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Original Research Paper

The role of light anhydrous silicic acid on physical stability of troglitazone solid dispersion under humidified conditions

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ABSTRACT

The aim of this study was to confirm whether light anhydrous silicic acid (Aerosil) could exhibit a stabilizing effect on the physical stability of solid dispersion under humidified conditions. Ternary solid dispersions consist of 50% troglitazone, and various ratios of polyvinyl pyrrolidone and Aerosil were prepared using the co-milling method and then evaluated for their crystallizing behavior under storage conditions. The results showed that Aerosil has a stabilizing effect against crystallizing in the dihydrate of troglitazone under humidified conditions and has an appropriate ratio range (Troglitazone/PVP/Aerosil = 50/30–20/20–30) in the ternary solid dispersion, when considering total quality satisfaction such as physical stability and dissolution. Furthermore, it was found that hydrophobized Aerosil R805 has a stronger stabilizing effect than hydrophilic Aerosil 200. The stabilizing mechanism was discussed based on the comparative results and possible molecular interaction.

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1. Introduction

During recent years, since the mainstream of drug discovery shifted to the target-based strategy and high throughput screening technology dramatically improved, these environmental changes provided more high-promise candidates than before. On the other hand, these candidates faced solubility issues and had poor bioavailability, since they were three-dimensionally-designed, had a complicated structure, and high molecular weight. Therefore, to adapt to these circumstances, formulation scientists have been conducting many challenging studies to overcome the solubility issues proactively, such as particle size reduction, solubilization, solid dispersion, and so forth.

Solid dispersions, composed of amorphous drug substance and carriers such as polymer, mesoporous material [1,2] and various silicates [3], were well studied and some of the solid dispersions achieved significant improvement in bioavailability. In addition, recent usability of micro-size filler material such as microcrystalline cellulose and talc was also identified [4]. Furthermore, the number of studies on ternary solid dispersion gradually increased [5–8]. On the other hand, a major challenge still exists in overcoming the physical instability with respect to crystallization leading

to lower bioavailability than expected. Though it is generally thought that solid dispersion with a higher glass transition temperature (T_g) is more stable, a polymer with higher T_g is preferred and the ratio of such polymer in solid dispersion tends to be increased [9]. In addition, the molecular interaction between a drug substance and a polymer, such as a hydrogen bond, is expected in some combinations. Furthermore, for dispersed materials, such as mesoporous material, various silicates and micro-size filler material, the interaction between drug substances and the surface of dispersed material was also discussed. However, it is also well known that solid dispersions stored under the international harmonization accelerate conditions, such as 40 °C and 75% RH, show less stability because of adsorbed moisture which decreases the T_g of solid dispersion as plasticizer. Nevertheless, there are few studies on the improvement methods of physical stability on humidified conditions, except for a packaging approach.

The aim of this study was to confirm whether light anhydrous silicic acid (Aerosil), commonly used in the pharmaceutical industry as flow aid, could exhibit a stabilizing effect on the physical stability of solid dispersion under humidified conditions. We employed the model solid dispersion system composed of troglitazone and polyvinyl pyrrolidone, since it had been reported that amorphous troglitazone changed to the dihydrate when stored at 40 °C and 94% RH for a few days [10]. Furthermore, the stabilizing mechanism against adsorbed moisture was speculated based on the comparative results between hydrophilic Aerosil 200 and hydrophobic Aerosil R805.

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2. Materials and methods

2.1. Materials

Troglitazone (Lot No. NR406, Fig. 1) was manufactured by Daiichi Sankyo Co., Ltd. (Japan) as an oral hypoglycemic agent. The molecular weight is 441.54. The solubility in the buffer from pH 1.2 to 6.8 at 37 °C is less than 1 µg/mL and in pH 9.0 at 37 °C is 41 µg/mL, showing that troglitazone is very poorly water soluble. Polyvinyl pyrrolidone K30 (PVP) was obtained from BASF Japan Ltd. (Japan). Light anhydrous silicic acid (Aerosil 200 and Aerosil R805) was kindly provided from Nippon Aerosil Co., Ltd. (Japan). Aerosil R805 is fumed silica which is obtained by reacting Aerosil 200 with an octylsilane, and shows almost the same physicochemical properties as Aerosil 200 except for the hydrophobicity.

2.2. Preparation

2.2.1. Preparation of solid dispersion

Troglitazone solid dispersions were prepared as a 5 g scale by co-milling with PVP, and Aerosil 200 or Aerosil R805 in accordance with Table 1. The high speed vibrating sample mill (TI-100, CMT Co., Ltd., Japan) was employed. The material and shape of sample containers/rods used were of zirconia and cylindrical shape, respectively. Each component was mixed in a sample container without a rod for 5 min. Then, components were milled for 15 min with a rod followed by cooling in the refrigerator for over 15 min to avoid excessive heating. This process was repeated until the total milling time reached 3 h. All milled powders were screened by passing through a 250 µm sieve to remove aggregates (mean particle sizes are from 3 to 10 µm, no trend of the formulations).

2.2.2. Preparation of humidified solid dispersion

About 100 mg of solid dispersion was placed into a glass vial and stored at 40 °C and 94% RH for 2 h, followed by enclosing the glass vial with a plastic cap tightly.

2.2.3. Preparation of troglitazone dihydrate

Troglitazone alone was milled in accordance with the same procedure described in Section 2.2.1. After sieving and confirming it to be amorphous by PXRD, milled powder was stored at 40 °C and 94% RH for 4 days. The stored powder had the same PXRD pattern of troglitazone dihydrate previously reported and was used as 100% dihydrate [11].

2.3. Characterization

2.3.1. Powder X-ray diffractometry (PXRD)

PXRD of solid dispersion was measured using Empyrean (Panalytical, Netherland) with Cu K α radiation at 45 kV/40 mA. The sample was step-scanned at 0.2° intervals from 5.00° to 40.00° (2-Theta) at the rate of 4.00°/min.

2.3.2. Apparent crystallinity of troglitazone

Troglitazone dihydrate and PVP were mixed with an agate mortar and pestle, followed by sieving through a 250 µm sieve, in order to prepare the calibration curve of crystallinity. The ratio of dihydrate troglitazone in the mixture was 5%, 10%, 20% and 50%. PXRD were measured in triplicate and then areas of the crystalline peaks were calculated with software (High Score, ver. 3.0.1, Panalytical, Netherland). The correlation coefficient and qualified level (QL) of the calibration curve were 0.986% and 6.5%, respectively. Apparent crystallinity was calculated and the crystallinity below QL was defined as 0%.

2.3.3. Differential scanning calorimetry (DSC)

DSC measurement of untreated solid dispersion and humidified solid dispersion was carried out in open aluminum pans and hermetically sealed aluminum pans, respectively, using a Q2000 (TA Instruments, US). Approximately 5–10 mg of sample was accurately weighed. The samples were heated to 10–30 °C above their T_g under nitrogen purge of 100 mL/min to cancel their heat history, followed by cooling to –20 °C. Then the samples were reheated at a rate of 10 °C/min, up to a final temperature of 200 °C. The T_g value was defined as the onset of the transition.

2.3.4. Dissolution test

Dissolution of troglitazone from solid dispersions was measured using Apparatus No. 2 (rotating paddle method) of JP16. The dissolution medium consisting of phosphate buffer (pH 9.0) was maintained at 37 ± 0.5 °C. About 25 mg of hydroxypropyl methylcellulose (HPMC) was added into the medium to inhibit the recrystallization of troglitazone during the dissolution test. Solid dispersion containing 100 mg of troglitazone was added to 500 mL of dissolution medium in a 1000-mL cylindrical vessel. The paddle rotation speed was set to 250 rpm. Dissolution medium was withdrawn at 5 min intervals for 60 min. The concentration of troglitazone in medium was determined using a UV-1600 UV spectrophotometer (Shimadzu, Japan).

2.3.5. Moisture sorption isotherm

Moisture sorption isotherm was measured using a DVS advantage vapor sorption analyzer (Surface Measurement System, UK). The weight change of each sample at 40 °C and 94% RH was collected until no weight change was observed. The condition was controlled by humid air and dry nitrogen purge. Samples were dried at 40 °C and 0% RH for 2 h prior to analysis.

2.3.6. True density

The true density of samples was measured using an Ultratracometer 1000 (Quantachrome Instruments, US) at room temperature. Helium gas was used to calculate the true density. The value of true density was used to calculate T_g of solid dispersion with the Gordon-Taylor equation in Section 3.2.

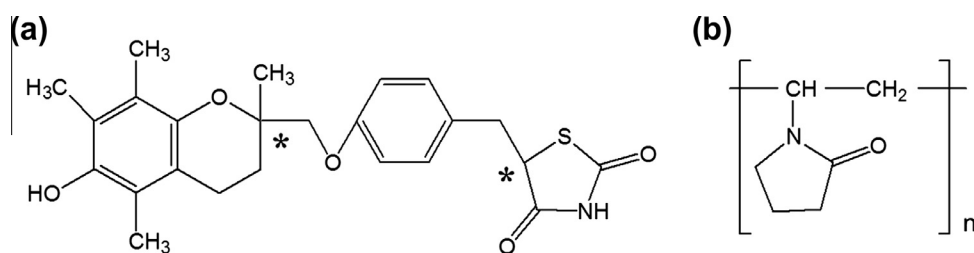


Fig. 1. Chemical structures of (a) troglitazone and (b) polyvinyl pyrrolidone. Asterisks represent asymmetric carbons.

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