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Research Article

COCRYSTALLINE PHASE TRANSFORMATION OF BINARY MIXTURE OF TRIMETHOPRIM AND SULFAMETHOXAZOLE BY SLURRY TECHNIQUE

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ABSTRACT

The purpose of this work was to characterize and investigate the transformation of cocrystalline phase in binary mixture of trimethoprim and sulfamethoxazole induced by slurry technique and to establish the rate of transformation at various temperatures. Cocrystallization was performed simply by adding distilled water as solvent to equimolar binary mixture of powder trimethoprim and sulfamethoxazole. A new solid phase was characterized by thermomicroscopy, scanning electron microscope, powder X-ray diffraction, differential scanning calorimetry. The rate of transformation in slurry was studied as function of storage temperature, measured by powder X-ray diffractometry. Physical characterization showed that the trimethoprim and sulfamethoxazole cocrystalline phase had a unique thermal, powder X-ray diffraction property. Cocrystals prepared by slurry technique were similar in PXRD pattern to those prepared by solvent methods. The transformation to cocrystalline phase was accelerated by increasing the temperature of storage. It could be concluded that slurry could be carried out to induce a new equimolar cocrystalline phase between sulfamethoxazole and trimethoprim**.** The rate of transformation to cocrystalline phase was affected by the temperature of storage.

Key words: Trimethoprim; sulfamethoxazole; cocrystalline phase; slurry technique and rate of transformation.

INTRODUCTION

It is well-known that pharmaceutical dosage forms containing multiple components can undergo interactions between various components or excipients that may lead to the physical and chemical change of certain constituents. In general, solid state or physical interaction beetwen two active solid ingredient or/and excipient could be classified as simple eutectics, solid solution and cocrystal (molecular compounds) [1]. This kind of interactions can cause difficulties in manufacturing process and lower the quality of final dosage form [2]. On the other hand, the interaction could be positive effect on physicochemical properties and performance of solid active ingredients. For example, interaction of some polymer with poorly soluble drugs in solid solution formation could enhance dissolution rate of drug and bioavailability [3].

Cocrystal formation has gained recent interest in application to pharmaceuticals. The ability to tailor the physicochemical properties of a drug substance via complexation is highly desirable for dissolution rate, bioavailability, stability and processing consideration [4-7]. Cocrystal may be defined as materials which contains two or more discrete molecular entities in the crystal lattice [8]. In pharmaceutical term, cocrystal was a formation of a molecular complex of an active pharmaceutical ingredient and a second molecule typically requiring complementary hydrogen bonding between the two components [9].

Pharmaceutical cocrystal could be prepared by several methods. At present, preparation of cocrystal is mainly achieved by solution cocrystallization approach such as solvent evaporation, antisolvent addition etc. Additionally, crystallization from the melt, solid state grinding and sealed heating has been employed [10-12].

A less-studied physical phenomenon is the slurries-induced formation of cocrystalline phase among two or more active solid materials or between the active solid materials and the excipients. Therefore, the aim of the present study was to characterize and investigate the formation of cocrystalline phase in binary mixture of trimethoprim and sulfamethoxazole induced by slurry technique and to establish the rate of transformation at various temperatures.

MATERIALS AND METHODS

Trimethoprim (TMP) and sulfamethoxazole (SMZ) was kindly obtained from P.T Pyridam (Imported from Virchow Lab. India, batch no. 09150307 and Shouguang Fukang Pharm. Co. Ltd. batch no. 200703342) respectively. Methanol (Merck) and Distilled water.

Preparation of TMP-SMZ cocrystal and physical mixture

TMP-SMZ Physical Mixture (PM) was prepared at equimolar ratio in glass vial by using a vortex mixer during five minutes. Cocrystal TMP-SMZ was prepared by solvent method. TMP (0.725 g) and SMZ (0.633 g) equimolar were dissolved in small amount of methanol at ambient temperature. The solution was slowly evaporated at room temperature during 48 hours to promote cocrystallization.

Transformation studies

The rate of transformation under three storage conditions was evaluated as follows. The equimolar physical mixture TMP and SMZ (0.725 and 0.633 g respectively) were suspended in 40 mL of distilled water. They were stored at 25 and 37 ^{0}C in a constant temperature water bath (GFL) at a shaking speed of 75 rpm. Samples were withdrawn at suitable time intervals and then immediately filtered under vacuum and dried at room temperature during 24 hours.

Hot-stage polarized optical microscopy

Microphoto of slurry product and cocrystal from solvent method were performed by Olympus BX5 polarizing optical microscope equipped with hot stage and camera (DSC-05 Sony Inc. Japan). Preliminary analysis of melting point of cocrystal phase was obtained using hot stage at heating rate at 2 ^{0}C/ min.

Scanning electron microscopy

Electron-micrographs of crystal habit of cocrystalline phase were examined using SEM (JEOL model JSM-6360LA, Tokyo, Japan). The specimen were mounted on a metal stub with double sided adhesive tape and coated under vaccum with gold-paladium (Au 80% and Pd 20%) prior to observation.

Differential scanning calorimetry

DSC analysis of approximately 1-4 mg samples in pin-holed aluminium crimped pans was performed using Rigaku ThermoPlus DSC Instrument (Japan), at heating rate of 10 ^{0}C per min over a temperature range 30-200 ^{0}C. Samples were purged with nitrogen gas at 60 mL/ min throughout the analysis.

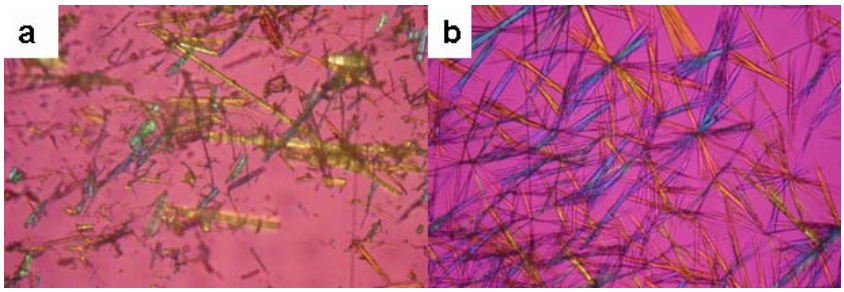

Fig. 1: Optical microphoto crystal habit a) powder sample after slurry technique and b) cocrystal by solvent method (methanol) Magnification 200 X

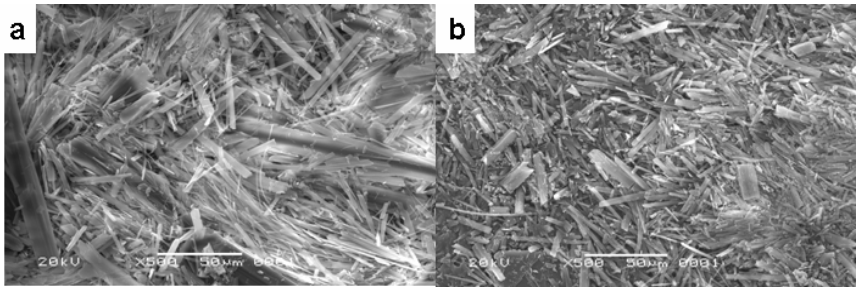

Fig. 2: SEM microphoto crystal habit a) powder sample after slurry technique and b) cocrystal by solvent method (methanol)

Powder X-ray diffraction analysis

Powder X-ray diffraction (XRD) profiles were taken with an X-ray diffractometer (RINT 2400, Rigaku Co., Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 100 mA; receiving slit, 0.15 mm; scan range, 5^0–40^0 (2θ); step size, 0.02^0; scanning speed, 1^0 /min. Sample powder was carefully loaded into a glass holder, and the sample surface was flattened softly to avoid particle orientation using a spatula and glass plate.

Determination of cocrystalline phase

Calibration curve were prepared by blending TMP-SMZ physical mixture in 1:1 molar ratio with the required amount of TMP-SMZ cocrystal homogeneously. Cocrystal used in calibration was prepared by solvent method (Erizal et al, 2008a). The total mass of each standard was 0.5 g. The standards prepared had 0, 10, 30, 50, 70, 90 and 100 per cent (by weight) TMP-SMZ cocrystal. The calibration curve for quantification of the percentage of cocrystalline phase was established based on the integrated intensity of the characteristic interference of diffraction peaks in range $5\text{-}10^0$ (2θ), which were normalized against the percentage of cocrystalline in binary mixture.

RESULTS AND DISCUSSION

Microscopic Analysis by Hot Stage Polarization and Electron Microscope

This analysis provided a preliminary characterization of cocrystalline phase in binary mixture of TMP-SMZ. Optical and electron microphoto was shown in Fig. 1 and 2. TMP-SMZ cocrystal from solvent method was needle shaped habit and was obtained wihin two days. Cocrystallization by slurry technique also yielded a same habit with cocrystal from solvent method, but still occurred a physical mixture of TMP and SMZ. A sharp melting point at around 180 ^{0}C was observed for the TMP-SMZ cocrystal. On the other hand, the sample from slurry technique had two range melting point at around 156-160 ^{0}C and 178-182.4 ^{0}C.

DSC analysis

DSC Analysis was performed to characterize the thermal behaviour

of TMP-SMZ cocrystalline phase in relation to the intact component and physical mixture of binary system. DSC thermograms for trimethoprim, sulfamethoxazole, Physical mixtures, cocrystal from solvent and slurry technique are presented in Figure 3. Trimethoprim and sulfamethoxazole showed a single endothermic peak at 174.19 and 206 ^{0}C respectively. TMP-SMZ cocrystal from solvent method showed only one endothermic peak at 182.22 °C indicated the formation of new crystalline phase of cocrystal between sulfamethoxazole and trimethoprim.

A single endothermic peak for cocrystal also indicated the absence of any bound solvent (solvate) or water in lattice crystal. The TMP-SMZ physical mixture showed three endothermic peaks at 131.20; 161.67 ^{0}C attributable to fusion of eutectic mixture and at 182.75 °C due to fusion of cocrystal. The exothermic peaks at 140 °C were attributed to recrystallization of mixture from melting. The results of DSC analysis matched with determination of melting point by hot stage microscope polarization, cocrystal from slurry technique had two endothermic peaks at 161.24 and 181.94 °C. The area (enthalpy) of endothermic peak at 161.24 °C was progressively decreased that indicating solid state transformation during slurry of binary mixture of TMP and SMZ.

Powder X-Ray diffraction analysis

PXRD was a powerful method for the characterization of formation of a new crystalline phase in solid state. The diffraction pattern of cocrystal should be clearly distinct from that of the superimposition of each of the compound If a true cocrystal has been formed beetwen two solid phases. PXRD pattern of each of cocrystal formers were exihibit a crystalline solid (Figure 5a-b).

Those had been a characteristic interferences peak at various diffraction angles (2ɵ). PXRD pattern of trimetoprim-sulfamethoxazole PM (Figure 5c), all the characteristics interferences peak of trimethoprim and sulfamethoxazole were observed. X ray single crystal structures of molecular complex sulfamethoxazole and trimethoprim have been reported [13]. (Figure 4) Showed PXRD pattern cocrystal from solvent had a similar pattern to calculated PXRD from X ray single crystal of sulfamethoxazole and trimethoprim. It proved that the cocrystal from solvent method had the same structure as known cocrystal. A different PXRD pattern for cocrystal of trimethoprim and sulfamethoxazole (Figure 5d) from those physical mixtures confirms the formation of a new cocrystal phase. The cocrystal had several

characteristic interference peaks at 2θ = 7.32; 11.5; 16.90; 19.15 and 24.18. The PXRD of slurry product (Figure 5e) showed interference peaks associated with trimethoprim and sulfamethoxazole decrease in intensity while new interference peaks appear. The cocrystalline phase formed by slurry technique exhibited identical powder XRD patterns to those grown from cocrystallization from methanol.

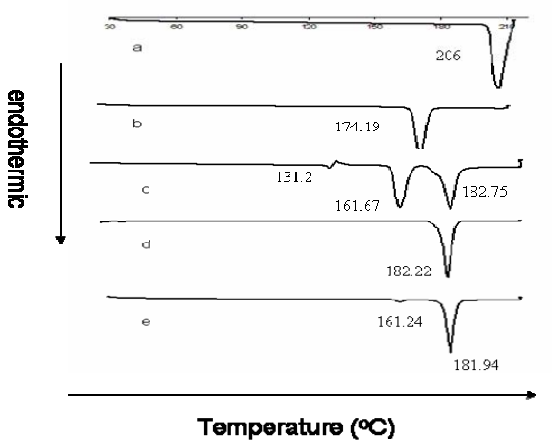

Fig. 3: DSC thermogram a) Intact trimethoprim, b) Intact sulfamethoxazole, c) physical mixture of trimethoprim and sulfamethoxazole, d) cocrystal from solvent method and e) cocrystal from slurry technique

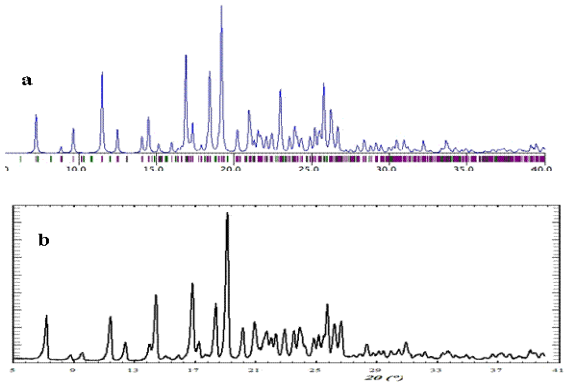

Fig. 4: PXRD pattern a) calculated PXRD of known cocrystal sulfamethoxazole and trimethoprim and b) cocrystal of sulfamethoxazole and trimethoprim from solvent method

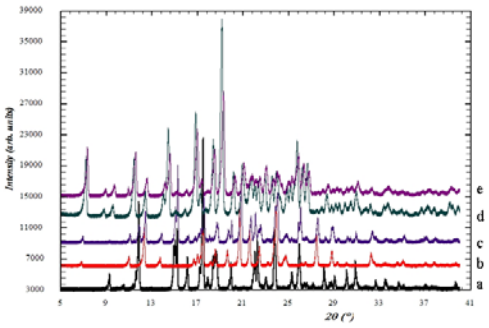

Fig. 5: PXRD patterns a) Intact trimethoprim, b) Intact sulfamethoxazole, c) physical mixture of trimethoprim and sulfamethoxazole, d) cocrystal from solvent method and e) cocrystal from slurry technique

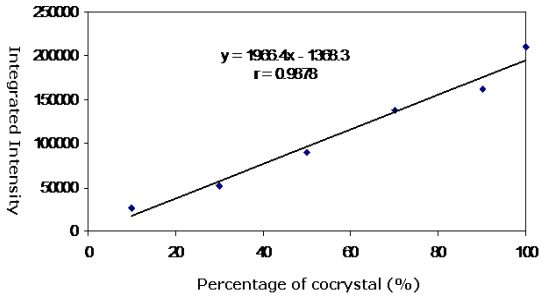

Fig. 6: Calibration curve of percentage cocrystal in binary mixture vs integrated intensity

PXRD calibration curve

The calibration curve for calculating percentage of cocrystalline phase in slurry product was determined based on integrated intensity of interference peaks at 2θ = 7.32. A good linear calibration curve was obtained (Figure 5) by plotting the percentage of cocrystal against the integrated intensity of characteristicinterference peak. *WinPLOTR (version* march *2007)* sofware was used to determining the integrated intensity in PXRD patterns.

Transformation phase studies

Transformation phase to cocrystalline phase in binary mixture of trimethoprim and sulfamethoxazole was performed by suspend the sample powder in 1:1 molar in distilled water and agitate at 75 rpm at various temperature 25 and 37 ^{0}C. The sample was collected at interval time 3, 24, 48 and 96 hours. The percentage of cocrystalline phase in slurry product increased with the prolongation of time storage as shown in Figure 6 and 7. Intensity of interference peak at 2θ = 7.32 was also observed increased by elevation of temperature during slurry technique. The rate of transformation profile was depicted in Figure 7. The slurry-mediated phase transformation was a complex process, due the fact that several mechanisms, such as dissolution of small amount particle, heterogeneous nucleation and then growth of new cocrystalline phase [14-15] The solid state transformation was highly temperature-dependent. The rate of many reactions increased about two to three time with each 10 ^{0}C rise in temperature [16-17].

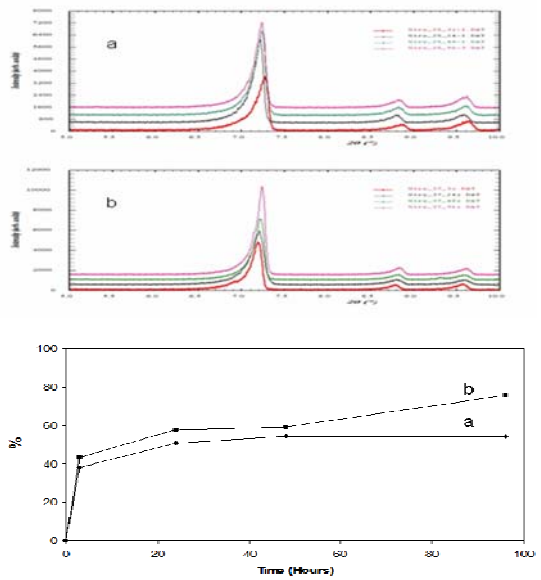

Fig. 8: The rate of transformation profile in slurry experiment at various temperatures a) 25 ^{0}C and b) 37 ^{0}C

CONCLUSION

It could be concluded that slurry technique induced a new equimolar cocrystalline phase between sulfamethoxazole and trimethoprim. The rate of transformation to cocrystalline phase was significantly affected by the temperature of storage.

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