A Study Showcasing Crystal Medley of Metformin Free Base: Virtual and Experimental Insights

Abstract

Objective: The present work reports the existence of polymorphism in metformin free base applying virtual and experimental approach.

Methods: The experimental screening of various polymorphs of metformin free base has been coupled with virtual approach resulting in isolation of three distinct crystal phases from different solvents/or solvent mixtures. The virtual screening of polymorphs was performed using Polymorph Predictor module of BIOVIA Material Studio (MS) software. A state-of-the-art approach was undertaken utilizing integrated molecular modeling and Monte Carlo simulation technology. The sophisticated tools were used to characterize the experimentally isolated forms such as Differential Scanning Calorimetry (DSC), Fourier Transform Infra-Red Spectroscopy (FTIR), Powder X Ray Diffraction (PXRD) and optical microscopy. Lattice energy landscape was examined to look for these observed forms. Crystal morphology study was conducted to analyse Morphologically Important (MI) facets.

Results: A list of potential polymorphs of the drug molecule was generated with varied lattice constants using MS. Crystal energy landscape obtained from the study provided systematic energy ranking to the polymorphs. DSC of these forms exhibited endothermic peaks at 134.01, 111.24 and 79.84°C respectively indicating them to be different forms of metformin base. Structure determination from powder patterns showed that although all the forms, form I, II and III crystallize out in same triclinic space group, P-1 but they possessed different crystallographic parameters and hydrogen bonding patterns. The predicted results were quite complacent with experimental observations with respect to lattice parameters. The three observed forms have been found as local minima in the lattice energy landscape of potential polymorphs.

Conclusion: The study explained the practical relevance of Crystal Structure Prediction (CSP) in studying the potential polymorphs of a drug molecule by successfully predicting various polymorphs of metformin free base. Out of all predicted polymorphs, three polymorphs were actually isolated experimentally. The information generated about the existence of multiple forms of metformin free base provides an opportunity to select and scale-up the desired crystal form well suited on bioavailability and stability grounds. The process can be escalated further to preclinical study, to emerge as an invaluable technology in future in increasing the efficiency of drug development process.

Keywords

Crystal Morphology; Crystal Structure Prediction (CSP); Lattice Energy Landscape; Metformin Free Base; Polymorphism; Powder X-Ray Diffraction (PXRD)
Introduction

Multifariousness in crystal forms of a drug molecule has become an interesting topic of discussion in the field of pharmaceuticals. This inherent tendency of the compounds to exist in various crystal forms is called polymorphism. In general polymorphism is classified into two major types, viz., monotropism and enantiotropism. This general behavior is based on their temperature linked stability. In the monotropic system, only one polymorph is stable below the melting point of the drug substance and in enantiotropic system, the substance exists in different crystal forms which are interconvertible based on their transition temperature (the temperature at which two polymorphic forms exhibit same free energy). Besides this polymorphism can be categorized into two types based on their arrangements in solid state, i.e., packing polymorphism and conformational polymorphism. In the former the differences are due to molecular packing in the unit cell and in the later case, the substances differ due to the presence of different conformers in their solid-state arrangements. Moreover, literature is flooded with reports and reviews on this interesting phenomenon of polymorphism [1-12]. From regulatory perspectives, a new polymorphic form is designated as a “pharmaceutical alternative” to the original form. Exploring various polymorphic forms of a drug molecule has become a critical part of research and development as phase transformations have a major impact on product quality and stability [1]. It is also quite useful from intellectual proprietary benefits for the pharmaceutical industry [3,4]. It is very well stated that different solid forms of a drug substance exhibit different physicochemical and biopharmaceutical properties such as solubility, dissolution, stability, manufacturability including flowability, tablet compaction, hygroscopicity, etc. This will ultimately affect the bioavailability and bioequivalence of that substance. Furthermore, different solid forms of the active pharmaceutical ingredients can possess variable organoleptic properties such as taste, color etc., [5-11]. Thus, in-depth knowledge of all the crystal forms should be acquired in advance in order to ensure the efficient and successful development of a robust product [12]. The present study focuses on the screening of various crystal forms of metformin free base. Metformin hydrochloride is a first line treatment of Type 2 diabetes [13]. Additionally, modern metformin has received a new attention due to its anti-ageing properties by dramatically increasing the healthspan of individuals making people healthy, active and alert years longer. This miracle pill favorably modulates the major biological outcomes associated with longevity such as inflammation, stress defence, cellular survival, autophagy and protein synthesis [14-16]. It has countless of other health benefits such as improvement of cognitive function, cardioprotection, anticancer properties, etc., [17]. The present study thus selected this important molecule to play with its solid-state properties and generated a list of lattice parameters of predicted crystal structures based upon their lattice energy and density as packing, pre-clustering, optimization and clustering. The eventual outcome of polymorph prediction is crystal lattice outcome which is focused on development timelines for the product in development. The literature survey has revealed that not much work has been done on polymorphic concepts of metformin free base. The final outcome of CSP, crystal energy landscape is looked upon for the experimentally observed crystal forms. This gives the idea about the lattice energy associated with these forms which in turn expresses the stability of these solid forms. Furthermore, morphology simulation of observed forms of metformin free base was performed. The final outcome, crystal habit generated from morphology study has assisted CSP in controlling the existence of various polymorphs of drug substance.

Methods

Virtual screening of polymorphs

The Crystal Structure Prediction (CSP) was implemented using Polymorph module of Biovia Material Studio (MS) software suite, version 7.0. The initial step of energy minimization involves geometry optimization using Dmol3 program and COMPASS forcefield technology of MS based on quantum mechanical methods, starting from the input molecular structure of metformin. It creates an optimized input structure for polymorph prediction. The hunt for the polymorphs was executed within most commonly occurring space groups i.e., P-1, Pbcn, P21/c, P212121, P2/c, C2/c and P21 [27] and was repeated thrice till all predicted crystal structures converges to equal energy minima. The Monte Carlo method of MS involves a systematic and stepwise approach towards polymorph prediction involving various steps such as packing, pre-clustering, optimization and clustering. The eventual outcome of polymorph prediction is crystal lattice energy landscape (energy versus density plot). It ranks the crystal structures based upon their lattice energy and density parameters and generates a list of lattice parameters of predicted structures within selected space groups [28-30]. This is further looked up for local minima (metastable crystal structures), global minima and thermodynamically most stable form.

Experimental screening of polymorphs

Metformin free base was isolated from commercial sample of Metformin HCl (procured from Thermo Fischer Scientific) as stated in United States patent US 6,031,004 and US 8,076,377 [25,26]. This free base form of metformin was
further explored for its polymorphic tendency and success was achieved with slow evaporation method. Different solid forms were successfully isolated by slow evaporation technique using various solvents/ or solvent mixture. The saturated solutions of metformin base in various solvents and solvent mixtures were heated below the boiling point of these solvent/ or solvent mixtures and then kept for evaporation at room temperature. Form I crystallized out from benzaldehyde in 9 days. Form II from 2-propanol appeared in 2 days and form III crystallized out from a solvent mixture of cyclohexane and toluene in 21 days. Crystals observed were filtered and stored in desiccator under controlled humid conditions till further characterization.

Characterization of polymorphs

Thermal analysis: DSC thermograms of isolated forms were interpreted using Q20 DSC instrument by placing the sample (3-5 mg) into sealed aluminium pans and scanning (50-300°; 10°C/min.; nitrogen purge of 50 mL/min.) Data was interpreted using Universal analysis 2000 software (TA Q series advantage software).

Fourier Transform Infra-Red Spectroscopy (FTIR): The spectral data of the observed forms of metformin free base pressed into pellet (containing 2- 4 mg sample dispersed in approx. 20 mg KBr) was collected over the range of 450-4000cm\(^{-1}\) using Perkin-Elmer RX-1 FTIR spectrophotometer (UK). For metformin, the free base spectra exhibited a notable band at 1670 cm\(^{-1}\) (C=\(\text{N}\) imine stretch).

Powder X- Ray Diffraction (PXRD): The samples of all the collected forms (about 200 mg each) were loaded on XPERT-PRO diffractometer using Cu- K\(\alpha\) radiation (1.54°C) and scanned at 20 values ranging from 3.5° to 49° with a step size of 0.0170°, scan step time set to 25.1996 s and slit size adjusted to 0.48°C. The diffractograms were recorded and analyzed using XPERT high score software.

Optical Microscopy: The overall macroscopic crystal habit of the different polymorphs was studied by observing optical micrographs of all the samples taken using a Leica DM3000 upright optical microscope with polarizer at an image resolution of 25X.

Crystal structure determination

This was done by collecting the PXRD patterns of observed forms and subjecting them to Reflex Plus module of Material Studio. It was performed following four basic steps i.e., indexing, Pawley fitting/ refinement, structure solution and Rietveld refinement [31]. X-cell (Newmann, 2003) indexing program was used for peak indexing to obtain various solutions of crystal lattices. The unit cell possessing highest Figure of Merit (FOM) was then subjected to refinement for attaining accurate lattice constants and lattice parameters. The outcome of unit cell was done from 10 cycles followed with a search for space groups. The optimized molecular structure was imported into the refined empty unit cell. The structure solution was finally carried out by exposing this whole assembly to Powder Solve program of Reflex Plus module of MS [31,32]. Rietveld refinement of the solved structure was executed to generate \(R_r\) (weighted Rietveld parameter) values which further confirms the similarity between a simulated and an experimental diffraction pattern. The final optimization of the structure was achieved using Forcite module of MS.

Crystal morphology simulation

The morphology prediction of the observed polymorphic modifications of was carried out using the Morphology module of MS [33,34]. The maximum h,k,l values (Miller indices) for the faces were set to 5 each with an upper limit of 100 growing faces. The minimum inter-planar spacing (\(d_{\text{ Binding}}\)) for face list generation was adjusted to 1.0 A°. Growth morphology algorithm working on the hypothesis that crystal face growth rate is proportional to its attachment energy [35-37] was then applied to observed crystal structures. The outcome generated is a list of growth faces along with their attachment energy (\(E_{\text{ att}}\)). The habit properties including aspect ratio was calculated.

Solubility study

The equilibrium solubility study of observed forms of metformin free base was carried out by shaking an excess of drug (approx. 20 mg) in 10 ml of distilled water using MSW-275 (Macro scientific works, New Delhi) water bath shaker preset at 37°C and 200 rpm for 24 hrs. The aliquots were passed through 0.45\(\mu\)m membrane filter and analyzed spectrophotometrically at \(\lambda_{\text{max}}=\) at 232 nm, \(E_1^1\) cm = 16,398. Concentration (C) of various forms was determined using the formula:

\[C = \text{Absorbance} \times \text{Dilution factor}\]

\[E_1^1\] cm

Results

Virtual analysis from Crystal Structure Prediction (CSP)

The virtual analysis of polymorph screening using Polymorph Predictor module of Biovia Material Studio was carried out starting from molecular structure of metformin (Figure 1). The simulation result was retrieved in form of a table that contains data on space groups, lattice energy and lattice constants corresponding to various predicted polymorphs. Out of the various generated structures, 60 unique sets were extracted corresponding based on low energy and high-density criteria (Table 1).
Characterization

The practically isolated three forms of metformin free base were analysed using sophisticated tools such as DSC, FTIR spectroscopy, PXRD and optical microscopy.

DSC thermograms - The difference in position of melting endotherms of forms I, II and III observed in DSC curves gives the indication of formation of multiple solid forms. The form I isolated from benzaldehyde had shown a sharp endotherm at 134.01°C. The form II obtained from 2-propanol exhibits melting endotherm at 111.24°C. Form III obtained from cyclohexane and toluene shows endothermic event at 79.84°C (Table 2, Figure 2 (a-c)).

### Table 1: CSP results of metformin base.

| S. No | Substance Label | Density (g/cm³) | Latent energy (kWh/kg) | α | β | γ |
|-------|-----------------|-----------------|-------------------------|---|---|---|
| 1     | M-1 | 150.08 | 0.72 | 22.17 | 6.18 | 99 | 99 | 99 |
| 2     | M-2 | 150.12 | 0.72 | 22.12 | 6.15 | 99 | 99 | 99 |
| 3     | M-3 | 150.03 | 0.41 | 22.31 | 6.05 | 99 | 99 | 99 |
| 4     | M-4 | 150.37 | 2.12 | 9.21 | 7.80 | 58 | 58 | 58 |
| 5     | M-5 | 150.58 | 8.71 | 6.04 | 6.02 | 99 | 99 | 99 |
| 6     | M-6 | 150.85 | 7.81 | 6.04 | 6.02 | 99 | 99 | 99 |
| 7     | M-7 | 151.21 | 27.95 | 6.41 | 9.01 | 99 | 99 | 99 |
| 8     | M-8 | 151.65 | 6.42 | 6.04 | 9.45 | 99 | 99 | 99 |
| 9     | M-9 | 151.32 | 6.41 | 6.01 | 6.71 | 99 | 99 | 99 |
| 10    | M-10 | 151.11 | 10.25 | 10.53 | 3.0 | 64.61 | 99 | 99 | 99 |

### Table 2: Melting point (°C) and DSC endotherms (°C) of metformin polymorphs/solvatomorph.

| Polymorph (solvent used for isolation) | DSC endotherm (°C) |
|----------------------------------------|-------------------|
| Form I (benzaldehyde)                  | 134.01            |
| Form II (2-propanol)                   | 111.24            |
| Form III (cyclohexane+ toluene)        | 79.84             |

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Figure 2a: DSC endotherm of form I of metformin.

Figure 2b: DSC endotherm of form II of metformin.

Figure 2c: DSC endotherm of form III of metformin.
FTIR Spectroscopy

Variations in the characteristic spectral frequencies of observed forms further demonstrates the existence of polymorphism in metformin free base. The information obtained from FTIR spectra (Table 3, Figure 3(a-c)) of form I, II and III indicated the differences in the intermolecular interactions within these modifications.

**Table 3:** Prominent peaks of metformin polymorphs in FTIR spectra.

| Functional group assignment | FTIR Peaks (cm⁻¹) |
|-----------------------------|-------------------|
|                             | Form I            | Form II           | Form III          |
| N-H primary stretching      | 3368              | 3369.21           | 3370.19           |
| N-H secondary stretching    | 3181.2            | 3167.16           | 3173              |
| C=N stretching              | 2250              | 2216              | 2278              |
| CH₂ N-H bending             | 1589.85           | 1557.91           | 1576.68           |
| O-H stretch                 | -                 | -                 | -                 |
| O-H bend                    | -                 | -                 | -                 |
| C-H asymmetric stretch      | -                 | -                 | -                 |

**Figure 3a:** FTIR spectrum of form I of metformin.

**Figure 3b:** FTIR spectrum of form II of metformin.
PXRD Study

The various peaks observed in PXRD scans (Figure 4) of three forms of metformin are given in Table 4. Sharp differences in their 2θ values clearly characterize them as different polymorphic forms.
Table 4: Prominent peaks (2θ) observed in PXRD patterns of four forms of metformin.

| Form I | Form II | Form III |
|--------|---------|----------|
| 7.98   | 8.02    | -        |
| 8.73   | 8.81    | -        |
| 9.93   | 9.92    | -        |
|        | 11.09   | 11.8     |
| 12.15  | 12.01   | -        |
| 12.72  | 12.57   | -        |
|        | 13.65   | 13.95    |
| 14.2   | 14.2    | -        |
| 15.87  | 15.78   | 15.72    |
| 16.12  | 16.08   | -        |
|        | 16.46   | -        |
|        | 16.76   | 16.78    |
| 17.2   | 17      | -        |
| 17.4   | -       | -        |
| 17.67  | -       | -        |
| 18.38  | 18.3    | 18.35    |
|        | 18.72   | -        |
| 19.33  | 19.26   | 19.01    |
| 19.95  | 19.92   | -        |
|        | 20.08   | -        |
| 20.72  | 20.65   | -        |
|        | 21.44   | 21.26    |
| 21.71  | 21.62   | -        |
| 22.4   | -       | -        |
| 22.65  | -       | 22.76    |
| 22.87  | -       | -        |
|        | 23.01   | -        |
| 23.82  | 23.38   | 23.77    |
| 24.2   | 24.21   | -        |
| 24.85  | -       | 24.88    |
| 25.33  | 25.29   | 25.56    |
|        | 25.95   | -        |
| 26.24  | 26.8    | 26.29    |
| 27.27  | -       | 27.07    |
| 28.13  | 28.1    | -        |
| 28.39  | 28.34   | -        |
|        | 28.59   | 28.67    |
|        | 29.16   | -        |
|        | -       | 29.87    |
|        | 30.06   | 30.01    |
| 30.67  | -       | 30.08    |
| 31.79  | 31.24   | 31.13    |
| 32.53  | -       | 32.82    |
| 33.01  | -       | -        |
| 33.68  | -       | -        |
|        | 34.44   | -        |
|        | 35.94   | 38.48    |
|        |         | 40.75    |

Crystal structure determination from PXRD patterns

The detailed analysis of crystal structures solved from PXRD patterns by Powder Solve program of MS was attempted and crystallographic parameters of predicted and observed forms are given in table 5.
Polymorph | Form I | Form II | Form III
--- | --- | --- | ---
Solvent used for re-crystallisation | Benzaldehyde | 2-Propanol | Cyclohexane+ toluene
Crystal system | triclinic | triclinic | triclinic
Space group | P-1 | P-1 | P-1
Z | 2 | 2 | 2

| Polymorph | Form I | Form II | Form III
--- | --- | --- | ---
α (Å) | Predt. 12.28 | Expt. 12.70 | 9.71 | 11.71 | 9.47 | 9.37
| | | | | | | 8.77
| | | | | | | 8.88
| | | | | | | 6.43
| | | | | | | 6.37
| | | | | | | 95.75
| | | | | | | 95.60
| | | | | | | 89.49
| | | | | | | 89.56
| | | | | | | 108.91
| | | | | | | 108.77
| | | | | | | -144.81
| | | | | | | -144.89
| | | | | | | -23.61
| | | | | | | -12.26

Table 5: Crystallographic data for polymorphs of metformin.

Morphology study

Crystal morphology and habit of the developed forms of metformin was studied using growth morphology algorithm of morphology module of MS starting from their respective crystal structures. It is based upon the hypothesis that the growth rate of a crystal face is proportional to its attachment energy ($E_{att}$). $E_{att}$ is a habit controlling factor which is defined as energy per mol of the molecule liberated when a new layer having thickness $d_{hkl}$ (hkl indicates the Miller indices assigning a set of faces that are equivalent by the symmetry of the crystal) is joined to the surface of the crystal). Thus, the crystal faces with lowest attachment energies (in terms of magnitude) are the slowest growing and, considered as morphologically most important facets [36,37].

| Polymorph | Form I | Form II | Form III
--- | --- | --- | ---
Aspect Ratio | 2.6 | 5 | 3.63 | 4 | 3.03 | 6
MI facets | | | 2.06 | | | -23.61
| | | | | | -12.26
| | | | | | -23.08

Table 6: Morphology prediction of isolated forms of metformin.
Figure 5: Simulated crystal habit and M.I. facets of observed form I of metformin.

Figure 6: Simulated crystal habit and M.I. facets of observed form II of metformin.

Figure 7: Simulated crystal habit and M.I. facets of observed form III of metformin.
Solubility study

The solubility study performed in distilled water at 37°C (Table 7) indicated that the form with highest lattice energy or stability (form III) was least soluble (201 ± 3.2). The solubility profile was thus found in accord with their lattice energy data.

| Form   | Solubility in distilled water at 37°C (mg/ml) ± SD |
|--------|---------------------------------------------------|
| Form I | 329 ± 1.2                                         |
| Form II| 307 ± 2.5                                         |
| Form III| 201 ± 3.2                                      |

Table 7: Solubility data of observed forms of metformin.

Discussion

The results of the prediction study compiled in a tabular form revealed the significance of CSP in acquiring the data on possible polymorphs of a drug molecule. The knowledge generated from lattice energy landscape would give an idea of prevalence of multiple solid forms of a drug molecule based on crystal packing space featuring low energy and high-density crystal structures. Polymorph Predictor module and user-friendly algorithms of Biovia MS has shaped CSP as a powerful tool to predict the crystal structures of a drug substance.

The sharp endothermic peaks of observed forms at different positions in DSC curves clearly gives a clue about the existence of different solid form of drug.

The shift in FTIR bands depicting changes in vibrational frequencies support the existence of different solid phases due to variable hydrogen bonding patterns. This technique helps in identifying functional groups involved in hydrogen bonding.

The unique differences in PXRD patterns of three forms has confirmed the prevalence of polymorphism in metformin free base. The marked appearance of new peaks and disappearance of certain prominent peaks supports the evolution of new solid phases.

Crystal structure determination was done from their PXRD patterns due to difficulty in growing single crystals of suitable dimensions. The crystal structure solutions have been successfully attempted by Powder Solve technology of Reflex Plus module of MS software. The form I tends to lie in P-1 space group with triclinic crystal system. It contains two molecules of metformin in a unit cell as indicated in figure 9b facing each other, turned upside down and joined with hydrogen bonds figure 9c. There is dimer formation through intermolecular hydrogen bonds involving N (5) H⋯N (5) interaction between two molecules. The two dimers are further linked via N (5) H⋯N (1) interaction. A sheet-like pattern of molecules is observed in 3-D view figure 9d.
The crystal form II crystallizes in triclinic crystal system with P-1 space group possessing two molecules of metformin in a unit cell (Figure 10b). The molecules are lying side by side to each other and turned upside down attached through hydrogen bonded dimeric motifs i.e., N (5) H···N (3) (Figure 10c). The dimmers are further connected to each other involving N (4) H···N (4) interaction. The 3-D view indicates linear chains of molecules arranged in a sheet form (Figure 10d).

The crystal form III existing in P-1 space group displays triclinic crystal system possessing two molecules of metformin in a unit cell (Figure 11b). Each molecule is connected to three other molecules arranged in a linear manner w.r.t. each other and turned upside down. Intermolecular dimeric motifs involving N (4) H···N (1) interaction are observed between the molecules (Figure 11c). N (3) H···N (4) interaction is observed between different dimers w.r.t. each other. The 3-D view shows linear chains of molecules with anti-parallel sequence (Figure 11d).
The simulated and experimental PXRD scans complement each other as interpreted from $R_{wp}$ value which further proclaims the neatness of crystal structure determination using powder technology (Figure 12(a-c)). $R_{wp}$ is a basic measure of similarity between a simulated and an experimental diffraction pattern of each crystal structure and is found out to be below 15%.

Figure 12a: Rietveld plot form I of metformin.

Figure 12b: Rietveld plot form II of metformin.

Figure 12c: Rietveld plot form III of metformin.
Structures corresponding to predicted and observed polymorphs of metformin free base found in crystal energy landscape are featured in table 5. The predicted and experimental results are found to be quite complacent with each other. It is clearly seen that developed crystal structures exists in the list of simulated results within an energy difference of 7.5 kcal/mol from the global minima. The simulated crystal structure nos. 6, 11 and 20 complement well with experimentally observed forms. The lattice energy diagram was generated from the predicted structures (Figure 13) depicting colorfully highlighted experimentally matched forms (mentioned under legend).

The interpretation of crystal energy landscape has very well positioned the experimentally observed solid forms of metformin as local minima within an energy difference of approximately 7.0 kcal/mol from the global minimum. This further indicates the existence of multiple metastable forms of the drug.

On interpretation of lattice energy landscape, form III occupies sixth position in the list of predicted structures generated form CSP runs and is nearest to the global minimum. It is high density form having approximately 2.5 kcal/mol higher energy than that of global minimum which further confirms it to be the most stable crystalline form. Form II exists as eleventh local minima in the lattice energy landscape. The relatively low lattice energy and highest density value provided it good stability as compared to other possible forms. Form I is found as the twentieth local minimum predicted in the study.

The morphology prediction has well demonstrated that lattice energy model has ranked the observed crystal forms in correct manner with respect to their stability and observing tendency.

The morphology prediction of various forms of metformin and their ranking in the lattice energy landscape are in good agreement with each other as far as the stability is concerned. (Table 1). It was concluded after careful examination that form I is most stable having highest $E_{att}$ of its M.I. facet (100), followed by form II (facet (010)), and form III (facet (1-10)). This also expresses the growing speed of crystal and their observing tendency during experimentation.

It is likely to understand that many low energies predicted structures have not assimilated as polymorphs as they may not be favored kinetically and thus may not be appear experimental crystallization temperatures. The higher aspect ratios (>7) can also be the other parameter for not observing

The interpretation of crystal energy landscape was generated through CSP runs showing experimentally observed three crystal forms of metformin.

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work can be facilitated by utilizing a CSP which can reduce the amount of time and costs of the experimental part of research and development. Metformin free base has a strong tendency to exist in variable crystal forms as shown by CSP and illustrated in the crystal energy landscape. Onset of multiple phases of drug molecule is depicted from thermograms and PXRD scans which is also backed by spectral analysis using FTIR. Crystal structure determination from PXRD patterns confirmed the development of three forms of metformin. The variation in solubility values further helps in selection of suitable form for isolation. The study insists in scrutinizing other parameters such as solvent effects on crystallization for more detailed vision on the polymorphic aspects of a drug molecule. The study plays a constructive role in accumulating the structurally diversified data of a drug molecule which further permits to select the desired crystal form for future development.

**Conflict of Interests**

All authors declare no conflicts of interest in this article.

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