissolution study for pure drug (PGZ) and different PGZ-CA eutectic formulations were carried out following the guidelines of US pharmacopoeia XXIII rotating paddle method in a dissolution apparatus (Electrolab, India). A specific amount of the formulation was placed in 900 ml sodium lauryl sulphate (SLS) solution (0.5%) in the dissolution vessel and 50 rpm rotation speed was set up. The temperature was set at 37 ± 0.5 °C for the entire period of time. Aliquots of 10 ml sample was withdrawn at pre-determined time interval from dissolution media along with the replenishment of fresh medium of same volume to maintain the sink condition.[16] Lamda max was set at 223 nm in UV-visible spectrophotometer (Shimadzu) for the analysis of samples in a triplicate manner.

2. 5. In silico Binding Interaction Study

Drug and excipient molecule interaction has been forecasted using AutoDock Vina 1.1.2 Software.[17] With the help of Marvin sketch the 3-D structures of PGZ, CA was generated. Since AutoDock Vina only recognizes PDBQT files, the MGL Tools software package was used to build PDBQT files for further enquiry.[18] By resizing the grid box, all of the three-dimensional centers and axes were appropriately aligned. After the successful generation of PDBQT files, the docking was conducted using the command prompt.[19] The PGZ was taken as a ligand against receptor CA. The finest binding was confirmed by the highest negative score.

2. 6. Statistical Analysis

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

3. Results and Discussion

3. 1. PGZ Eutectic Product

In the current research, PGZ-CA eutectic formulations were prepared using the solvent evaporation method (Table 1). After the preparation, sharp needle-shaped crystals were observed (Figure 1). The possible structure

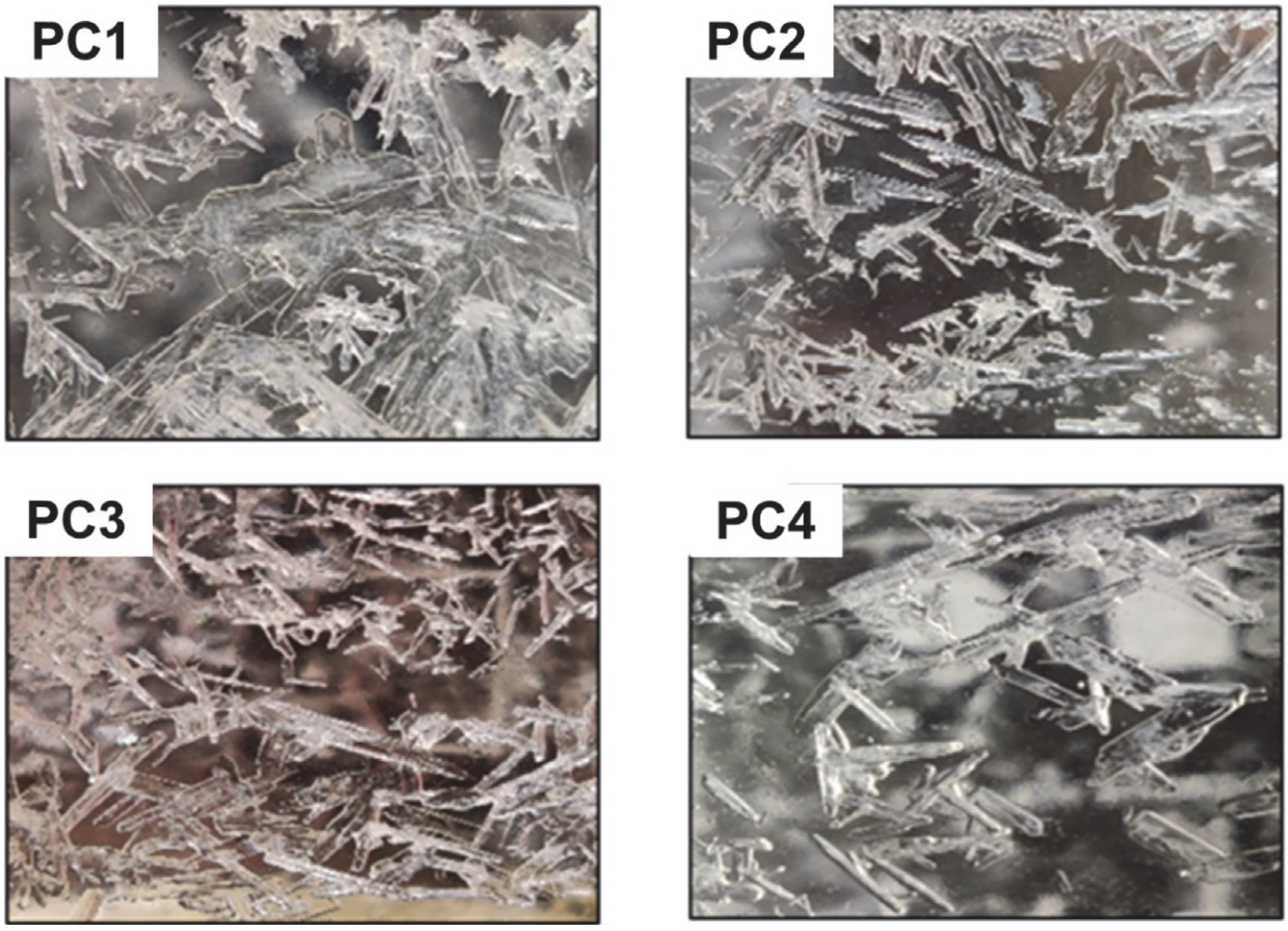

Figure 1. Photographs of prepared PGZ-CA eutectic product

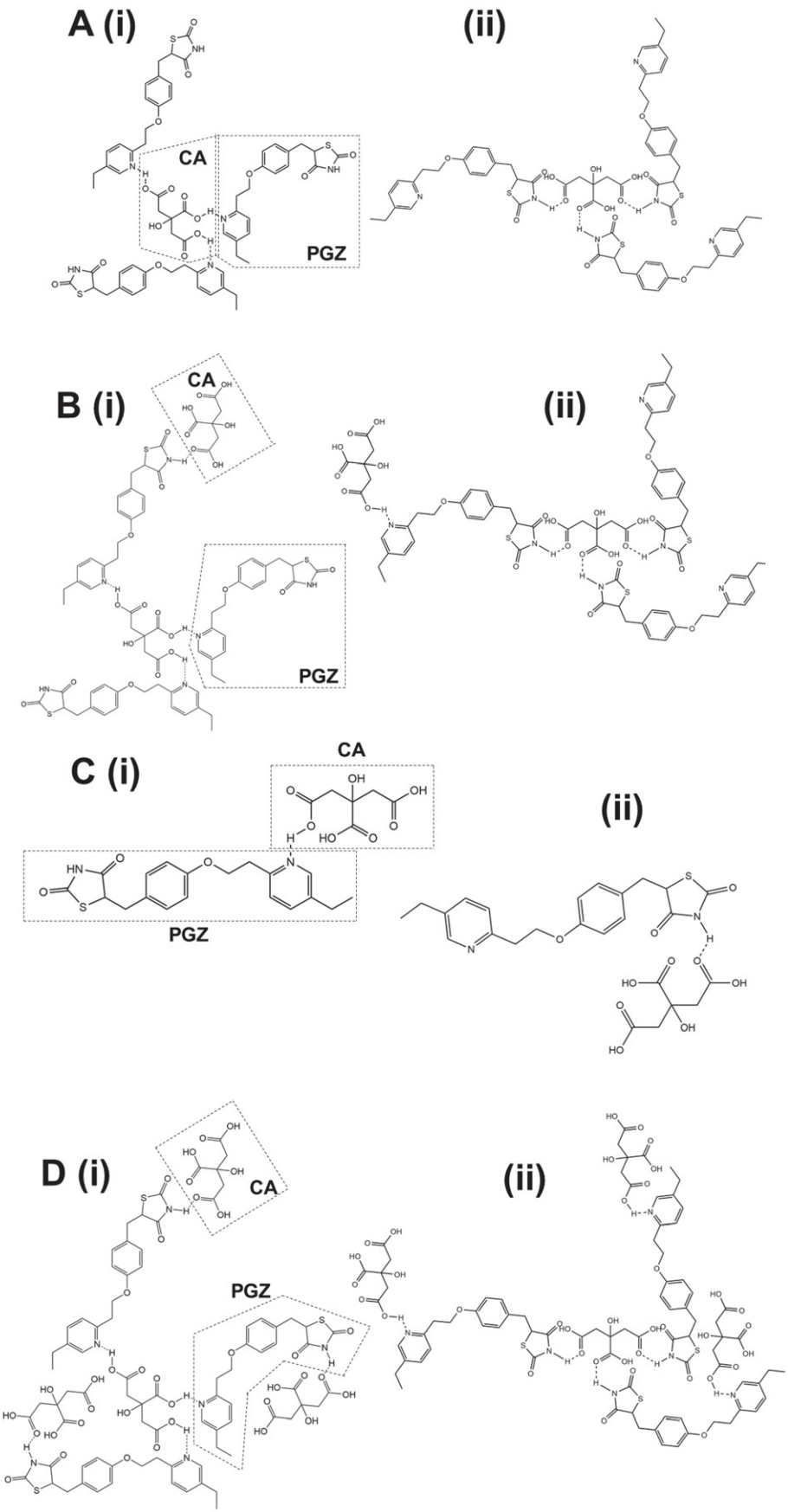

Figure 2 Proposed formation of eutectics of pioglitazone with CA: (A) PC1; (B) PC2; (C) PC3; (D) PC4

of co-crystal of PGZ with CA in different ratios are represented in Figure 2.

3. 2. Characterization

3. 2. 1. FTIR Spectroscopy

The FTIR spectra of pure PGZ and its eutectic formulations with CA are presented in Figure 3. The FTIR spectrum of pure PGZ showed the presence of a characteristic peak at 3416 cm^{-1} owing to N-H stretching of aromatic amine,[20] as well as two distinct peaks at 2927 and 2743 cm^{-1} representing aliphatic C-H stretching. The carbonyl (C=O) stretching vibration is assigned to the strong absorption peak at 1742 and 1684 cm^{-1} whereas, the peaks at 1618 and 1242 cm^{-1} are the indication of presence of aromatic ring and C-O group respectively.[21]

PGZ peak at 1509 and 1552 cm^{-1} due to N-H in-plane bending vibration (in general 1630–1500 cm^{-1}) has little been broadened or shifted in prepared eutectic products.[22] The changes might have occurred due to weak bond formation between N-H of thiazolidine and carbonyl group of citric acid (carbonyl-thiazolidinedione or carboxyl-pyridine bond development). FTIR results of the eutectics also revealed C=O stretching and C-S stretching within 1675–1685 cm^{-1} and 1330–1335 cm^{-1} respectively. In addition, these spectra of eutectic products presented a broadened peak in the range of 3412–3418 cm^{-1}, which may be due to the formation of hydrogen bonding between CA and PGZ. The FTIR peak at 1742 and 1684 cm^{-1} in PGZ is either broadened or absent in prepared eutectics because of the interaction between PGZ and CA. As a result, the changes might be considered to be due to the formation of eutectics with the organic acid molecules.

3. 2. 2. DSC

The DSC thermograms of pure PGZ and its eutectic products with CA are presented in Figure 4. The characteristic single endotherm at 195.61 °C confirmed the melting point of PGZ.[23,24] The melting endotherm of prepared eutectic samples differed significantly from those of pure PGZ. All the eutectic formulations exhibited endotherm noticeably below the melting point of pure PGZ. Also the disappearance of the sharp endothermic peak of the PGZ in the formulations supported the formation of eutectics with co-former in different molar ratios. After analyzing all of the DSC data, it was found that the PGZ was formed its eutectics. Thus, DSC thermogram confirms that there is no sign of chemical incompatibility in developing non-covalent derivatives (eutectics).

3. 2. 4. PXRD

When the functional groups are compatible for effective formation of non-covalent bond, size and shape of the parent molecule favors a crystal packing, then a cocrystal will form but on the other hand, when the functional groups are compatible to form non-covalent bonding but they lack to form a crystal packing, then eutectic will produce. The PXRD pattern of pure PGZ and its eutectic formulations with CA are presented in Figure 5. Pure PGZ showed 2θ values at 8.764, 17.64, 18.897, 20.830, and 21.223 indicating crystallinity.[23] The characteristic peaks of PGZ were either absent or shifted a little with smaller intensity or broadened in prepared PGZ-CA eutectic formulations. In addition, the intensity of the parent peak was found to be decreased may be due to the formation of eutectics. The data obtained from the PXRD analysis showed that the FWHM (full-width half maximum), particle size

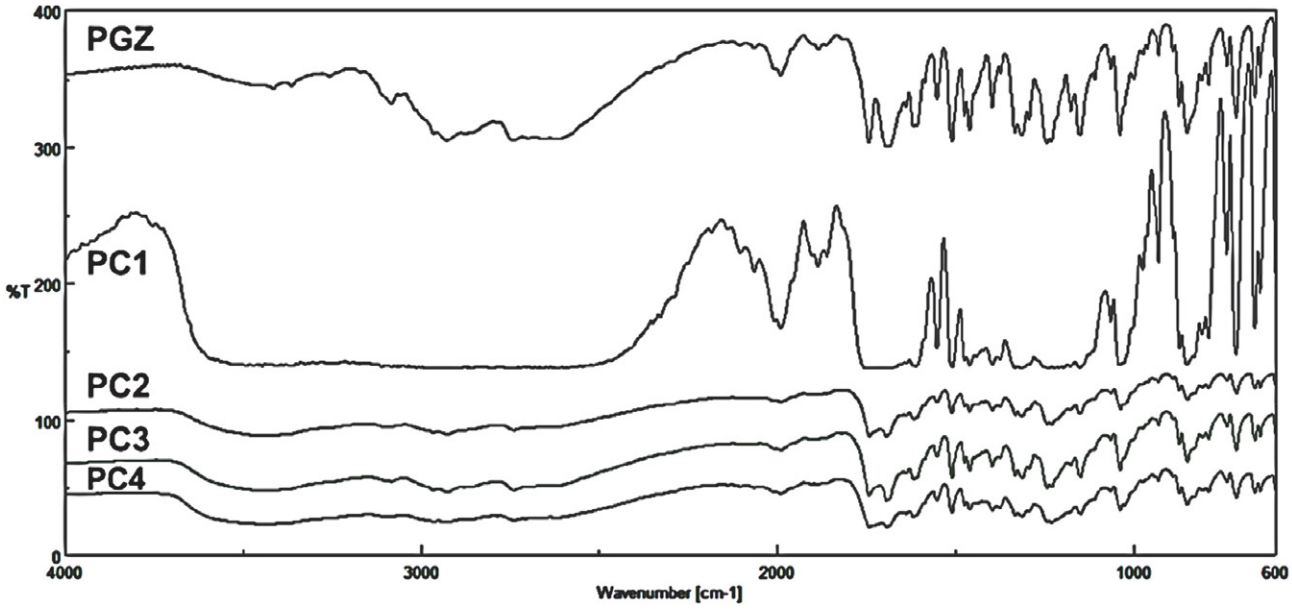

Figure 3. FTIR spectra of pure PGZ and PGZ-CA eutectic formulations

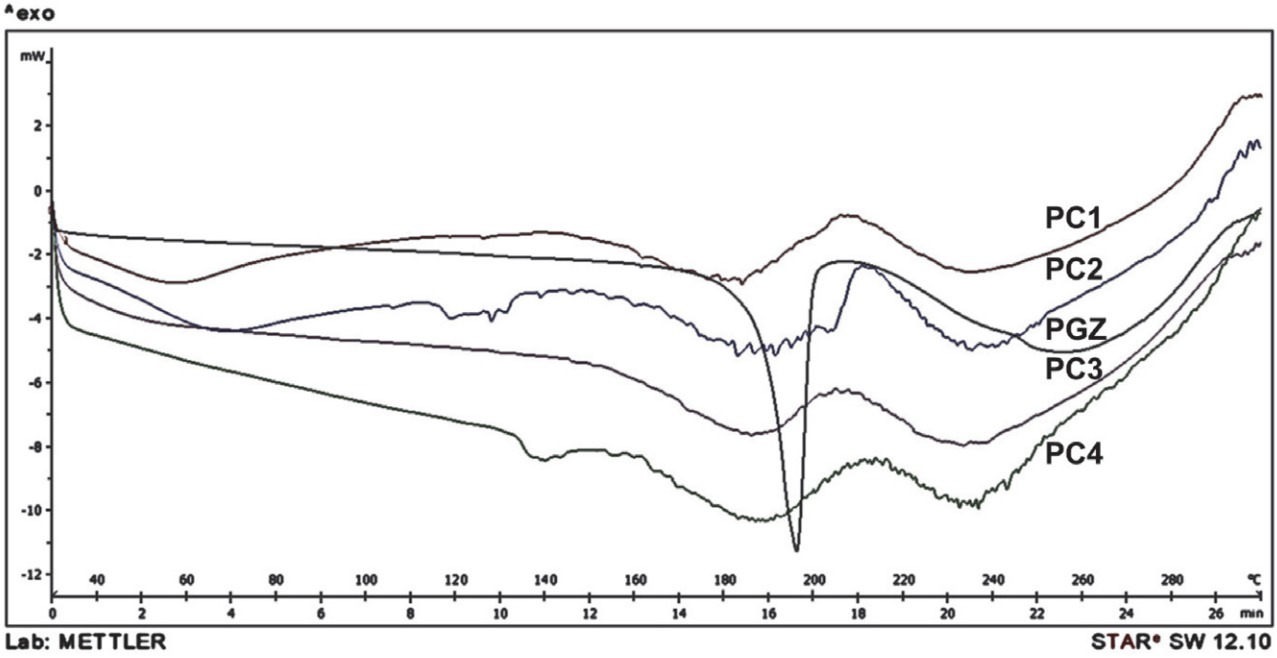

Figure 4. DSC thermograms of PGZ and PGZ-CA eutectic formulations

of the formed eutectics was found decreased than the pure drug (PGZ) (Table 3).

Table 2: List of XRD peaks observed in PGZ and prepared eutectic formulations

Sample code	2θ value observed
PGZ	8.76, 17.64, 18.90, 20.83, 21.22
PC1	8.94, 21.04, 23.29, 26.50, 32.02
PC2	10.80, 15.64, 21.14, 23.53
PC3	8.89, 15.87, 21.00, 23.26
PC4	9.08, 16.08, 20.56, 26.72, 28.77

Particle size is an important parameter to calculate because of proper understanding in microstructural parameters. To calculate crystallite particle size, Scherrer method is the most commonly used method depending on the XRD peaks broadening data. The most traditional method to calculate the crystallite size is the Scherrer method. For determination of crystallite size (D) of the prepared crystal, the Scherrer's equation is stated as:

$$D = \frac{k\lambda}{\beta Cos\theta} \quad (1)$$

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., 0.154056 nm for Cu Kα1 radiation; ß is the broadening of the peaks and that is also known as peak width at half maxima (FWHM) measured in radians and finally θ is the Bragg's angle of diffraction.

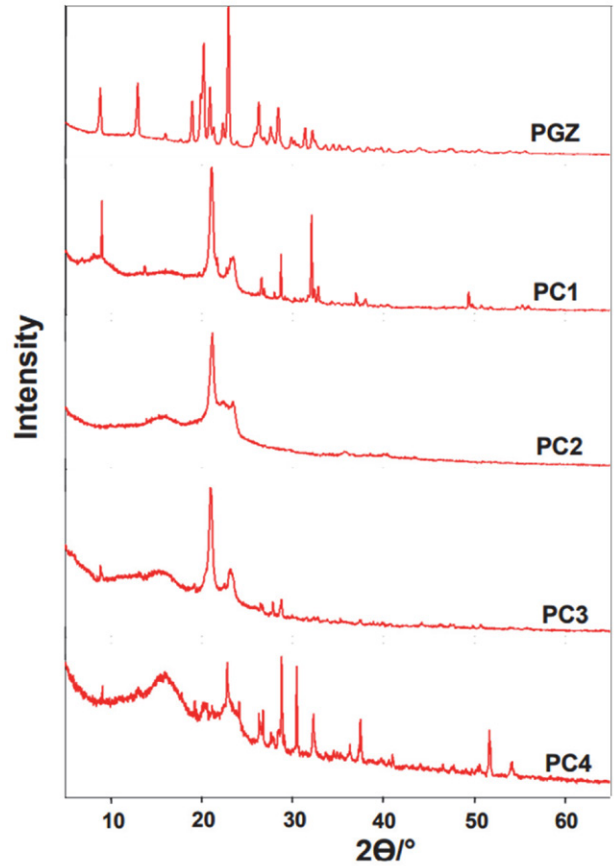

Figure 5. XRD pattern of PGZ and PGZ-CA eutectic formulation

Crystal distortion and deformity was occurred due to the induced strain and the strain was calculated by using the equation:[15]

$$\varepsilon = \frac{\beta}{4tan\theta} \qquad (2) \qquad (2)$$

Table 3. Crystallite properties of eutectics of pioglitazone with citric acid estimated from XRD

Eutectic code	FWHM	Particle size (nm)	Strain (10^{-3})	Dislocation Density (m^{-2})
PGZ	0.209±0.05	40.65±10.31	4.36±1.04	2.42±0.61
PC1	0.621±0.15	13.68±3.27	12.2±2.91	21.371±5.11
PC2	0.525±0.21	17.28±6.23	10.6±4.32	13.39±4.82
PC3	0.203±0.03	40.39±6.02	6.46±0.94	2.45±0.36
PC4	0.33±0.11	26.58±9.51	7.31±2.22	5.65±2.02

Particle size of PC1 was found lowest as compared to other eutectic formation as well as pure PGZ. The difference in dislocation density and strain value between PZA and PGZ-CA eutectics was observed because of weak bond formation between PGZ and CA. Eutectic PC1 showed highest strain value maybe due to higher deformation activity between molecules in a material. From this data we can assume PC1 formed a strong eutectic formation.

3. 2. 3. SEM

SEM photographs of pure PGZ (a) and PGZ-CA eutectic formulation (b) is presented in Figure 6. Characteristic crystal morphology is seen in the micrograph of pure PGZ while that geometry is slightly different in the eutectic product. Presence of lamellar structure or microstructure composed of alternating fine layers in the eutectic product attributed due to the partial deformation of PGZ crystal. The attainment of eutectic formation using CA as organic co-former was also supported by DSC and PXRD.

3. 3. *In vitro* Drug Dissolution

The presence of food disrupts absorption, leading to delays in peak plasma concentration, sometimes extending up to 5–6 hours. Several studies demonstrated various formulations of PGZ like SMEDDS,[26] nanosuspension,[27] multilayered tablet,[28] floating tablet,[29] transdermal patch,[30] etc. having limitations like entrapment efficacy of SNEDDS, physical stability of nanosuspension, lamination in multilayered tablets etc. Other approaches were also applied to enhance the solubility of PGZ like the preparation of inclusion complex,[31] using poloxamer 188 and 407,[30] using natural polymer Pullulan[33] and all the studies exhibited an increase in solubility and dissolution profile as compared to pure PGZ. Other approaches were also applied to enhance the solubility of PGZ like the preparation of inclusion complex,[31] using poloxamer 188 and 407,[32] using natural polymer Pullulan[33] and all the studies exhibited an increase in solubility and dissolution profile as compared to pure PGZ.

In vitro drug dissolution is a crucial physicochemical parameter frequently used to assess the possible risk of the dissolution-rate controlled absorption of a chemical entity. Owing to its kinetic nature, *in vitro* drug dissolution assumes a better correlation with *in vivo* drug dissolution. Therefore, to quantitatively evaluate the impact of the solid-state modification on the drug dissolution behavior, *in vitro* drug dissolution was estimated in 0.5% SLS solution. *In vitro* PGZ release pattern of pure PGZ and its eutectic formulations with CA, at different molar ratios are presented in Figure 7**.** From the *in vitro* drug dissolution profile, it was observed that PC1 (containing 3:1 molar ratio) showed the highest release (67.55%) as compared to other PGZ-CA eutectic formulations. observed that among all prepared eutectic formulations of PGZ-CA. The potential reason for this increase in solubility could be linked to the poorly water-soluble active pharmaceutical ingredient (API) interacting non-covalently with a more water-soluble co-former.

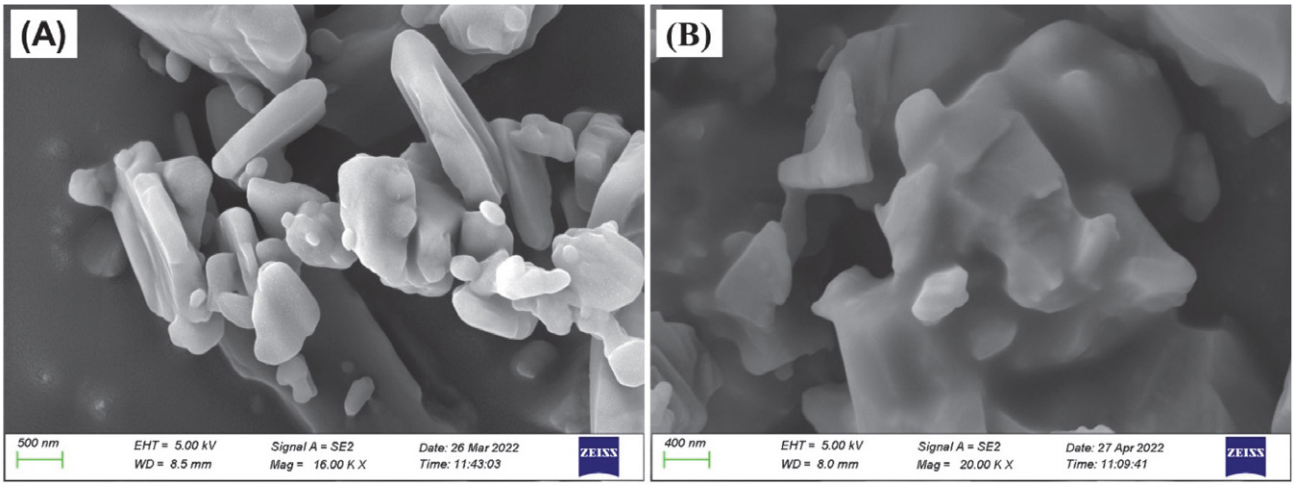

Figure 6. SEM photograph of (A) pure PGZ (magnification: 16k ×), (B) PGZ-CA eutectic formulation (PC1) (magnification: 20k ×)

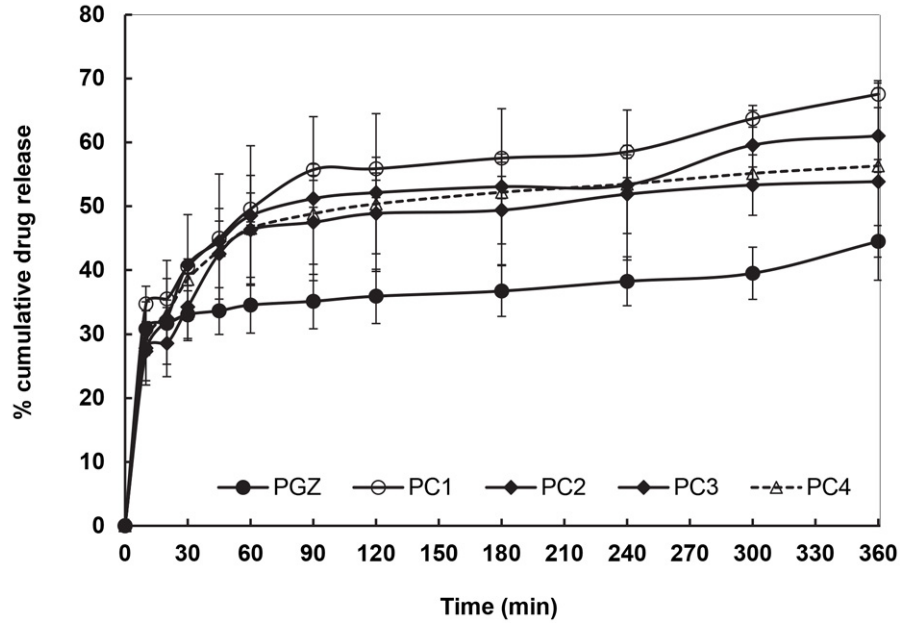

Figure 7. *In vitro* PGZ dissolution pattern of pure PGZ and PGZ-CA eutectic formulations

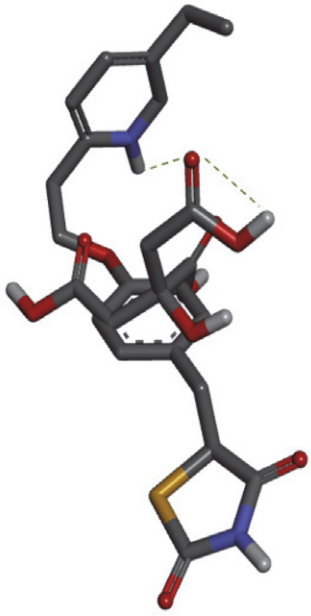

Figure 8: Pictorial elucidation of *In-silico* binding interactions of pioglitazone-CA

Linear defects on atomic scale are the reason behind dislocation which favorably enhanced the drug dissolution. Highest dislocation density was observed in PC1 which exhibited the maximum dissolution profile as compared to pure drug and other eutectic products.

3. 4. Drug-excipient Molecular Interaction

The objective of this *in silico* molecular docking study is to uncover specific information about the drug-excipient molecule interaction affinity and types of interaction between them, if any.[18] The PGZ was taken as a ligand against receptors like CA. The finest binding was confirmed by the highest negative score.[19] The molecular interaction study revealed a stable binding interaction between PGZ and excipient molecules (organic acid molecule i.e., CA used to prepare eutectic formulations of PGZ). *In silico* binding interactions and potential binding sites are depicted using a pictorial format in Figure 8. The detailed binding interactions have been elucidated in Table 4. The negative energy verified that all of these eutectic formulations of PGZ had stable binding.

Table 4. *In silico* binding interaction and potential binding of PGZ-CA eutectic formation

Formulation code	Docking score (kcal/mol)	Bond type	Bond distance (Å)
PGZ-CA	–2.2	Conventional hydrogen bond	2.5

4. Conclusion

Eutectic products of pioglitazone were made ready using CA as the co-former in different molar ratios by solvent evaporation technique. The combination of PGZ-CA formed eutectic rather than cocrystal possibly by weak carbonyl-thiazolidine or carboxyl-pyridine bond development. The difference in dislocation density and strain value of PGZ vs PGZ-CA eutectics could be the cause of weak

bond formation between PGZ and CA and highest strain value of PC1 might be due to the peak deformation activity compared to PC2, PC3, and PC4. Particle size of PC1 was also found lowermost rather than that of pure PGZ and other eutectics. The findings of the *in vitro* dissolution test demonstrated that the PC1 (PGZ-CA as 3:1 molar ratio) exhibited maximum dissolution of drug (68%) compared to other prepared eutectic formulations (54 to 61%) and pure PGZ (44%) after 360 min. In addition, *in silico* molecular docking study demonstrated the binding score of –2.2 kcal/mol.

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Conflict of interest:

The authors report that there is no potential conflict of interest to declare.

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Povzetek

V tem delu smo razvili evtektike pioglitazone (PGZ) z uporabo citronske kisline (CA) kot sooblikovalca ter proučili vpliv CA na lastnosti kristalitov in raztapljanje. Evtektike pioglitazona in CA (PC1, PC2, PC3 in PC4) smo pripravili v različnih molskih razmerjih (3:1, 3:2, 1:1 in 3:4) z enostavno metodo izparevanja topila. Opazili smo razliko v gostoti dislokacij in vrednosti deformacije eutektikov. Najvišjo vrednost deformacije je imela PC1, kar bi lahko pripisali najvišji deformacijski aktivnosti v primerjavi s PC2, PC3 in PC4. Šibke vezi med karbonil-tiazolidinom ali karboksil-piridinom so verjetno povzročile nastanek evtektikov PGZ-CA namesto kokristala z vrednostjo sidranja –2,2 kcal/mol. Prav tako je PC1 imela najmanjšo velikost delcev v primerjavi s čistim PGZ in drugimi evtektiki. Po 360 minutah je PC1 dosegla najvišjo stopnjo raztapljanja zdravila (68 %) v primerjavi z drugimi evtektiki (54 do 61 %) in PGZ (44 %).