Effects of Polyethylene Glycol on the Size of Agglomerated Crystals of Phenytoin Prepared by the Spherical Crystallization Technique

YOSHIKAWASHIMA,* TETSURO HAMADA, HIROYUTI TAKEUCHI and MOTONARI OKUMURA

Department of Pharmaceutical Engineering, Gifu Pharmaceutical University, 5–6–1, Minotanaka-gashi, Gifu 502, Japan

(Received February 17, 1986)

The effects of polyethylene glycol (PEG) 4000 dissolved in the crystallization solvent on the size of agglomerated crystals of phenytoin prepared by the spherical crystallization technique with a bridging liquid (i.e. isopropyl acetate) were investigated. The average diameter of agglomerated crystals at equilibrium, where the rates of growth and destruction of the agglomerates were balanced, decreased linearly with PEG concentration, since the PEG reduced the cohesive force tending to agglomerate the crystals of the bridging liquid by decreasing the interfacial tension and the wettabity of the bridging liquid. Changes in the compaction of the crystal agglomerates and in the kinematic viscosity of the dispersing medium with increasing PEG concentration caused the agglomeration rate to change non-linearly with respect to PEG concentration.

Keywords—phenytoin; spherical crystallization; polyethylene glycol; interfacial tension; contact angle

Introduction

The spherical crystallization technique has been developed by the present authors for obtaining pharmaceutical crystals with improved micromeritic properties, dissolution rate and bioavailability.1) By employing this technique, needle-like crystals of salicylic acid could be transformed into spherical agglomerates with free-flowing and directly compressible properties.2) Spherically agglomerated crystals of aminophylline were produced directly during the reaction of theophylline with ethylenediamine.3) A novel complex of indomethacin and meprazol mine with improved solubility and micromeritic properties was also prepared.4) In our previous study,5) agglomerated crystals of phenytoin incorporating polyethylene glycol (PEG) were prepared with isopropyl acetate as a bridging liquid to improve the bioavailability of the drug. In this process, the bridging liquid preferentially wetted the precipitated crystals and agglomerated them into spherical forms. It was also found that the sizes of agglomerates decreased with increasing concentration of PEG added to the crystallization solvent. The aim of the present study was to elucidate the role of PEG in determining the size of the agglomerate. In this study, the interfacial tension between the bridging liquid and the dispersing medium, the contact angle of the bridging liquid against the crystal, and the viscosity of the dispersing medium were assumed to be the main factors determining the agglomeration behavior in the liquid.6) The effects of PEG in the crystallization medium on those factors were investigated.

Experimental

Materials—Phenytoin (JPX grade) was a gift from Dainippon Pharmaceutical Co., Osaka (Aleviatin, lot PN076). PEG 4000 (Kishida Chemical Co., Osaka) and all other chemicals were of reagent grade.

Preparation of Spherically Agglomerated Crystals of Phenytoin with PEG—Spherically agglomerated crystals of phenytoin with PEG were prepared by means of the same procedure as described in the previous paper.5)
Phenytoin (4 g) was dissolved in 20 ml of 1 N sodium hydroxide at 40 °C. This solution was poured into a mixture of isopropyl acetate (13.5 ml) used as a bridging liquid and 0.07 N hydrochloric acid (280 ml), containing PEG 4000 (PEG). The system was thermally controlled at 20 °C and was agitated at 600 rpm using a turbine type agitator with 6 blades. The average diameter of agglomerated crystals was determined by a sieve analysis.

**Measurement of Physicochemical Properties of the System** — Contact Angle of Isopropyl Acetate against Crystals: The contact angle of isopropyl acetate against crystals of phenytoin in aqueous solutions of PEG was measured. A mixture of 50 ml of PEG solutions of various concentrations (0—20% (w/v)), 100 ml of isopropyl acetate and an excess of phenytoin was kept in a flask for 2 d at 20 °C to attain equilibrium. Undissolved crystals of phenytoin were filtered off, and the aqueous PEG and the organic isopropyl acetate phases were separated and used as media for measuring the contact angle. Raw crystals of phenytoin (2 g) were compressed into a tablet (diameter, 2 cm, porosity 0.1—0.2) at 100 kg/cm² for 1 min, then further compressed at 200 kg/cm² for another 1 min. The contact angle of the isopropyl acetate against this tablet of phenytoin in the aqueous solution of PEG was measured by the hanging drop method. A small drop of the isopropyl acetate (diameter < 0.5 mm) was allowed to rest on the tablet surface in a rectangular glass cell filled with the aqueous solution of PEG. The contact angle of the drop was measured directly with a contact angle meter (CA-A, Kyowa Kagaku Co., Tokyo). The contact angle varied continuously with the penetration of the drop into the tablet. In this study, the extrapolated value at time = 0 was taken as the contact angle, as reported by Köhli and Itou.

**Interfacial Tension between Isopropyl Acetate and the Aqueous Solution of PEG** — The media used in the test were prepared in the same way as those used for the measurement of contact angle. The interfacial tension between the aqueous solution of PEG and the isopropyl acetate was determined by a drop weight method at 20 °C.

**Viscosity of the Crystallization Solvent** — The viscosity of the crystallization solvent was measured by using the Ostwald visco-meter at 20 °C.

**Results**

**The Average Diameter and Surface Topography of the Agglomerated Crystals**

The precipitated crystals of phenytoin were agglomerated simultaneously with the crystallization, and the size of the agglomerates increased with the degree of agitation of the system. The average diameter of the agglomerated crystals of phenytoin at equilibrium, where the agglomeration was completed, is plotted against the PEG concentration in the crystallization solvent in Fig. 1. The average diameter decreased linearly with increasing PEG concentration. The plots of the average diameter of the agglomerates recovered at residence time = 50 min against the PEG concentration did not show a linear relationship, however (Fig. 1). Scanning electron microscopic photographs of the agglomerated crystals prepared with various concentrations of PEG in the crystallization solvent are shown in Fig. 2. While no differences were found in the sizes and the shapes of the constituent crystals of the agglomerate, the surface topography of the agglomerate varied with the concentration of

![Fig. 1. Effect of PEG Concentration in the Crystallization Solvent on the Average Diameter of Agglomerate](image-url)
PEG. At concentrations of PEG \( \leq 0.5\% \) (w/v), the agglomerate was found to be composed of aggregates as shown in Fig. 2(a), (b). When the concentration of PEG was higher than 0.5\% (w/v), the diameter of aggregates in the agglomerate was reduced and the surface of the agglomerate became smooth. With increasing concentration of PEG, the constituent crystals were closely compacted on the surface of the agglomerate as shown in Fig. 2(c)—(f).
The Effects of Polyethylene Glycol on the Physicochemical Properties of the System

The contact angle of isopropyl acetate against crystals of phenytoin in aqueous PEG solution increased with increasing concentration of PEG (Fig. 3). This indicated that PEG decreased the wettability of the crystals by the bridging liquid. The interfacial tension between the bridging liquid and the aqueous solution of PEG decreased linearly with increasing concentration of PEG, as shown in Fig. 4. The kinematic viscosity of the crystallization solvent increased with increasing concentration of PEG, resulting in a decrease of movement of the agglomerated crystals in the crystallization medium (Fig. 5).

Discussion

The size of an agglomerate is determined by the balance between the cohesive force of the bridging liquid tending to agglomerate the crystals and the destructive force applied to the agglomerate due to the external force caused by agitation. The cohesive force of the bridging liquid arises from the interfacial tension between the bridging liquid adhering to the crystal and the dispersing medium, and the wettability of the crystal by the bridging liquid. The inertial force applied to the agglomerate due to the agitation is assumed to be the main destructive force. The findings in Figs. 3 and 4 indicate that the cohesive force of the bridging liquid for the agglomeration decreased with increase of the concentration of PEG in the crystallization solvent. The balance between the cohesive and destructive forces determining the size of agglomerate moved in favor of destruction of the agglomerate with increasing concentration of PEG, leading to a decrease in the size of the agglomerate at equilibrium, as shown in Fig. 1. When PEG was added to the system, the cohesive force of the bridging liquid was reduced, resulting in a decrease in the agglomeration rate. At the concentration of PEG = 5% (w/v), the photographs of agglomerate in Fig. 2 revealed that the elemental crystals were closely compacted in the agglomerate. The reduced cohesive force of the bridging liquid allowed the elemental crystals in the agglomerate to be easily compacted by the external stress. The bridging liquid would be forced to move to the outer surface from the interstices in the agglomerate by the compaction, promoting further agglomeration. Therefore the compaction of the agglomerate was responsible for increasing the agglomeration rate, leading to the
increase in the size of the agglomerate at 50 min in Fig. 1. However, at concentrations of PEG = 5% (w/v), the increased kinematic viscosity (Fig. 5) would reduce the collision frequency of the agglomerates in the vessel and the agglomeration force of the bridging liquid would be further decreased. These two factors would lead to the subsequent decrease in size of the agglomerates at 50 min in Fig. 1.

Acknowledgement The gift of phenytoin from Dainippon Pharmaceutical Co., Osaka (Aleviatin, lot PN076), is gratefully acknowledged.

References