DESIGNING OF STABLE CO-CRYSTALS OF AZITHROMYCIN USING SUITABLE COFORMERS

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ABSTRACTS
In this present study, a new co-crystal of azithromycin with nicotinamide and naringenin has been developed with improved solubility. Azithromycin is a class II drug with poor aqueous solubility; hence an attempt has been made to improve its solubility through co-crystallization technology. In this study, the coformers selected were nicotinamide and naringenin based on ease of hydrogen bond formation. The co-crystal of azithromycin with nicotinamide was prepared in three ratios (1:1, 1:2, and 2:1) by dry grinding and slow solvent evaporation method. The co-crystal of azithromycin with naringenin was prepared in three ratios (1:1, 1:2, and 2:1) by dry grinding and slow solvent evaporation method. The formation of the co-crystal was confirmed by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffractometry (PXRD). Azithromycin-Nicotinamide cocrystal 1:1 prepared by the dry grinding method was increased by 6.85 fold as compared to pure drug. Azithromycin-Naringenin cocrystal 1:1 prepared by solvent evaporation method was increased by 3.06 fold as compared to pure drug.

Keywords: Co-crystal; Solubility; Zoledronic Acid; Biopharmaceutics Classification System (BCS) Class II Drug; Hydrogen Bonding.

INTRODUCTION
Azithromycin is an azalide a subclass of acid-stable macrolide antibiotics with a 15-membered azlactone ring. It was approved by the Food and Drug Administration for clinical use in 1992. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. It is a member of a new generation of macrolide antibiotics and has several advantages over erythromycin. It also has enhanced antimicrobial activity which allows for once-daily dosing, but it has low bioavailability. Azithromycin is a broad-spectrum antimicrobial agent. It has bioavailability is approximately 37%. According to the Biopharmaceutical Classification System, Azithromycin can be classified as a class II drug. Furthermore, it is a substrate of p-gp which is also responsible for the low bioavailability of ATZ due to ileal clearance (biliary plus intestinal excretion clearance). During the development and formulation of any active pharmaceutical ingredient (API) that is to be delivered in a solid form, a wide range of stringent performance parameters (e.g., solubility, dissolution rate, thermal stability, etc.) needs to be carefully considered. Pharmaceutical co-crystallization is a reliable method to modify the physical and technical properties of drugs such as solubility, dissolution rate, stability hygroscopicity, and compressibility without altering their pharmacological behavior. By using the novel approach of generating cocrystals of azithromycin with suitable coformers there is an opportunity to improve the solubility and (or) permeability of active pharmaceutical ingredient (API) resulting in novel dosage forms. The aim of the current study is to develop azithromycin cocrystals, by using suitable coformers like nicotinamide and naringenin and confirmation of cocrystal formation by solid-
state characterization (Fourier transform (FT) IR, differential scanning calorimetry (DSC), and X-ray diffraction (XRD)) and analyzing the increased solubility of the prepared cocrystal by HPLC method.

**EXPERIMENTAL**

**Materials**
Azithromycin (AZT) was obtained as a gift sample from Nulife Pharmaceuticals, Pune, Maharashtra. Nicotinamide was purchased from Suvidhinath Laboratories, Baroda, and Naringenin was purchased from Sigma-Aldrich SAFC, Buchs, Switzerland. Acetonitrile (HPLC grade) and methanol (HPLC grade) was provided by Finar chemicals, Ahmedabad. Orthophosphoric acid (85% pure) and potassium dihydrogen phosphate were purchased from Merk Laboratories Pvt Ltd., Mumbai, India.

**Methods**

**Selection of Coformer**
One of the main challenges in cocrystal development is coformer selection that is compatible with specific APIs. To effectively prioritize coformer for the cocrystal screening approaches like supramolecular synthon approach, Cambridge structural database, and Hansen solubility parameter. In the current study, the supramolecular synthon approach is used for coformer selection which includes the following steps a) Choosing the target API. b) Knowledge of hydrogen bonding between the API and coformer to find the complementary functional groups for API which is capable of forming a hydrogen bond. Azithromycin (target molecule) has 5 hydrogen bond donors and 13 hydrogen bond acceptors. Nicotinamide (coformer-1) has 1 hydrogen bond donor and 2 hydrogen bond acceptors, likewise naringenin (coformer-2) 3 hydrogen bond donors and 5 hydrogen bond acceptors (Fig.-1). Based on this information, there is a high probability of hydrogen bonding for azithromycin with coformer-1 and coformer-2.

![Chemical Structures of A) Azithromycin, B) Nicotinamide, C) Naringenin](image)

**Preparation of Cocrystal**
Cocrystals were prepared by techniques like slow evaporation and dry grinding. In this study, cocrystals were prepared in the molar ratios 1:1, 1:2, and 2:1 of azithromycin with nicotinamide and naringenin through a slow solvent evaporation method. Required amounts of API and coformer are accurately weighed and saturated solutions are prepared separately by adding a little amount of solvent (methanol). The two solutions are then mixed and evenly spread on a petri dish covered with aluminum foil with holes. The solution was allowed to evaporate at room temperature until the sample is completely dry. The cocrystals were prepared in the molar ratios 1:1, 1:2, and 2:1 of azithromycin with nicotinamide and naringenin through the dry grinding method. Desired amounts of azithromycin and coformer are weighed and triturated in motor and pestle with constant speed. Later the cocrystals were collected for further analysis.

**Solid State Characterization Studies**

**FTIR**
Shimadzu FTIR: 8300 systems (Kyoto, Japan) was used to obtain the spectra for the developed complexes, physical mixture, and pure zoledronic acid. The infrared spectrum was collected over a range of 4000–500 cm\(^{-1}\). (Twenty-five scans, resolution 4 cm\(^{-1}\)). Preparation of the disc involved dispersing the sample in KBr and then grinding with applied pressure (1000 psig).
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DSC
Shimadzu TA: 60WS thermal analyzer was used to carry out a thermal analysis. The required amount of sample (about 5 mg) was placed in aluminum pans (0.1 mm thickness) and then crimped with an aluminum lid. The test ran at the temperature range of 25–300°C with a temperature increase of 10°C/min. All prepared cocrystals and physical mixtures of API and coformer were analyzed.

XRD
Rigaku mini flex 600 X-ray diffractometer (Rigaku Co., Tokyo, Japan), operated at 600 W (X-ray tube), with a fixed tube current (15 mA) and a fixed voltage (40 kV) was used to achieve the X-ray powder diffraction pattern. The X-ray beam (diffracted) was monochromated by a graphite monochromator and detection was carried out by a standard scintillation counter. Diffraction intensities were measured over a range of 5–80° (2θ).

Saturated Solubility Studies
The shake flask method was used to determine the equilibrium dynamic solubility of pure azithromycin, physical mixture, and co-crystals of azithromycin. Phosphate buffer pH 6.0 (IP) and 65% v/v ethanol was used to prepare samples by adding excess quantities of each API or physical mixture or cocrystals into injection vials containing 3 mL of the solvent. Thereafter all the prepared samples were shaken in Laptop orbital shaking incubator maintaining the temperature of 37°C at 100 rpm. After 24 h, samples were collected and centrifuged at 10000 rpm maintaining the temperature of 37°C. Then, separate the clear supernatant solution and sufficiently diluted it to fall in calibration range before injecting it into the HPLC system. The samples were analyzed using the developed HPLC method. The samples were quantified using the developed HPLC method with a photodiode array (PDA) detector.

HPLC Method
Cocrystals were analyzed by Shimadzu HPLC (Kyoto, Japan), a system controlled by LC solution software and equipped with an LC-10 ADVP (quaternary pump), SIL-10 ADVP (Auto-injector), an SPD M-10A VP (photodiode array detector). The separation was carried out on a Kromasil 100 C18 (5.0 micron, 250 × 4.6 mm) column. 85:15% (v/v) methanol: phosphate buffer (pH 8.00) in the ratio was used as mobile phase (MP). Prepare mobile phase by adding 100ml of 0.2M potassium dihydrogen phosphate and 93.6 ml of 0.2M sodium hydroxide in 1000 mL of milli-Q water and pH was made to 8.0 ± 0.02 with 10% orthophosphoric acid. Filter buffer through a membrane (0.45 µ) using a filtration assembly (vacuum) and then degassed by ultrasonication for ten minutes prior to use. A flow rate of 1.2 mL/min was maintained and the column was maintained at 40°C. PDA detector was used to estimate azithromycin. Sample was injected (25 µL) and allowed to run time for 10 min. Azithromycin has a retention time of 9.2 min (Fig.-2).

DSC Results of Azithromycin and Nicotinamide Cocrystals
The difference in the melting pattern of cocrystals was observed when compared to pure azithromycin (125.67°C). The azithromycin and nicotinamide cocrystals were prepared by the dry grinding method, where the batch of 1:1 showed an endothermic peak at 119.48°C and 137.46°C, and cocrystals batches of 1:2 showed an endothermic peak at 112.67°C and cocrystals batches of 2:1 show an endothermic peak at 116.75°C respectively, which is slightly different from pure azithromycin and nicotinamide at 125.67°C and 137.55°C respectively. The azithromycin and nicotinamide cocrystals were prepared by a slow solvent
evaporation method, where the batch of 1:1 showed an endothermic peak at 110.31°C, and 133.38°C and cocrystals batches of 1:2 showed an endothermic peak at 103.19°C and 132.89°C and cocrystals batches of 2:1 showed an endothermic peak at 143.83°C respectively, which is slightly different from pure azithromycin and nicotinamide at 125.67°C and 137.55°C respectively. Thus, it was concluded that there is significant interaction between azithromycin and nicotinamide used for the cocrystal preparation (Fig.-3, 4 and Table-1).

![DSC Thermograms](image1)

**Fig.-3: DSC Thermograms** AZT: Azithromycin pure drug; NAM: Nicotinamide pure drug; AZT-NAM PM: Azithromycin-Nicotinamide physical mixture; AZT-NAM DG1: Azithromycin-Nicotinamide DG 1:1; AZT-NAM DG2: Azithromycin-Nicotinamide DG 1:2; AZT-NAM DG3: Azithromycin-Nicotinamide DG 2:1

![DSC Thermogram](image2)

**Fig.-4: DSC Thermogram** AZT: Azithromycin pure drug; NAM: Nicotinamide pure drug; AZT-NAM PM: Azithromycin-Nicotinamide physical mixture; AZT-NAM SE1: Azithromycin-Nicotinamide SE 1:1; AZT-NAM SE2: Azithromycin-Nicotinamide SE 1:2; AZT-NAM SE3: Azithromycin-Nicotinamide SE 2:1

**Table-1: DSC Data Azithromycin and Azithromycin-Nicotinamide Cocrystals**

| Sample          | Melting Endotherm  |
|-----------------|--------------------|
| AZT             | 125.67°C           |
| NAM             | 137.55°C           |
| AZT-NAM PM      | 122.59°C and 142.99°C |
| AZT-NAM DG1     | 119.48°C and 137.46°C |
| AZT-NAM DG2     | 112.67°C           |
| AZT-NAM DG3     | 116.75°C           |
| AZT-NAM SE1     | 110.31°C and 133.38°C |
| AZT-NAM SE2     | 103.19°C and 132.89°C |
| AZT-NAM SE3     | 125.67°C and 137.55°C |

**DSC Results of Azithromycin and Naringenin Cocrystals**

The difference in the melting pattern of cocrystals was observed when compared to pure azithromycin (125.67°C). The azithromycin and naringenin cocrystals were prepared by the dry grinding method, where the batch of 1:1 showed an endothermic peak at 125.05°C, and cocrystals batches of 1:2 showed an endothermic peak at 125.19°C and cocrystals batches of 2:1 showed an endothermic peak at 127.55°C. Thus, it was concluded that there is significant interaction between azithromycin and nicotinamide used for the cocrystal preparation. The azithromycin and naringenin cocrystals prepared by a slow solvent evaporation method, a batch of 1:1, 1:2, and 2:1 did not show endothermic peaks (Fig.-5, 6 and Table-2).
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Fig.-5: DSC Thermogram AZT: Azithromycin pure drug; NAR: Naringenin pure drug; AZT-NAR PM: Azithromycin-Naringenin physical mixture; AZT-NAR DG1: Azithromycin-Naringenin DG 1:1; AZT-NAR DG2: Azithromycin-Naringenin DG 1:2; AZT-NAR DG3: Azithromycin-Naringenin DG 2:1

Fig.-6. DSC Thermogram AZT: Azithromycin pure drug; NAR: Naringenin pure drug; AZT-NAR PM: Azithromycin-Naringenin physical mixture; AZT-NAR SE1: Azithromycin-Naringenin SE 1:1; AZT-NAR SE2: Azithromycin-Naringenin SE 1:2; AZT-NAR SE3: Azithromycin-Naringenin SE 2:1

Table-2: DSC Data of Azithromycin and Azithromycin-Naringenin Cocrystals

| Sample         | Melting Endotherm |
|----------------|-------------------|
| AZT            | 125.67°C          |
| NAR            | 261.99°C          |
| AZT-NAR PM     | 128.53°C          |
| AZT-NAR DG1    | 125.05°C          |
| AZT-NAR DG2    | 125.19°C          |
| AZT-NAR DG3    | 127.55°C          |
| AZT-NAR SE1    | -----             |
| AZT-NAR SE2    | -----             |
| AZT-NAR SE3    | -----             |

FT-IR results of Azithromycin and Nicotinamide Cocrystals

Hydrogen bonding is the characteristic of cocrystal formation. The C=O amide group in nicotinamide showed a peak at 1681.93 cm⁻¹. On forming cocrystals of azithromycin with nicotinamide in 1:1, 1:2, and 2:1 ratios prepared by dry grinding and slow solvent evaporation method, the intensity of the C=O amide group (1681.93 cm⁻¹) peak decreased in the cocrystal and the broadening of OH group peak indicates the formation of hydrogen bond (Figs.-7 to 14).

Fig.-7: FTIR Spectra of Azithromycin API
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FT-IR Results of Azithromycin and Naringenin Cocrystals
Hydrogen bonding is the characteristic of cocrystal formation. FTIR spectra revealed that co-crystals were formed as the spectra were different with broadening at a frequency range of the OH group (3558.67 – 3410.15cm⁻¹) when compared to that of pure azithromycin. The ketone group (C=O) in azithromycin shows a peak at 1720.50cm⁻¹. On forming Cocrystals of azithromycin with naringenin in 1:1, 1:2, and 2:1 ratios prepared by the dry grinding method, the intensity of the C=O ketone group (1720.50cm⁻¹) peak in azithromycin decreased slightly in the cocrystal and the broadening of OH group peak indicates the formation of intermolecular hydrogen bond as C=O is an acceptor and OH is a donor (Figs.-17, 18, 19). On forming Cocrystals of azithromycin with naringenin in 1:1, 1:2, and 2:1 ratios prepared by the solvent evaporation method, the intensity of the C=O ketone group (1720.50cm⁻¹) peak in azithromycin decreased in the cocrystal and the broadening of OH group peak indicates the formation of intermolecular hydrogen bond as C=O is an acceptor and OH is a donor (Figs.-20, 21, 22).
confirms the development of a new crystalline phase (Figs.-23 to 29 and Table-3). The shifting of 100% intensity in comparison with the pure drug is mainly due to interplanar distance (d angle) indicating the different arrangement of molecules. It shows significant differences in the entire diffraction pattern. The intensity of the X-ray diffraction pattern of Azithromycin API at a 2θ angle of 9.5552 was found to be 100%. The cocrystal of azithromycin with nicotinamide of 1:1 ratio prepared by dry grinding method showed 100% at 9.8909 2θ angles, whereas the cocrystal of azithromycin with naringenin of 1:1 ratio prepared by solvent evaporation method showed 100% at 12.1556 2θ angles. The shifting of 100% intensity in comparison with the pure drug is mainly due to interplanar distance (d angle) indicating the different arrangement of molecules. It confirms the development of a new crystalline phase (Figs.-23 to 29 and Table-3).

**XRD**
When XRPD results of pure drug and cocrystals (AZT-NAM-DG1, AZT-NAR-SE1) were compared, cocrystals showed significant differences in the entire diffraction pattern. The intensity of the X-ray diffraction pattern of Azithromycin API at a 2θ angle of 9.5552 was found to be 100%. The cocrystal of azithromycin with nicotinamide of 1:1 ratio prepared by dry grinding method showed 100% at 9.8909 2θ angles, whereas the cocrystal of azithromycin with naringenin of 1:1 ratio prepared by solvent evaporation method showed 100% at 12.1556 2θ angles. The shifting of 100% intensity in comparison with the pure drug is mainly due to interplanar distance (d angle) indicating the different arrangement of molecules. It confirms the development of a new crystalline phase (Figs.-23 to 29 and Table-3).
Fig.-23: PXRD of Azithromycin API

Fig.-24: PXRD of Nicotinamide

Fig.-25: PXRD of Azithromycin-Nicotinamide Physical Mixture 1:1

Fig.-26: PXRD of Azithromycin-Nicotinamide Cocrystals 1:1 Prepared by Dry Grinding Method

Fig.-27: PXRD of Naringenin

Fig.-28: PXRD of Azithromycin-Naringenin Physical Mixture 1:1
Saturated Solubility Studies
Solubility Study of Azithromycin-Nicotinamide Cocrystals
The saturation solubility of pure Azithromycin in phosphate buffer pH 6.0 was found to be 14351.53 μg/ml after 24 hrs. The cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by dry grinding method showed dynamic solubility of 9486.67 μg/ml, 11842.66 μg/ml, and 10251.57 μg/ml after 24hrs respectively. Whereas the cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by solvent evaporation method showed dynamic solubility of 13441.77 μg/ml, 7043.05 μg/ml, and 11068.30 μg/ml after 24hrs. There was no improvement in the solubility of cocrystals when compared to pure azithromycin (Table-4).

| Table-4: Solubility Values of AZT-NAM Cocrystals in Phosphate Buffer pH 6.0 |
|---------------------------|---------------------------|---------------------------|
| Batch                    | Solubility in phosphate buffer pH 6.0 (μg/ml) | Folds decreased |
| AZT-PM                   | 14320.62                  | 1.00                      |
| AZT-NAM DG1             | 9486.67                   | 1.51                      |
| AZT-NAM DG2             | 11842.66                  | 1.21                      |
| AZT-NAM DG3             | 10251.57                  | 1.40                      |
| AZT-NAM SE1             | 13441.77                  | 1.07                      |
| AZT-NAM SE2             | 7043.05                   | 2.04                      |
| AZT-NAM SE3             | 11068.30                  | 1.30                      |

The saturation solubility of pure Azithromycin in 65% Ethanol was found to be 49564.90 μg/ml after 24 hrs. The cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by dry grinding method showed dynamic solubility of 339284.27 μg/ml, 136207.41 μg/ml, and 181457.55 μg/ml after 24hrs respectively. Whereas the cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by solvent evaporation method showed dynamic solubility of 50200.70 μg/ml, 52209.58 μg/ml, and 49538.66 μg/ml after 24hrs (Fig.-30 and Table-5).
Solubility Study of Azithromycin-Naringenin Cocrystals

The saturation solubility of pure Azithromycin in 65% Ethanol was found to be 14027.70 μg/ml after 24 hrs. The cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by dry grinding method showed dynamic solubility of 5379.38 μg/ml, 4170.42 μg/ml, and 6880.03 μg/ml after 24hrs respectively. Whereas the cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by solvent evaporation method showed dynamic solubility of 6527.97 μg/ml, 5804.96 μg/ml, and 6583.19 μg/ml after 24hrs. There was no improvement in the solubility of cocrystals when compared to pure azithromycin (Table-6).

Table-6: Solubility Values of AZT-NAR Cocrystals in Phosphate Buffer pH 6.0

| Batch     | Solubility in phosphate buffer pH 6.0 (μg/ml) | Folds decreased |
|-----------|-----------------------------------------------|-----------------|
| AZT       | 14027.70                                       | -----           |
| AZT-NAR PM| 10758.63                                       | 1.30            |
| AZT-NAR DG1| 5379.38                                       | 2.31            |
| AZT-NAR DG2| 4170.42                                       | 3.36            |
| AZT-NAR DG3| 6880.03                                       | 2.04            |
| AZT-NAR SE1| 6527.97                                       | 2.15            |
| AZT-NAR SE2| 5804.96                                       | 2.42            |
| AZT-NAR SE3| 6583.19                                       | 2.13            |

The saturation solubility of pure Azithromycin in 65% Ethanol was found to be 41487.90 μg/ml after 24 hrs. The cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2, and 2:1 prepared by dry grinding method showed dynamic solubility of 102977.80 μg/ml, 102977.80 μg/ml, and 79562.88 μg/ml after 24hrs respectively. Whereas the cocrystal form of Azithromycin with Nicotinamide in the ratio 1:1, 1:2 and 2:1 prepared by solvent evaporation method showed dynamic solubility of 127059.06 μg/ml, 76569.79 μg/ml, and 44237.28 μg/ml after 24hrs (Fig.-31 and Table-7).

CONCLUSION

Azithromycin was able to form stable cocrystals with nicotinamide and naringenin in different ratios. The cocrystals formed were characterized and the analysis for saturation solubility was carried out. The formation of the cocrystals was confirmed by solid-state characterization which included PXRD, DSC, and FTIR, the results of which proved the structural modifications in the cocrystal. PXRD results exhibited changes in the peak locations and patterns indicating the development of a new crystalline phase. DSC
thermogram showed different melting patterns for cocrystals when compared to the pure drug. These results were also supported by the FTIR spectrum that confirmed the hydrogen bond formation.

![Saturation Solubility Studies of Batches of AZT-NAR Cocrystals in 65% Ethanol](image)

Table 7: Solubility Values of AZT-NAR Cocrystals in 65% Ethanol

| Batch     | Solubility in 65% Ethanol (µg/ml) | Folds increased |
|-----------|-----------------------------------|-----------------|
| AZT       | 41487.90                          | ----            |
| AZT-NAR PM| 133014.69                         | 3.21            |
| AZT-NAR DG1| 102977.80                        | 2.48            |
| AZT-NAR DG2| 79562.88                         | 1.92            |
| AZT-NAR DG3| 45618.56                         | 1.10            |
| AZT-NAR SE1| 127059.06                        | 3.06            |
| AZT-NAR SE2| 76569.79                         | 1.85            |
| AZT-NAR SE3| 44237.28                         | 1.07            |

A 6.85-fold increase in the saturation solubility of cocrystals of azithromycin with nicotinamide of a 1:1 ratio prepared by the dry grinding method was observed in its co-crystallized form which is very high compared to the solubility of cocrystals with naringenin of 1:1 ratio prepared by solvent evaporation method having fold increase of 3.06. Thus, the cocrystallization with nicotinamide improved the solubility of azithromycin, and good permeability is expected which has to be studied furtherly.

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