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Original Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF TELMISARTAN BY TELMISARTAN-OXALIC ACID CO-CRYSTAL FORMATION

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ABSTRACT

Objective: Telmisartan (TMS), an angiotensin II receptor antagonist used for the prevention and treatment of hypertension has a very low solubility in water, so its dissolution rate is low. The aim of this study is to improve the water solubility and dissolution rate of TMS by telmisartan-oxalic acid (TMS-OXA) co-crystal formation.

Methods: Co-crystal was prepared by solvent-drop grinding and solvent evaporation methods with methanol as solvent. Initial characterization was performed by powder X-ray diffraction (PXRD). Co-crystal formation of TMS-OXA was also characterized by differential thermal analysis (DTA), Fourier transform infrared (FTIR) spectroscopy, polarized microscopy, and scanning electron microscope (SEM) photomicrograph. Solubility test was performed in water media at 25°C, whilst dissolution rate test was performed using the paddle method in 900 mL of pH 7.5 phosphate buffer solution at 37±0.5°C for 60 min.

Results: The PXRD patterns of TMS-OXA after both preparation methods were different from its starting components. There was no difference in the powder X-ray diffraction pattern between two preparation methods. The polarized photomicroscope and SEM photomicrograph showed the habit TMS-OXA co-crystal was a rhomboid shape. The solubility test showed the TMS-OXA co-crystal has 11.7 fold higher than pure TMS. The dissolution rate test showed that TMS-OXA co-crystal has percentage of TMS dissolved after 60 min higher than pure TMS.

Conclusion: The co-crystal TMS-OXA formation can increase the solubility and dissolution rate of TMS.

Keywords: Telmisartan, Oxalic acid, Co-crystal, Solubility, Dissolution.

INTRODUCTION

Telmisartan (TMS) is angiotensin II receptor antagonist used for the prevention and treatment of hypertension. TMS is class II drug in Biopharmaceutical Classification System (BCS) with low solubility and high permeability, so its bioavailability is very low. One of the efforts that have been conducted to improve the solubility and dissolution rate of TMS is through the formation of solid dispersions with polyvinylpyrrolidone [1] or chitosan [2] and the formation of an inclusion complex with β-cyclodextrin [3]. The weakness of the solid dispersion technique is the instability of physical form of drug substances in storage [4, 5]. The enhancement of solubility by this technique generally alters the physical form of the drug becomes more amorphous. The unstable amorphous form tends to be re-transformed into the crystalline form in storage, so it can change the solubility of the drug.

Co-crystals can improve the physicochemical properties of the API (active pharmaceutical ingredient), including solubility, dissolution rate, physical and chemical stability, compressibility, and hygroscopicity without affecting its pharmacological activity [6]. Pharmaceutical co-crystal is a solid form built using synthon-based design, where the API and co-crystal former molecules (coformer) connected through strong supramolecular synthons [7]. Co-crystal formation depends on the functional groups between API and coformer, to allow for the occurrence of hydrogen bonds or other forms of solid interaction. TMS structure consists of two imidazole rings and an aromatic carboxylic acid. TMS molecule has some hydrogen bond acceptors, including aromatic nitrogen (N_{arom}) in the imidazole rings and carbonyl group. Aromatic carboxylic acid can also act as a hydrogen bond donor due to the presence of a hydroxyl group. Carboxylic acid has the hydrogen bond donor that is easy to participate in hydrogen bonding. In the Cambridge Structural Database (CSD), molecules that mentioned above contain a type of hydrogen bond donor to interact with imidazole ring and another carboxylic acid. Caffeine and theophylline are examples of APIs that have imidazole ring. Some co-crystals between caffeine and some carboxylic acids, namely oxalic acid [8], salicylic acid [9], and glutaric acid [10] have been studied. As well as caffeine, theophylline also formed co-crystal with oxalic acid [11], benzoic acid [12] and salicylic acid [13].

Based on the chemical structures shown in fig. 1, TMS has a great chance to form a co-crystal with OXA. It is very important to prepare TMS-OXA co-crystal, so it can improve solubility and dissolution rate of TMS. The purpose of this study was to prepare and characterize of TMS-OXA co-crystal.

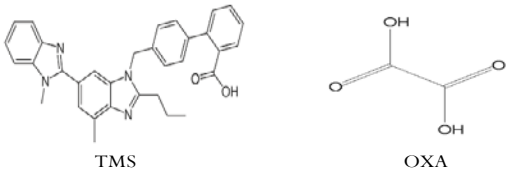

Fig. 1: Chemical structure of TMS and OXA

MATERIAL AND METHODS

Materials

TMS commercial material with purity of >99% was obtained from Glenmark Pharmaceutical Limited, Mumbai, India (batch no. 0171200922). Oxalic acid dihydrate (OXA) was obtained from Merck Chemicals Indonesia. Methanol and other reagents were purchased from Merck Chemicals Indonesia without any purification.

Preparation of TMS-OXA co-crystal by solvent-drop grinding

An equimolar of mol fraction mixture of TMS (128.5 mg, 0.25 mmol) and OXA (31.5 mg, 0.25 mmol) was placed in a mortar and 50 µl of methanol was added. The mixture was milled for 10 min. After milling, the product was dried and stored at an ambient temperature.

Preparation of TMS-OXA co-crystal by solvent evaporation

An equimolar of mol fraction mixture of TMS (64 mg, 0.125 mmol) and OXA (15.5 mg, 0.125 mmol) was added to 8 ml of methanol in a vial and gently heated at 50°C. The solution was allowed to evaporate slowly at the ambient conditions.

Characterization by PXRD

PXRD data were collected on a Philips PW1710 X-ray diffraction system. The sample was scanned within the scan range of 2θ = 5° to 35° continuous scan, at a scan rate of 2°/min. The X-ray tube was operated at 40 kV, 30 mA.

Characterization by DTA

The DTA data of pure components and TMS-OXA co-crystal was collected on a Mettler Toledo FP90. The samples were heated from 30° to 300°C at a heating rate of 10°C/min under nitrogen atmosphere.

Characterization by FTIR

Infrared spectrums were recorded using an FTIR Affinity-1 spectrophotometer (DRS-8000) Shimadzu, Japan. The dried pure TMS, OXA and TMS-OXA co-crystal samples were previously ground and mixed thoroughly with potassium bromide (KBr), an infrared transparent matrix, at 1:5 ratio of sample and KBr. The KBr powder was used as blank for background correction in FTIR studies. Forty five scans were obtained from 4000 to 400 cm^{-1}.

Characterization by polarized microscope

One to two mg of a physical mixture between TMS and OXA was placed on object glass. A drop of methanol was added to each physical mixture until dissolved and allowed to recrystallize. Recrystallization process was observed under a polarizing microscope. The microscopic images were recorded with an Optilab Advance digital color camera attached to the Olympus BX-53 polarized microscope.

Characterization by scanning electron microscope (SEM)

The electron microscopy measurements were performed at JEOL JSM-6360LA scanning electron microscope. Specimens were mounted on the metal sample holder with a diameter of 12 mm using a double-side adhesive tape and coated with gold-palladium under vacuum.

Solubility test

The solubility of TMS in water from TMS-OXA co-crystal and pure TMS was tested at room temperature using an orbital shaker. Excess amounts of the compound were added to 10 mL of water, mix it continuously and then filtered after 24 h of equilibration. The bulk solutions were measured spectrophotometrically using Shimadzu 1601-PC spectrophotometer at 295 nm. The calibration curve for BV (y=0.0503x-0.0124) was linear from 2 to 16 µg/ml (r=0.9999). The experiments were carried out in triplicate.

***In vitro* dissolution**

Dissolution test of TMS from TMS-OXA co-crystal and pure TMS was carried out in pH 7.5 phosphate buffer solution (900 ml, 37±0.5°C, 75 rpm) for 60 min using the USP XXIII paddle apparatus (ZRS-6G, Tianjin, China). At predetermined time intervals, 10 ml samples were with drawn and spectrophotometrically assayed (Shimadzu 1601-PC spectrophotometer) for drug concentration at 295 nm.

RESULTS AND DISCUSSION

Preparation of TMS-OXA co-crystal

In this research, to produce TMS-OXA co-crystal was used solvent-drop grinding (also refered to liquid-assisted grinding, wet cogrinding) and solvent evaporation methods. Solvent-drop grinding involves the grinding of two materials together and a small quantity of solvent [14]. This method is more cost-effective and environmentally friendly than the solution method, because it only uses less solvent [15, 16]. The presence of a small amount of solvent can act as a catalyst in the co-crystal formation [17].

PXRD Pattern

Powder X-ray diffractometer (PXRD) is the main instrument used to characterize the co-crystal formation. The new solid phase was formed, if the resulting PXRD pattern of the solid product after grinding pure solid compounds (API and coformer) is different from the reactants [18]. The PXRD patterns for TMS, OXA, and TMS-OXA co-crystals prepared by solvent-drop grinding (SDG) and solvent evaporation (SE) are shown in fig. 2.

The PXRD pattern of TMS raw material used in this study is consistent with the PXRD pattern of TMS Form A that has been previously reported [19]. The diffractograms of the products after solvent-drop grinding are different from starting components. The characteristic peaks of TMS and OXA were dis appeared, whilst new peaks appear after solvent-drop grinding process.

The changes in the position of the peaks after the solvent-drop grinding process indicate the formation of TMS-OXA co-crystal. There is no difference in the PXRD pattern of co-crystal prepared by solvent-drop grinding and solvent evaporation. The peak's position of TMS-OXA co-crystal is shown on the table 1.

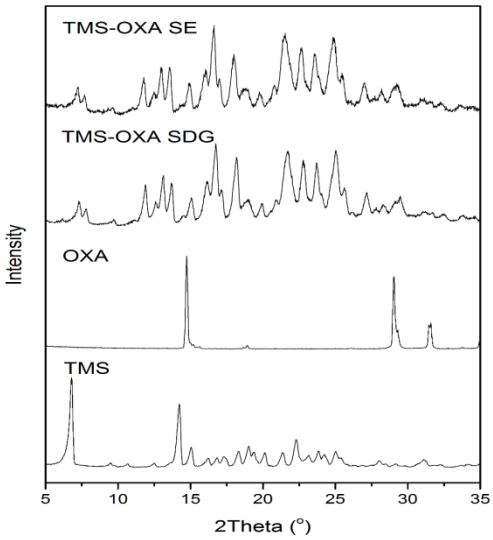

Fig. 2: PXRD patterns of TMS-OXA co-crystals prepared by solvent-drop grinding (SDG) and solvent evaporation (SE) compared to its starting components

Table 1: Main peaks of TMS-OXA co-crystal compare to its pure components

2Theta (°) position		
TMS	**OXA**	**TMS-OXA Co-crystal**
6.8	6.0	7.3
9.5	29.0	11.9
14.3	31.5	16.8
15.1	35.0	18.2
18.3	37.0	21.7
19.0	39.7	25.0

Thermogram DTA

Thermograms DTA of TMS-OXA co-crystal from solvent evaporation result and each starting component are shown in fig. 3. The melting point (T_{peak}) of TMS form A is 268.8°C. OXA melt and dehydrated at 107°C followed by decomposition [20]. T_{peak} of TMS-OXA co-crystal is 222.2°C, whilst two endothermic peaks at 231.8 and 264.2°C are decomposition results of OXA after hydrogen bond was broken. There is no endothermic peak due to loss of water at around 80-110°C. This indicates the TMS-OXA co-crystal contains no water hydrates.

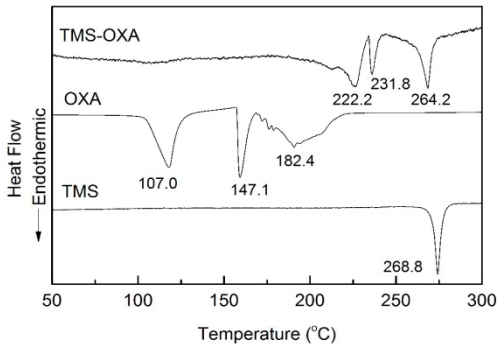

Fig. 3: Thermogram DTA of TMS-OXA co-crystal compared to its starting components

FTIR Spectra

Infrared spectroscopy can be a very powerful tool in detecting co-crystal formation, especially when a carboxylic acid is used as a co-former and/or when a neutral O-H· · ·N hydrogen bond is formed between an acid and a base [6]. The IR spectra of TMS, OXA and the co-crystal are compared in fig. 4. As shown in the fig. 4, TMS has the intense peak at 1695 and 1603 cm^{-1} due to carbonyl (C=O) and imine (C=N) stretching, respectively. The hydrogen stretching region exhibits the aromatic C-H stretching band at 3063 cm^{-1} and aliphatic C-H stretching at 2956 cm^{-1}.

An O-H group of OXA is present in the region 3100-2500 cm^{-1}due to presence of dihydrate water in the molecule, whilst the intense peak at 1695 cm^{-1} due to C=O stretching. In the TMS-OXA co-crystal, the C=O group stretching of TMS shift to 1693, whilst the C=N stretching shift to 1646 cm^{-1}. The presence of shifting in the vibrational frequencies of TMS and OXA indicates the formation of supra molecular hetero synthon of the co-crystal. The loss of a broad band OH group of water molecules in oxalic acid dihydrate after the formation of co-crystal can show the absence of water in TMS-OXA co-crystal. This is consistent with DTA result.

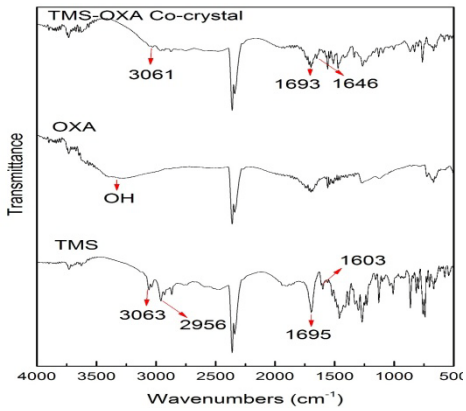

Fig. 4: FTIR spectra of TMS-OXA co-crystal compared to its starting components

Polarized microscope photo

The co-crystallization process of TMS-OXA was observed under polarized microscope after the addition a drop of methanol. As shown in fig. 5, TMS-OXA co-crystal has different crystal habit from its pure components. Fig. 5 present optical microscope photos of TMS crystal with long needle shape, whilst OXA present in rod habit. The change of needle-shaped crystal of TMS and rod-shape crystal of OXA to rhomboid-shape crystal after recrystallization of its physical mixture indicates the formation TMS-OXA co-crystal.

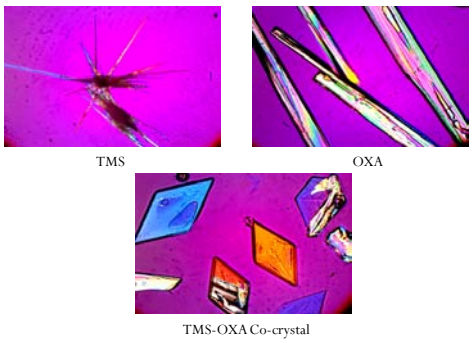

Fig. 5: Polarized microscopy photo of TMS, OXA, and TMS-OXA co-crystal

SEM photomicrograph of co-crystal

Crystal's morphology of TMS-OXA co-crystal after solvent evaporation from methanol solution is shown in fig. 6. It is marked with 100 µm label. This co-crystal is rhomboid-shape. This shape has generally good tablet ability. Mechanical properties (flow rate, compressibility, compactibility, and tensile strength) of TMS-OXA co-crystal are ongoing.

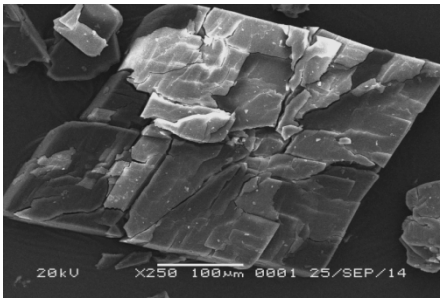

Fig. 6: Photomicrograph SEM of TMS-OXA co-crystal

Solubility test

Solubility experiments showed that solubility of TMS in the water increased in the TMS-OXA co-crystal. The solubility of TMS in water solvent is found to be 3.9±0.2 µg/mL, whilst the solubility of TMS-OXA co-crystal is found to be 45.5±0.8 µg/mL. The solubility of the TMS-OXA co-crystal has 11.7 fold higher than pure TMS. The enhancement of TMS solubility is allegedly due to the existence of hydrogen bonds between TMS and OXA in TMS-OXA co-crystal. The improved solubility of TMS through the co-crystals formation with saccharin and glutaric acid has previously been reported [21].

Dissolution test

The dissolution profiles of pure TMS and TMS-OXA co-crystal are shown in fig. 7. The dissolution rate test showed that TMS-OXA co-crystal has the percentage of TMS dissolved after 60 min or dissolution percentage ($DP_{60\ min}$) higher than pure TMS, consistent with the solubility difference. $DP_{60menit}$ in pH 7.5 phosphate buffer

solution for pure TMS and TMS-OXA co-crystal were 7.7 and 55.7%, respectively.

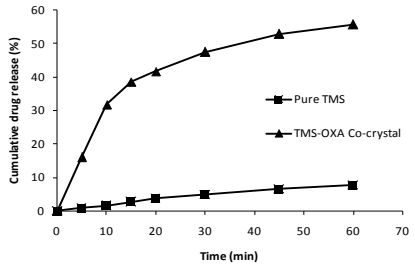

Fig. 7: Dissolution profiles of TMS obtained from pure TMS (-■) and TMS-OXA co-crystal (-▲)

CONCLUSION

Co-crystal formation between telmisartan and oxalic acid has been characterized by PXRD, DTA, and FTIR. The PXRD patterns shown TMS-OXA co-crystal is different from its starting components. FTIR spectrums show a shift of the carbonyl (C=O) and imide (C=N) groups of TMS due to supra molecular hetero synthon with $N_{aromatic}$ of the imidazole ring of TMS. The crystal habit of TMS-OXA is different from its starting components. The TMS-OXA co-crystal formation can increase the solubility and dissolution rate of TMS and potential to be developed in pharmaceutical solid dosage form.

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CONFLICT OF INTERESTS

Declared None.

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