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Original Article

Nano Co-crystal Engineering Technique to Enhance the Solubility of Ezetimibe

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ABSTRACT

Background: Co-crystals have been highly promising for tailoring physico-chemical properties of Active pharmaceutical ingredient (API) by coupling with co-former. **Objectives:** The objective of the present work was to prepare and characterize novel nano co-crystals of Ezetimibe by different methods in various ratios of co-formers and to optimize the formulation based on the enhancement in solubility and dissolution rate. **Methods:** Ezetimibe nano co-crystals were prepared employing oxalic acid, succinic acid and maleic acid as co-formers by solvent evaporation method and anti-solvent method. **Results:** Instrumental analysis of co-crystals (DSC, IR, SEM and XRD) was performed to characterize the novel nano co-crystals. Dissolution studies and chemical stability were assessed and compared with pure Ezetimibe. The formulation with maleic acid as a co-former in the molar ratio of Ezetimibe and maleic acid (0.4:0.4) was found to be efficient than oxalic acid and succinic acid. The co-crystal dissolution profile in distilled water containing 0.5% SLS showed 18.8 folds increase in the dissolution efficiency and was found to be 95.2% within 45 min. **Conclusion:** The results demonstrate feasibility of co-crystallization method using maleic acid as co-former to enhance the solubility of poorly soluble drug Ezetimibe.

Key words: Anti-solvent, Co-Formers, Maleic Acid, Oxalic acid, Solubility, Solvent evaporation, Succinic acid.

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INTRODUCTION

The oral route is the most preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order to a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in gastric fluids. For hydrophobic drugs, the dissolution process acts as the rate controlling step, which determines the rate and degree of absorption. Thus, one of the major challenges to development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or in soluble in water.[1]

Bioavailability of poorly water soluble hydrophobic drugs (class II and class IV in biopharmaceutical classification system) is limited by solubility and dissolution rate. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity and/or increasing surface area. Several studies have been carried out to increase the rate of drugs dissolution by increasing the particle size. However, the fine drug particles have high tendency to agglomerate due to Vander Waals attraction or hydrophobicity, which both result in decrease in surface area over time.[2,3]

The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development. The development of nano co-crystals as a practically viable method to enhance bioavailability of poorly water soluble is to overcome the limitations of previous approaches such as salt formation, solubilization by co-solvents, particle size reduction and solid dispersion.[4]

One of the challenging tasks in the pharmaceutical industry is to discover ways of improving the physicochemical properties of active pharmaceutical ingredients (APIs). The solubility, dissolution rate, melting point, moisture sorption tendency and compressibility of APIs and/or recipients affect the bioavailability, design, processing, manufacturing and stability of the resultant dosage form.[5] Pharmaceutical co-crystals are attractive to the pharmaceutical industry because they offer multiple opportunities to modify the chemical and/or physical properties of an API without making or breaking covalent bonds.

Co-crystals may be defined as crystalline materials that consist of two or more molecular species held together by non covalent forces. In the recent years Pharmaceutical nano co crystals are highly promising in enhancing the dissolution rates and thus, improved bioavailability and efficacy of medication.[6] In pharmaceutical industry, it has been a major lucrative wherein the solid properties of pharmaceutical active agents have been modulated using complementary molecules in the form of cocrystal formers (CCFs). Co-crystals containing an active pharmaceutical ingredient (API) can improve the physiochemical properties such as solubility/dissolution rate, stability and mechanical properties of an API. Nano-scaling will further advance these characteristics compared to their conventional forms because of a larger surface to volume ratio of nano sized particles, one can further improve properties of an API (e.g. dissolution rate). The enhanced dissolution rate of a nanocrystal is mainly due to the increased surface area. A slight increase in solubility owing to the curvature and the high-energy surfaces of nanosized particles will also contribute to faster dissolution. The components in a co-crystal exist in a definite stiochiometric ratio and assemble via non-covalent interactions such as hydrogen bonds, ionic bonds, - or Vander Waals interactions rather than by ion pairing. Further, co-crystals have

different crystal structures than the pure components, contain different intermolecular packing patterns and as such they often exhibit widely different physical properties than the pure components.[7]

MATERIALS AND METHODS

Materials

Ezetimibe was gifted by Lupin Pharmaceuticals Ltd., whereas Oxalic acid, Maleic acid, Succinic acid, Methanol and Ethyl acetate was gifted by SD-Fine chemicals.

METHODOLOGY

Preparation of Nano Co-crystals of Ezetimibe by Solvent evaporation method

Drug and the co-former (oxalic acid, succinic acid, maleic acid) in both w/w (1:0.25, 1:0.50, 1:0.75, 1:1) and mmol in a ratio of (0.1:0.1, 0.2:0.2, 0.3:0.3 and 0.4:0.4) were dissolved in desired amount of ethyl acetate. This mixture was kept on hot plate at 75°C with continuous stirring. After getting clear solution the mixture was kept aside for two days. Nano co-crystals thus formed were collected and crystals were stored away from light and moisture.

Preparation of nano cocrystals of ezetimibe using antisolvent method[7]

Drug and the co-former (oxalic acid, succinic acid, maleic acid) in both w/w (1:0.25, 1:0.50, 1:0.75, 1:1) and mmol in a ratio of (0.1:0.1, 0.2:0.2, 0.3:0.3 and 0.4:0.4) were separately dissolved in methanol. This solution was injected slowly into anti-solvent (water) at room temperature with moderate stirring. The formed product was dried at room temperature for 2 days. The formed Nano co-crystals was collected and stored away from light and moisture.

Evaluation of Nano Co-Crystals
Solubility studies

Saturated solutions of samples were prepared and these samples were kept in orbital shaker for 24 hrs. After 24 hr the samples were centrifuged for 15-20 min and then they were analyzed at 233 nm (UV).

Solubility studies of pure drug in purified water

Solubility of ezetimibe in purified water was determined.

Dissolution

Dissolution studies were performed with prepared nano co-crystals using USP II (paddle) apparatus in distilled water containing 0.5% SLS, at a temperature of 37.5°C; 75 RPM. Samples were withdrawn at regular intervals and were analyzed at 233nm (UV).

Assay

Assay of prepared nano co-crystals were determined in distilled water. Accurately weighed amount of nano co-crystals equivalent to 10 mg of drug was taken in 100 ml volumetric flask, 20 ml of methanol was added and shaken to dissolve the drug. The volume was made up to 100 ml with distilled water. These were filtered and 1ml of aliquot of the above solutions were taken and diluted to 10 ml with distilled water. The absorbance of these solutions was determined at 233 nm against blank. The percentage assay was calculated from the standard curve.

Drug- Excipient Compatibility Studies

The optimized formulations were evaluated for drug Excipient interaction studies via differential scanning calorimetry (DSC), X-ray diffractometry (XRD) and Fourier transformer Infrared spectroscopy (FTIR).

Particle size

The particle size of optimized formulation SE8 was determined by diluting or redispersing the samples with deionized water to ezetimibe concentration of 0.2 mg/ml prior to determination. The particle size was measured at 25°C using light scattering by Malvern Zetasizer. The polydispersity index was used to measure the size distribution. Measurement was performed in triplicates and the mean values were recorded.

Differential Scanning Calorimetric

The thermal properties of samples were characterized by DSC on SHIMADZU DSC-60 differential scanning calorimeter (Japan). Samples were placed on the non-hermetic aluminum pans. The sample cell was equilibrated at 25°C and heated at a rate of 10°C/min over the range of 25-250°C.

Fourier Transform Infrared Spectroscopy

SHIMADZU 8400s FTIR Spectrophotometer (Japan) was used for the characterization of samples and KBR pellet method was used for the characterization

X-ray diffraction (XRD)

XRD analysis was performed using SHIMADZU XRD 7000 (Japan). Shimadzu X-ray diffract meter XRD-7000 is a compact and general purposed X-ray. Diffract meter equipped with a - gone meter as standard. The goniometry is scanned in vertical direction with high precision in angle, so it makes us capable to measure various types of samples, the powder samples, thin film samples are hard to set and the samples are easy to dissolve by heat. The data processing software work under the latest OS "Windows.NT/2000".

Analytical methodology for estimation of ezetimibe

The analytical method for estimation of ezetimibe for the determination of its max and quantification of nano co-crystals before proceeding the experiment. Drug concentration of 30 µg/ml was scanned in distilled water with 0.5% SLS. An absorption maximum of 233 nm is obtained. The standard graph of ezetimibe in distilled water with 0.5% SLS was prepared at this max.

RESULTS

Evaluation of Nano Co-Crystals

Nano co-crystals were prepared by two methods. They are solvent evaporation method, anti-solvent method according to their formulation codes. These are evaluated for solubility, assay and dissolution studies.

Assay

The assay of optimized ezetimibe SE8 ezetimibe, maleic acid co-crystals (mmol) (0.4:0.4) was performed and was found to be 99.4%pure.

Solubility studies

Solubility of ezetimibe in purified water was found to be 0.072 mg/ml. With the solvent evaporation method maximum solubility of 1.36 mg/ml was observed with the drug. It has been observed that as the particle size decreases the solubility of ezetimibe (mmol) increases in solvent evaporation method. This may be due to the formation of hydrogen bonds between the drug and maleic acid.[8] hence solvent evaporation method was optimized.

Solubility studies of ezetimibe was performed by increasing the amount of maleic acid and it was observed that even after increasing the amount of maleic acid , solubility of ezetimibe was not increased. Hence SE8 formulation was optimized.

Table 1: Formulation of Ezetimibe co-crystals (mmol) by Solvent evaporation method and Anti solvent method.

Ingredients	SE1/AS1	SE2/AS2	SE3/AS3	SE4/AS4	SE5/AS5	SE6/AS6	SE7/AS7	SE8/AS8	SE9/AS9	SE10/AS10	SE11/AS11	SE12/AS12
Ezetimibe(mg)	40.94	81.88	122.82	163.76	40.94	81.88	122.82	163.76	40.94	81.88	122.82	163.76
Oxalic acid (mmol)(mg)	12.6(0.1:0.1)	25.2(0.2:0.2)	37.8(0.3:0.3)	50.42(0.4:0.4)	-	-	-	-	-	-	-	-
Maleic acid(mmol) (mg)	-	-	-	-	11.6(0.1:0.1)	29(0.2:0.2)	35.42(0.3:0.3)	47.23(0.4:0.4	-	-	-	-
Succinic acid (mmol)(mg)	-	-	-	-	-	-	-	-	11.8(0.1:0.1)	23.61(0.2:0.2)	35.42(0.3:0.3)	47.23(0.4:0.4)
Solubility(mg/ml) by SE method	0.021±0.001	0.024±0.001	0.029±0.001	0.034±0.01	0.860±0.01	1.27±0.01	1.320±0.01	1.360±0.01	0.030±0.004	0.050±0.002	0.060±.01	0.070±.01
Solubility(mg/ml) by AS method	0.028±0.001	0.030±0.001	0.039±0.001	0.041±0.001	0.095±0.001	0.101±0.01	0.211±0.03	0.291±0.01	0.035±0.004	0.052±0.002	0.058±0.004	0.069±0.001
Folds of enhancement by SE method	0.29	0.33	0.40	0.47	11.9	17.2	18.3	18.8	0.41	0.69	0.83	0.97
Folds of enhancement by AS method	0.38	0.41	0.54	0.56	1.31	1.40	2.93	4.04	0.48	0.72	0.80	0.95

Note: SE-Solvent evaporation method; AS-Anti solvent method; 20ml ethyl acetate was added to all formulations in SE; 20ml methanol was added to all formulations in AS.

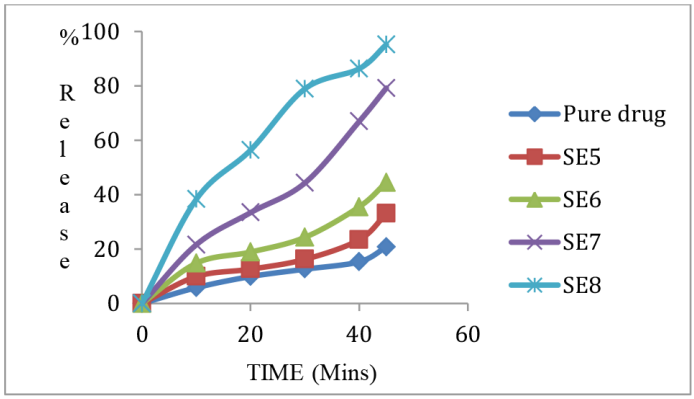

Figure 1: Percentage release profile of Ezetimibe nano co-crystals containing maleic acid in 0.5%SLS.

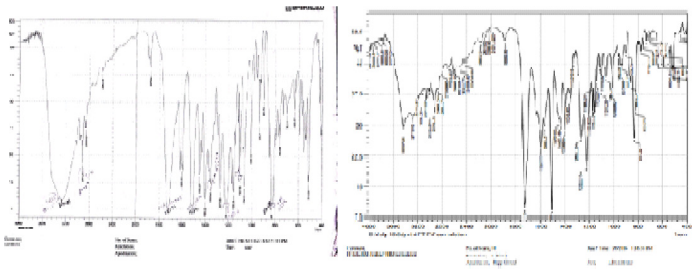

Figure 2: FTIR of Ezetimibe; FTIR of formulation SE8.
Note: SE8= Ezetimibe-Maleic acid co-crystals

Dissolution studies

Dissolution studies of all the formulations were performed according to the parameters the given Ezetimibe has shown only 20% release in 45 min. this was observed due to the poor solubility of the drug which belongs to BCS class II.[9]

In-vitro dissolution profile of nano co-crystals by Solvent evaporation method

Dissolution studies of all the formulations were performed according to the parameters. Formulation containing 0.4 Mmol (drug and co-former ratio) showed maximum release of 95.2% in 45 min.

Interaction studies of Ezetimibe by FTIR

FTIR studies were done to verify if there was any interaction between the pure drug and various co-formers employed. The FTIR graphs, with drug and various co-formers were mixed and the blend was formulated into IR pellet and scanned. The different plots are given below.

- FTIR spectra of Ezetimibe and maleic acid have bands at 3266.29 cm^{-1} and 3058.89 cm^{-1} which are corresponding to (O-H) respectively which have been shifted to 3279.10 in the co-crystals formed .
- The bands at 1721.32 cm^{-1} of Ezetimibe and 1706.86 cm^{-1} of maleic acid which are corresponding to (C=O) respectively have been shifted to 1730.21 cm^{-1} in the co-crystals formed.
- The bands at 1446.51 cm^{-1} of Ezetimibe which is corresponding to (C-N) has been shifted to 1450.52 cm^{-1} which is likely due to the charge transfer of interaction between tertiary nitrogen of Ezetimibe with maleic acid.

- These peak shifts strongly indicates the formation of hydrogen bond and other weak interactions between the Ezetimibe and maleic acid.

Particle size

The particle size of prepared nano cocrystals was found to be 226.4 ± 53 nm and had a polydispersity index value of 0.540.

Thermal Analysis By Dsc

Pure drug and formulation were subjected for DSC analysis to evaluate the change in crystalline of formulations. DSC thermo grams are illustrated through following figures

From the DSC analysis, it was observed that the thermo grams of the co-crystals Figure 3. are showing melting point (130°C) that is less than the API. This difference in pattern can be attributed to formation of eutectic, melting at a lower temperature than either of the two pure components drug (163.5C) and maleic acid (135°C)[10] From the results it appears that co-crystals obtained from API may be promoting additional co-crystallization and therefore maximizing the yield of co-crystals.

Crystallinity by XRD

Pure API and co-crystal formulation subjected for XRD analysis and following figures are their respective XRD graphs.

Co-crystal formation was confirmed by the presence of characteristic ezetimibe peaks at 15.6°, 17.1°, 18.6°, 19.2°, 20.8, 21.6°,22.6°, 23.3°, 25.1°, 28.0° and 29.9° which are according to the previous literatures and were observed with intense peak at 19.24 .

Ezetimibe – maleic acid co-crystals in Figure 4 exhibited a unique XRD pattern that allowed them to be distinguished from Ezetimibe and maleic acid individually. It had peaks at the following 2 angles 18.5°,18.8,19.4°,20.7°, 21.1°, 21.8°,22.6°,23.2°, 23.5°,24.3°,25.2°, 26.2°, 27°, 27.7°, 28.1° and 30° and were observed with intense peak 27.7.

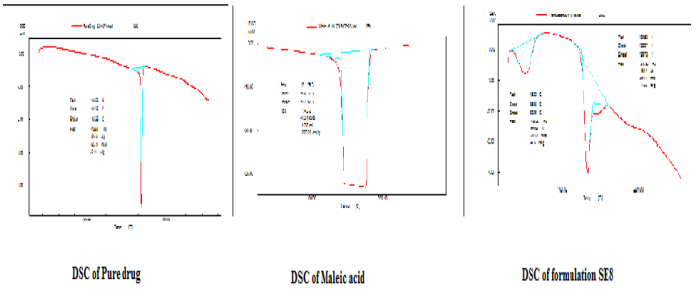

Figure 3: DSC curve of pure drug; Maleic acid; formulation SE8.

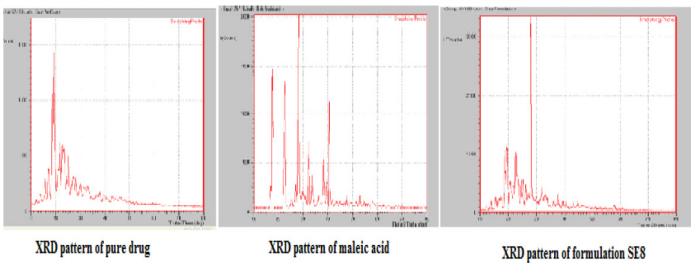

Figure 4: XRD patters of pure drug; Maleic acid; formulation SE8.

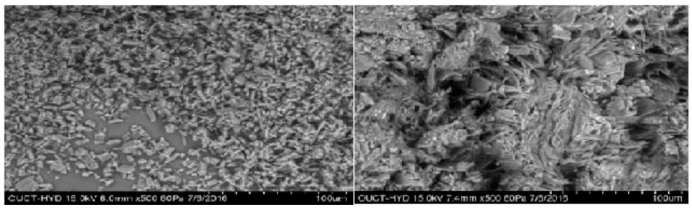

Figure 5: SEM Image of Ezetimibe; SEM Image of Formulation SE8.

Major peak at 19.2° of pure Ezetimibe Figure 4 was missing in the co-crystal phase, whereas, peak at 27.7° was observed. This confirms the formation of a new co-crystal phase. The probable conclusion which can be drawn from the XRD results is that the process facilitates co-crystallization.[11]

SEM Results

Surface morphology was studied using scanning electron microscope. Significant changes in the surface morphology were observed due to formulation process. Below mentioned figures represents the SEM results.

Ezetimibe, as obtained from the supplier featured smaller particles as shown in Figure 5. The drug- maleic acid co-crystals formed from conventional sized ezetimibe were irregular shaped flake structures, as shown in Figure 5. Some of the crystals featured sharp edges while others had less defined edges and more irregular shape. Different surface morphology for co-crystals can be attributed to the particle size of API chosen for the formulations which in turn have influence on the crystal lattice during crystallization.

DISCUSSION

Solubility enhancement of Ezetimibe was performed by using nano-cocrystal engineering technique by using two different methods .i.e, by using solvent evaporation method and anti-solvent method.

Ezetimibe - oxalic acid, maleic acid and succinic acid are connected by N…H hydrogen bonds between the basic N atom of Ezetimibe and H atom of oxalic acid, maleic acid and succinic acid. Supra molecular synthons that can occur in common functional group such as carboxylic acids,amidesandalcoholsareparticularlyamenabletoformsupramolecular hetero synthons. The strong hydrogen bond includes (N-H…O), (O-H…O), (N-H…N) and (O-H…N). The weak hydrogen bond includes –C-H...O and C-H…O=C.

Ezetimibe is containing two hydrogen bond donors and three hydrogen bond acceptors.[12] Two molecules of ezetimibe – maleic acid are connected by strong N-H…O hydrogen bonds forming a hydrogen bond dimer in a cyclic motif,[13] which indicates potential for co-crystal formation based on molecular hydrogen bonding. Maleic acid being strong hydrogen bond acceptor and receptor was selected as the co-former to prepare co-crystals. Co-crystals of nevirapine prepared by using maleic acid as a co-former the aqueous solubility was enhanced[14,15] and Co-crystals of exemestane and maleic acid showed high dissolution rate.[16]

Solvent evaporation method in mmol (0.4:0.4) using maleic acid as a co-former was observed to enhance the solubility of ezetimibe upto 18.8 folds compared to anti-solvent method in mmol (0.4:0.4) basis and this is because, for co-crystals solubility increases with the solubility of co-crystal conformers, co-former transition concentration increases with co-crystal and co-former solubilities,[17] maleic acid being highly

water soluble enhances the solubility of the co-crystals compared to Ezetimibe pure drug.

A check was done by increasing the amount of maleic acid in mmol, but it was observed that though the amount of maleic acid there was no further increase in the solubility of ezetimibe.

In anti-solvent method, both methanol and water are polar, both molecules exhibit hydrogen bonding where the hydrogen in one molecule is weakly covalently bonded to the oxygen in an adjacent molecule.[17] The co-crystals prepared by this anti-solvent method demonstrated high solubility than that of pure drug because of the addition of anti solvent reduces the solute solubility in the resultant system.[11] Out of the three co-formers used in this process, co-crystal prepared using maleic acid as a co-former showed better solubility than that of oxalic and succinic acid. Maleic acid has a higher dipole moment which enables intermolecular bonding with water molecules.[14] But the dissolution profile of maleic acid was decreased in this method.

The dissolution data was evident that the pure drug was showing slow release than the formulation containing a co-former. The formulation prepared by solvent evaporation method showed a good release in 45 min compared to the pure drug and anti-solvent method, suggesting that co-crystallization of ezetemibe with maleic acid has favored the dissolution of ezetemibe by molecular hydrogen bonding. It is speculated that maleic acids strong hydrogen bonding ability to ezetimibe might have increased the ability of co-crystal to interact with water molecules. We have concluded that dissolution was influenced by the co-former and also by changes in the particle size increasing surface area which contribute to faster dissolution.[17]

In anti-solvent method, both methanol and water are polar, both molecules exhibit hydrogen bonding where the hydrogen in one molecule is weakly covalently bonded to the oxygen in an adjacent molecule.[14] The co-crystals prepared by this anti-solvent method demonstrated high solubility than that of pure drug because of the addition of anti solvent reduces the solute solubility in the resultant system.[11] Out of the three co-formers used in this process, co-crystal prepared using maleic acid as a co-former showed better solubility than that of oxalic and succinic acid. Maleic acid has a higher dipole moment which enables intermolecular bonding with water molecules.[14] But the dissolution profile of maleic acid was decreased in this method.

Further the optimized formulation was evaluated for SEM, XRD and DSC.

The FTIR studies were done and the peak shifts strongly indicates the formation of hydrogen bond and other weak interactions between the ezetimibe and maleic acid.

SEM results indicated significant changes in the surface morphology due to formulation process. The drug-maleic acid co-crystals formed from conventional sized ezetimibe were irregular shaped flake structures, as shown in Figure 5 some of the crystals featured sharp needle edges while others had less defined edges and more irregular shape. Different surface morphology for co-crystals can be attributed to the particle size of API chosen for the formulations which in turn have influence on the crystal lattice during crystallization. The particle size of prepared co-crystals was found to be 226.4 ± 53 nm and had a polydispersity index value of 0.540 indicating that the optimized formulation is polydiperse in nature.

DSC analysis, it was observed that the thermograms of the co-crystals had shown melting point (130°C) that is less than the API. This difference in pattern can be attributed to formation of eutectic, melting at a lower temperature than either of the two pure components drug (163.5°C) and according to the previous literature maleic acid is showing a melting temperature of (142°C). The thermal behavior of co-crystals was distinct with a different melting temperature from that of pure compound this suggests the formation of new phase. So the co-crystals formed from the API may be promoting additional co-crystallization and therefore maximizing the yield of co-crystals.

XRD studies have shown an intense peak at 27.7° which indicated the formation of a new co-crystal phase. The probable conclusion which can be drawn from the XRD results is that the process facilitates co-crystallization.

CONCLUSION

In the present study, Nano co-crystals of ezetimibe were prepared and evaluated using different methods (Solvent evaporation method and Anti solvent method) employing different ratios of co-formers. The formulations were optimized in comparison with solubility of pure drug.

The combination of a suitable conformer (Maleic acid) and a simple methodology (Solvent evaporation process) has allowed us to obtain nano sized cocrystals with significantly increased solubility and dissolution, which contribute to enhanced oral bioavailability of poorly water soluble drugs.

Future scope

The formulation can be further developed as conventional tablets with enhanced dissolution and bioavailability studies need to be performed on animals.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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