

Solubility Enhancement of Clozapine by Co-Crystals

Prachi Gohil¹, Hitesh Jain², Satyajit Sahoo³, D. B. Meshram⁴

¹Student, Pioneer Pharmacy College, Sayajipura, Vadodara

^{2,3}Associate Professor, Pioneer Pharmacy College, Sayajipura, Vadodara

⁴Principal, Pioneer Pharmacy College, Sayajipura, Vadodara

Abstract:

Cocrystallization of drug with coformers is a promising approach to alter the solid state properties of drug substances like solubility and dissolution. The objective of the present work was preparation, formulation and evaluation of the clozapine cocrystal by screening various coformers. Clozapine co-crystals were prepared using different coformers like benzoic acid, fumaric acid, sodium saccharin and sodium acetate. Cocrystals were prepared using solvent evaporation method and solvent drop grinding method. The prepared co-crystals were evaluated for saturation solubility, drug content, dissolution studies, XRD studies and DSC analysis.

Key words: Clozapine, co-crystals, Sodium Saccharin, DSC, XRD

Introduction

The concept of solubility enhancement of a therapeutically active moiety is essentially required in the modern days as it directly influences the drug bioavailability profile[1]. Crystal engineering provides several possibilities to develop single- or multi-component alterations of an API, including the synthesis of pharmaceutical cocrystals [2]. Pharmaceutical cocrystals are defined as crystals that comprise two or more discrete neutral molecules at a stoichiometric ratio and bond together via noncovalent bond interactions, in which at least one of the components is API and the others are pharmaceutically acceptable ingredients [3]. A coformer is “a component that interacts nonionically with the API in the crystal lattice, is not a solvent (including water), and is typically nonvolatile. The key advantage in cocrystallization is non-modification of pharmacological activity of drug, while their pharmaceutical properties get modified [4].

Clozapine (CLO) is a potent antipsychotic widely used to suppress both positive and negative symptoms of schizophrenia and some neuroleptic responses. Clozapine is classified as a class II drug according to biopharmaceutics classification systems (BCS), due to its high permeability and low solubility. The bioavailability of CLO is 27 %. The aim of the present study is to prepare chemically and physically stable clozapine co-crystals with improved solubility and dissolution rate. Clozapine co-crystals was prepared using different coformers like benzoic acid, fumaric acid, sodium saccharin and sodium acetate.

Method of Preparation

1. By Solvent Evaporation Method

In this method, clozapine and coformers were mixed together in different molar ratios (1:1, 1:3, and 1:5) and dissolved in methanol. Then, the solution was kept for complete evaporation of solvent for crystals formation [5, 6].

2. By Solvent Drop Grinding Method

In the solvent drop grinding method, the clozapine and coformers were mixed together in different molar ratios (1:1, 1:3, 1:5) in mortar and pestle and stirred for 45 min to form cocrystals with continuous addition of methanol [7].

Characterization of Co-crystals

▪ Saturation Solubility

The solubility was determined by dissolving excess amount of cocrystals in 10ml volumetric flask containing water. The solution was kept on shaker for 24 hrs, filtered and analyzed in UV spectrophotometer at 290nm [8, 9].

▪ Drug Content

Drug content was determined by dissolving cocrystals equivalent to 25 mg clozapine in 25 ml in distilled water. The solution was filtered and analyzed in UV spectrophotometer at 290nm [10].

▪ Dissolution Study

Dissolution study of drug and co-crystals was carried by taking 900ml of phosphate buffer pH 6.8 solution at $37 \pm 0.5^\circ\text{C}$ using a type II apparatus with a rotation speed of 50 rpm for 60 minutes. The sample was withdrawn at an interval of 10 min and analyzed in UV spectrophotometer at 290nm [11, 12].

▪ X- Ray Diffraction

The products were packed compactly in sample holder by using a glass slide and characterized for their physical state by utilizing an X-ray powder diffractometer. The powder X-ray diffraction data collection was performed by scanning 100-200 mg of sample powder at an angle range of $2\theta = 10-45^\circ$, scan rate $2^\circ/\text{min}$, with a voltage of 40 kV[12, 13].

• DSC analysis

Thermal data were obtained by differential scanning calorimeter. About 2-3 mg of samples were weighed accurately using electronic analytical balance was crimped between the aluminum pans using hydraulic press. The samples were scanned in the temperature range of 30 to 300°C at a heating rate of $10^\circ\text{C}/\text{min}$ under a continuously purged dry nitrogen flow rate 50 ml/min [14, 15].

Results

• Saturation solubility studies

Table 1: Solubility Studies of Co-Crystals Prepared by Solvent Evaporation Method

Formulation code	Drug : Co-former	Ratio	Solubility (mg/ml) (n=3, \pm SD)
SE1	Clozapine : Benzoic acid	1:1	0.248 ± 0.0545
SE2	Clozapine : Benzoic acid	1:3	0.704 ± 0.0558
SE3	Clozapine : Benzoic acid	1:5	0.868 ± 0.0251
SE4	Clozapine : Fumaric acid	1:1	2.150 ± 0.0312
SE5	Clozapine : Fumaric acid	1:3	1.372 ± 0.0191

SE6	Clozapine : Fumaric acid	1:5	1.292 ± 0.0313
SE7	Clozapine : Sodium saccharin	1:1	0.790 ± 0.0245
SE8	Clozapine : Sodium saccharin	1:3	1.023 ± 0.0680
SE9	Clozapine : Sodium saccharin	1:5	2.423 ± 0.0945
SE10	Clozapine : Sodium acetate	1:1	0.640 ± 0.0365
SE11	Clozapine : Sodium acetate	1:3	0.832 ± 0.0075
SE12	Clozapine : Sodium acetate	1:5	0.959 ± 0.0406

Table 2: Solubility Studies of Co-Crystals Prepared by Solvent Drop Grinding Method

Formulation code	Drug : Co-former	Ratio	Solubility (mg/ml) (n=3, ±SD)
SG1	Clozapine : Benzoic acid	1:1	0.197 ± 0.0170
SG2	Clozapine : Benzoic acid	1:3	0.459 ± 0.0225
SG3	Clozapine : Benzoic acid	1:5	0.597 ± 0.0211
SG4	Clozapine : Fumaric acid	1:1	1.474 ± 0.0835
SG5	Clozapine : Fumaric acid	1:3	1.087 ± 0.0348
SG6	Clozapine : Fumaric acid	1:5	0.890 ± 0.0165
SG7	Clozapine : Sodium saccharin	1:1	0.602 ± 0.0217
SG8	Clozapine : Sodium saccharin	1:3	0.994 ± 0.0153
SG9	Clozapine : Sodium saccharin	1:5	1.826 ± 0.0184
SG10	Clozapine : Sodium acetate	1:1	0.359 ± 0.0254
SG11	Clozapine : Sodium acetate	1:3	0.491 ± 0.0217
SG12	Clozapine : Sodium acetate	1:5	0.644 ± 0.0070

Solubility of all the formulation was determined and the formulation which shows better solubility were selected for further evaluation. In the solvent evaporation method SE4 and SE9 shows better solubility. In the solvent drop grinding method SG4 and SG9 shows better solubility. From these, SE9 shows the highest solubility of 2.423 ± 0.0945 .

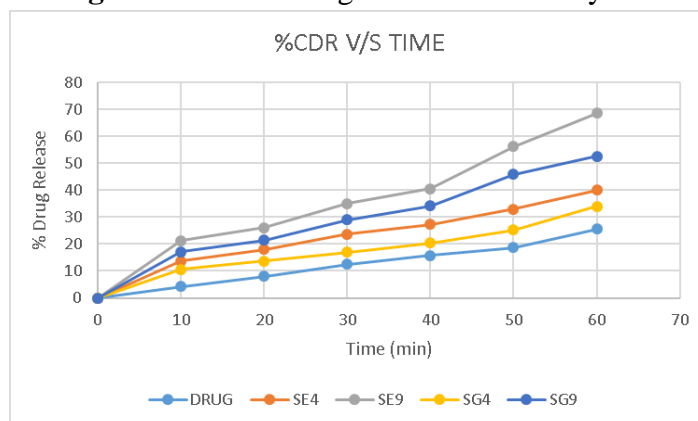
- Drug content**

Table 3: Drug Content Studies for Co-crystals

Formulation code	Drug : Co-former	Ratio	Drug Content (n=3, ±SD)
SE4	Clozapine : Fumaric acid	1:1	97.21 ± 0.54
SE9	Clozapine : Sodium saccharin	1:5	98.73 ± 0.26
SG4	Clozapine : Fumaric acid	1:1	96.32 ± 0.77
SG9	Clozapine : Sodium saccharin	1:5	98.19 ± 0.25

• **Dissolution studies**

Figure 1: Invitro Drug Release for Co-crystals



• **X- ray diffraction studies**

Figure 2: XRD Diffractogram of Clozapine

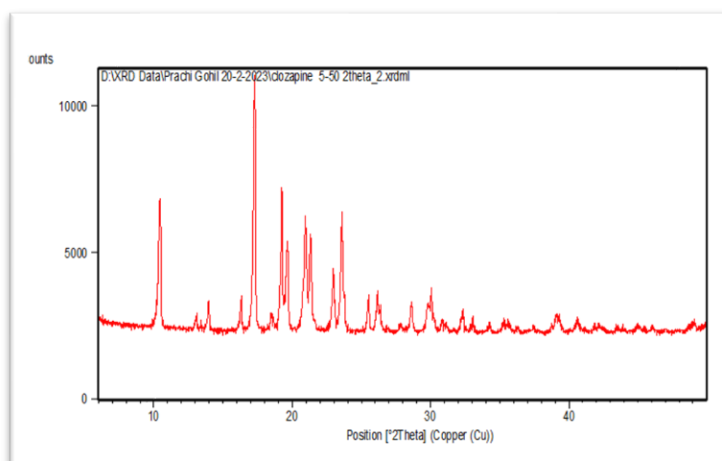
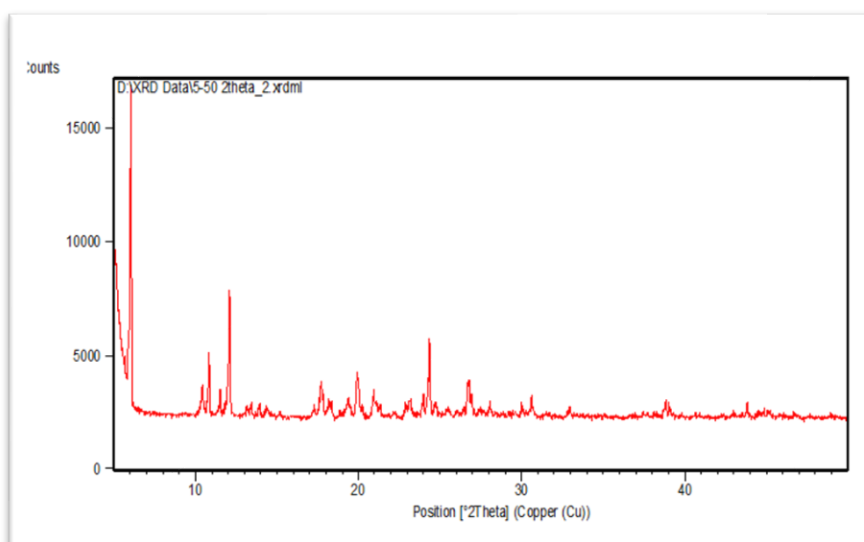


Figure 3: XRD Diffractogram for Co-crystals (SE9)



XRD analysis of pure drug and cocrystals was performed by using XRD model ‘XPRT PRO’ instrument with continuous scanning type at 2θ angle position. In case of cocrystals newer peaks was generated in the XRD spectrum and shows high intensity than the XRD diffractogram of clozapine. But here, the generation of newer characteristic peaks conformed the formation of newer crystalline structure.

- **DSC analysis**

Figure 4: DSC Thermogram of Clozapine

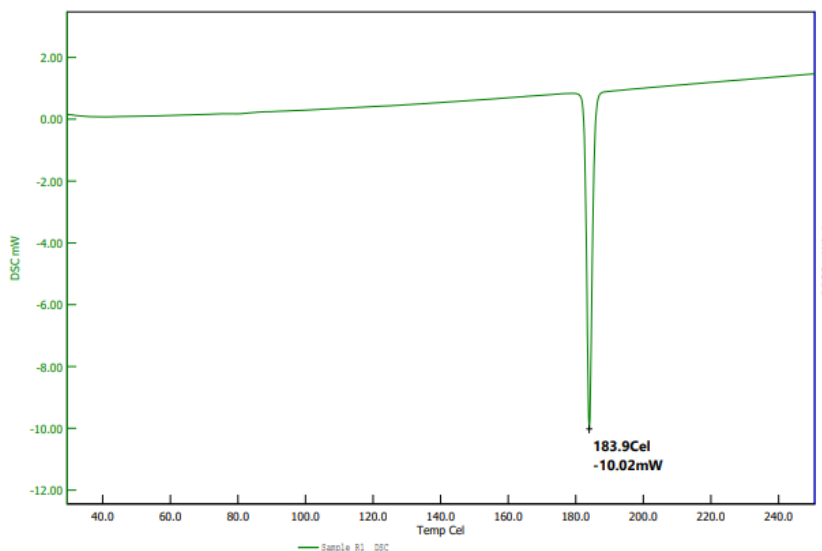
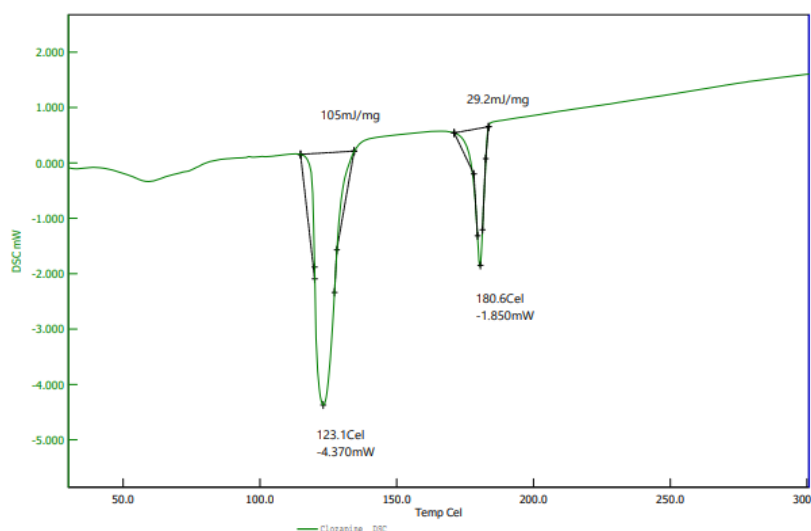


Figure 5: DSC Thermogram of Co-crystals (SE9)



DSC analysis was used to evaluate the phase transformation during the formation of cocrystals. DSC thermograms of clozapine shows endothermic peak at 183°C corresponding to its reported melting point. There was a shift in the thermogram observed in the case of clozapine cocrystal and the peak were obtained at 180.6°C and 123°C. The non-covalent interaction between the drug and conformer is an indication of the formation of cocrystals. This non-covalent interaction between drug and conformer is occurred due to the formation of a hydrogen bond between the polar functional group. This interaction resulted into the change in the molecular structure of the cocrystals formed which gives a new crystalline form of drug with altered physical properties such as solubility and melting point.

Conclusion

Co-crystals of clozapine were prepared using different coformers like benzoic acid, fumaric acid, sodium saccharin and sodium acetate to enhance the solubility and dissolution rate of clozapine. Co-crystals were prepared by solvent evaporation method and solvent drop grinding method taking different ratios (1:1, 1:3, 1:5) of drug and coformer. The prepared cocrystals were evaluated for its solubility, drug content, drug release, X- ray diffraction studies and DSC analysis. Co-crystals prepared by solvent evaporation method shows better solubility. Among different drug polymers ratio co-crystals of clozapine : sodium saccharin in 1:5 ratio shows better solubility of 2.423 ± 0.0945 , drug content of 98.73 ± 0.26 and drug release of 68.61%. From these it can be concluded that the cocrystals shows better solubility and drug release than the pure drug.

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