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Preparation of directly compressible powders of a physical mixture and a complex of theophylline–phenobarbital using spray-drying

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Summary

A directly compressible powder of the physical mixture and the complex of theophylline and phenobarbital was prepared directly from droplets using a spray-drying technique. Aqueous or ammonium hydroxide slurries of theophylline and phenobarbital, with colloidal silica or methylcellulose, were atomized by a centrifugal wheel atomizer into a drying chamber held at various temperatures. The products prepared from the aqueous slurry were physical mixtures of theophylline and phenobarbital with a small amount of the molecular complex. From the ammonium hydroxide slurry, the molecular complex containing a small amount of theophylline or phenobarbital was prepared. The parameters affecting the amount of the molecular complex contained in the resultant products were the amounts of excipients, i.e. colloidal silica or methylcellulose, and the composition ratio of theophylline to phenobarbital in the formulation used for spray-drying. Drying temperature also affected the amount of the molecular complex in the products.

Introduction

Spray-drying techniques have been widely used as efficient drying methods for heat-sensitive foods, chemicals and pharmaceuticals due to the rapid evaporation of solvent. One of the recent advances in this technique is the direct preparation of

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solid particulates from liquid droplets by chemical reaction. Crosby and Abdul-Rahman (1973) produced ammonium sulfate spheres by the reaction of liquid droplets of orthophosphoric acid with gaseous ammonia. Takenaka et al. (1982) prepared solid particulates of theophylline–ethylenediamine complex directly from liquid drops. Kawashima et al. (1983) have proposed a significantly improved spray-drying method for the preparation of solid particulates of aminopyrine–barbital complex for tableting, which combined synthesis, drying and agglomeration into one process.

The primary objective of the present study was to prepare directly compressible solid particulates of theophylline–phenobarbital mixtures by means of a spray-drying method. Theophylline is frequently used as a diuretic, cardiac stimulant or a vasodilator agent. Phenobarbital is sometimes co-administered with theophylline to depress the central nervous stimulant action of theophylline. The preparation of directly compressible powder of a theophylline–phenobarbital mixture imparts many advantages to pharmaceutical processing. While attempting to achieve the above goal, it was necessary to investigate the parameters affecting the theophylline–phenobarbital complex formation during spray-drying in order to avoid formation of a theophylline–phenobarbital complex which has been shown to exhibit slower absorption and poorer bioavailability than the physical mixture (Bettis et al., 1973).

Materials and Methods

Spray-drying technique

A uniform aqueous or 2.8% ammonium hydroxide slurry containing 10.5–21 g of theophylline (Wako Junyaku), 9–13.5 g of phenobarbital (Hoei Chemicals), 0–15 g of colloidal silica (Aerosil 200, Japan Aerosil) and 0–2.0 g of methylcellulose (1500 cps, Wako Junyaku) was prepared by agitating the above mixture with a jet-type homomixer (HV-M type, Tokushyukika) for 20 min. The resultant slurry was atomized into a drying chamber held at 90–145 $\pm$ 5°C with a centrifugal wheel atomizer (Iwaki Kikai) driven at 30,000 rpm. The feeding rate of the liquid for atomization was 20–33 ml/min. The dried products were collected by a cyclone collector. The detailed formulations for spray-drying and the various drying temperatures used are tabulated in Table 1.

Measurement of the drug content and identification of the spray-dried products

Theophylline and phenobarbital contents in the products were measured spectrophotometrically (Hitachi model 556 spectrophotometer). Theophylline was determined in distilled water at 280 nm. In 0.1 N sodium hydroxide solution, phenobarbital was determined spectrophotometrically at 256 and 288.3 nm with a double-beam spectrophotometer to cancel the absorption of theophylline. The molar absorptivities at 256 and 288.3 nm are 5.69×10^3 for theophylline and 7.33×10^3 and 418 for phenobarbital, respectively. The standard calibration curve for determination of phenobarbital was represented by Eqn. 1:

$$y = 0.0305x + 0.0022 \quad (1)$$

TABLE 1

FORMULATION FACTORS AND MANUFACTURING CONDITIONS FOR SPRAY DRYING

	Theophylline * (g)	Phenobarbital (g)	Colloidal Silica (g)	Solvent (ml)	Drying Temperature (°C)	Methylcellulose (w/v%)
(1) Type of solvent	21 (2)	13.5	10	Water, 600 2.8% NH_4OH, 600	125 ± 5	–
(2) Amount of excipient (colloidal silica)	14 (2)	9	0, 5, 10, 15	2.8% NH_4OH, 500	125 ± 5	–
(3) Amount of theophylline	10.5 (1), 14 (1.34) 17.5 (1.67), 21 (2)	13.5	10	2.8% NH_4OH, 500	125 ± 5	–
(4) Content of binder (methylcellulose)	21 (2)	13.5	10	2.8% NH_4OH, 500	125 ± 5	0, 0.083, 0.167, 0.330
(5) Drying temperature	14 (2)	9	5	2.8% NH_4OH, 500	90, 110, 125, 145 ± 5	–

* The values in parentheses are the molecular content ratio of theophylline-to-phenobarbital.

where y is the absorption difference at 256 and 288.3 nm and x is the concentration of phenobarbital (μg/ml). Identification of spray-dried products was carried out by infrared (IR) spectrophotoscopy (A-102, Nihon Bunko) and X-ray analyses (JDX Nihon Denshi).

Construction of phase diagram for theophylline–phenobarbital system

The phase diagram for the theophylline–phenobarbital system was constructed using a differential scanning calorimeter (DSC, Rigaku) to determine the proportions of theophylline and phenobarbital of the reference complex for identifying the spray-dried products. Mixtures of theophylline and phenobarbital in various compositions contained in a beaker were gradually heated until a melt was obtained. The melt was allowed to cool to room temperature. The resolidified finely powdered sample was heated with a differential scanning calorimeter (DSC, Rigaku) at a heating rate of 10°C/min.

Results and Discussion

Phase diagram for the theophylline–phenobarbital system

The phase diagram for the theophylline–phenobarbital system was constructed from DSC data as shown in Fig. 1. The phase diagram can be divided into two eutectic systems, having eutectic temperatures of 161 and 243°C. The intermediate maximum at 255°C and 39% weight fraction (corresponding to 0.33 mole fraction) of phenobarbital indicated that the molecular complex having 2 moles theophylline and 1 mole phenobarbital was formed. The phase diagram prepared in the present study coincided fairly closely with that obtained by Guillory et al. (1969). Based on this phase diagram, the reference molecular complex was prepared by a fusion

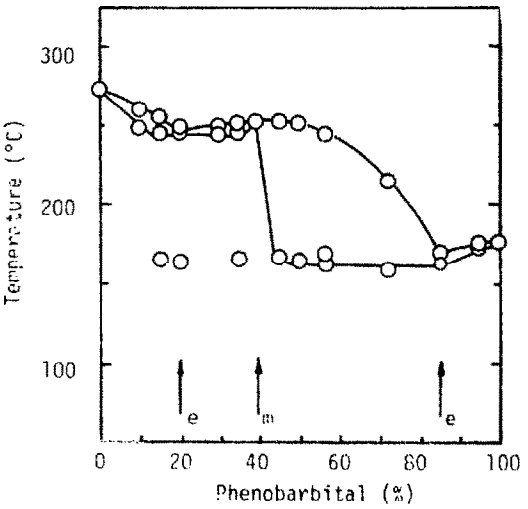

Fig. 1. Phase diagram for theophylline–phenobarbital system constructed from DSC data. e, eutectic point; m, molecular compound.

method for identifying the spray-dried products. The mixture of theophylline (0.0173 mole) and phenobarbital (0.00865 mole) was fused and resolidified by the method described in the Materials and Methods section.

Compressibility and identification of the spray-dried products

All of the spray-dried products obtained through the present work were free-flowing fine powders with spherical form as determined by optical microscopy. All products were directly compressible, whereas the direct tableting of the spray-dried theophylline was impossible because of rough surface topography as investigated previously (Takenaka et al., 1982). The resultant tablets prepared by a single punch machine (KUI type, Erweka G.m.b.H.) were hard enough for practical use (hardness: 5–10 kg by means of a hardness tester (TBT type, Erweka G.m.b.H.). Including colloidal silica into the formulation for spray-drying improved the compressibility of the resultant products, resulting in harder tablets.

The X-ray diffraction patterns of the physical mixture of theophylline and phenobarbital, the molecular complex and the spray-dried products prepared from

Fig. 2.

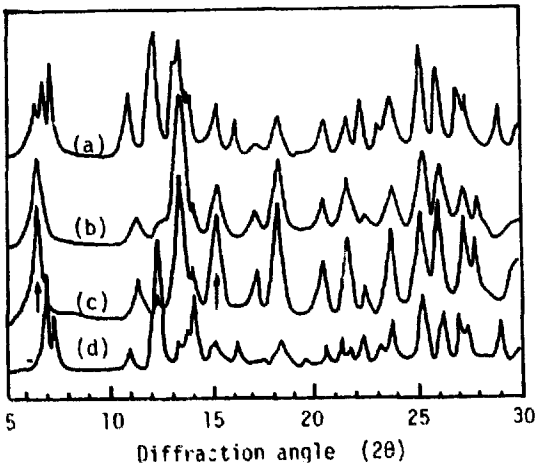

Fig. 2. X-Ray diffraction patterns of various solids containing theophylline and phenobarbital (molecular ratio = 2:1). (a) Spray-dried products from aqueous slurry; (b) spray-dried products from ammonium hydroxide slurry; (c) molecular complex; (d) physical mixture; ↑, represents characteristic diffraction peaks of molecular complex.

Fig. 3.

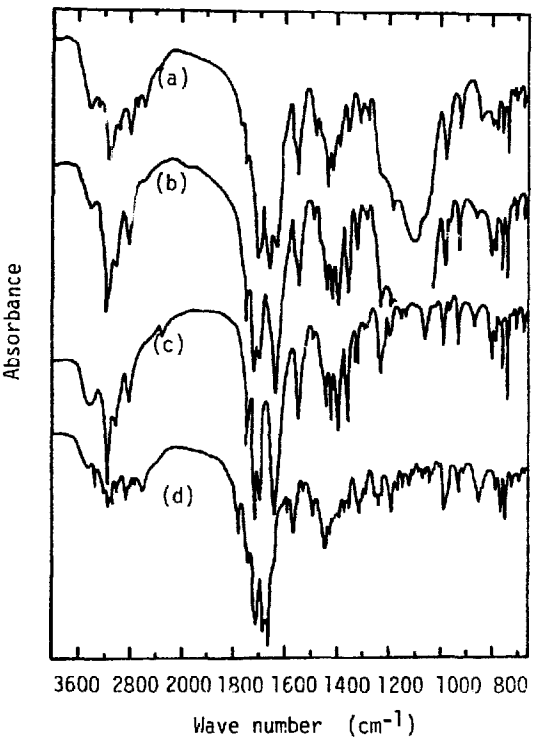

Fig. 3. IR spectra of various solids containing theophylline and phenobarbital (molecular ratio = 2:1). (a) Spray-dried products from aqueous slurry; (b) spray-dried products from ammonium hydroxide slurry; (c) molecular complex; (d) physical mixture.

the aqueous and the ammonium hydroxide slurry of theophylline (17.5 g, 0.097 mole) and phenobarbital (13.5 g, 0.058 mole) are shown in Fig. 2. The pattern of the spray-dried products prepared from the aqueous slurry overlaps that of the physical mixture except for weak diffraction peaks at diffraction angles 6.8° and 15.5°, identifying the molecular complex. This finding suggested that the spray-dried products from aqueous slurry were the physical mixtures of theophylline and phenobarbital with a small amount of the molecular complex, whereas the pattern of the products prepared from the ammonium hydroxide slurry coincided with that of the reference molecular complex. This finding was also confirmed by comparing the infrared (IR) spectra of the spray-dried products with those of the molecular compound and the physical mixture as shown in Fig. 3.

Parameters affecting molecular complex formation

In Table 2 are shown the effects of the colloidal silica contained in the ammonium hydroxide slurry on the contents of the drugs in the spray-dried products. The composition of the spray-dried product collected by the cyclone collector was reasor ably similar to that in the slurries even in the absence of colloidal silica. These results are in contrast to a previous report (Kawashima et al., 1983) in which pyrabital (aminopyrine–barbital complex) was used. In that work, inclusion of excipients such as colloidal silica were necessary to obtain reasonable drug content. Compared with melting points of aminopyrine (107–109°C) and barbital (188–192°C), those of theophylline (270–274°C) and phenobarbital (174–178°C) were rather high. A small amount of melt adhered to the drying chamber wall with the theophylline–phenobarbital system, while considerable amounts of melt were found for the aminopyrine–barbital system presumably due to the lower melting points of the components of the latter system. The molecular content ratio of theophylline to phenobarbital in the spray-dried products from the cyclone collector were found to be larger than 2 as shown in Table 2. The products were a mixture of the molecular complex and theophylline, which was detected by IR spectroscopy and X-ray analyses. The molecular content ratio of theophylline to phenobarbital in the spray-dried products without colloidal silica was higher than that with colloidal

TABLE 2

EFFECT OF AMOUNT OF COLLOIDAL SILICA ON THEOPHYLLINE AND PHENOBARBITAL CONTENT IN THE SPRAY-DRIED PRODUCTS

Amount of colloidal silica in formulation (g)	Theophylline content (%)	Phenobarbital content (%)	Colloidal silica (%)	Molecular content ratio of theophylline-to-phenobarbital
0 (0%)	70 (61)	30 (39)	0 (0)	3.00 : 1
5 (18%)	52 (50)	30 (32)	18 (18)	2.27 : 1
10 (30%)	46 (42)	24 (27)	30 (30)	2.46 : 1
15 (39%)	38 (37)	17 (24)	45 (39)	2.95 : 1

Data in brackets represent theoretical content %.

silica. Unless using colloidal silica, some phenobarbital melts adhered to the drying chamber wall were found since the melting point of phenobarbital was lower than that of theophylline. When increasing amounts of colloidal silica were introduced into the formulation, the molecular content ratio of theophylline to phenobarbital in the spray-dried products decreased from 3.0 to 2.27 and then increased to 2.95. Incorporation of 18 or 30% colloidal silica in the slurry enhanced the collecting efficiency of phenobarbital in the cyclone collector by decreasing the quantity of phenobarbital melt adhering to the drying chamber wall, which increased the content of phenobarbital in the spray-dried products. When 15% colloidal silica was used in the slurry, the ratio of theophylline to phenobarbital again increased, perhaps indicating that colloidal silica carried theophylline more easily than phenobarbital into the cyclone collector. This may be due to the fact that theophylline adheres less strongly to the drying chamber wall than does phenobarbital.

Takenaka et al. (1971) found that incorporation of a binder such as methylcellulose, polyvinylpyrrolidone, carboxymethylcellulose, etc., into the formulation to be spray-dried improved agglomeration of the dried particles. In the present study, the effects of methylcellulose concentration in the formulation on the theophylline–phenobarbital composition of the product obtained upon spray-drying were studied and the results are shown in Fig. 4. The theophylline content in the product was almost constant, irrespective of methylcellulose concentration in the formulation. On the other hand, the phenobarbital content in the product decreased linearly resulting in an increasing molecular ratio of theophylline to phenobarbital in the products (Fig. 4b). The products obtained were a mixture of the molecular complex and excess theophylline, as determined by IR and X-ray analyses.

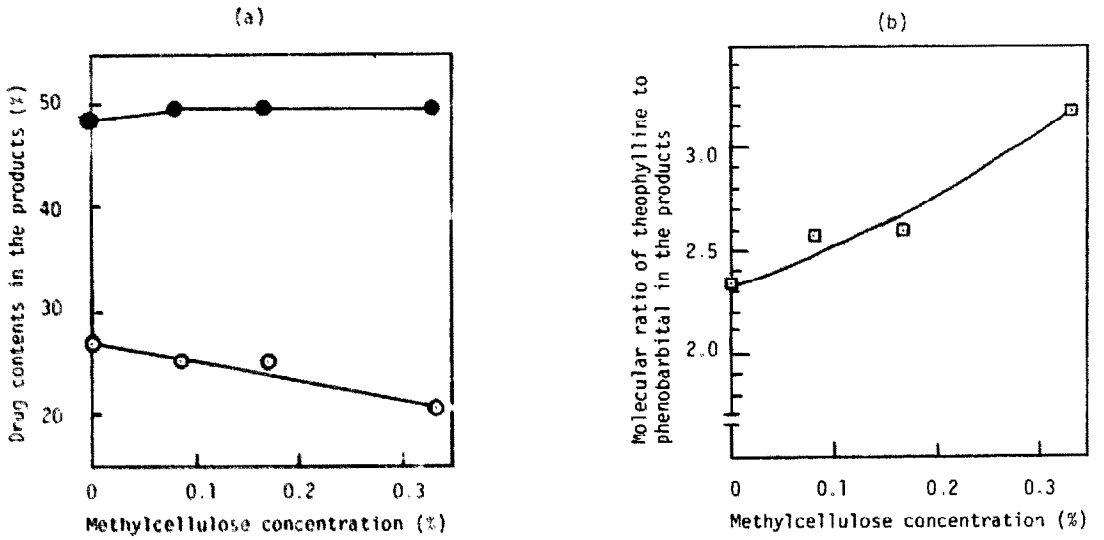

Fig. 4. The effect of methylcellulose concentration on the theophylline and phenobarbital contents in the spray-dried products from ammonium hydroxide slurry. (a) Drug contents in the product (%): ● = theophylline, ⊙ = phenobarbital; (b) molecular ratio of theophylline to phenobarbital in the spray-dried products.

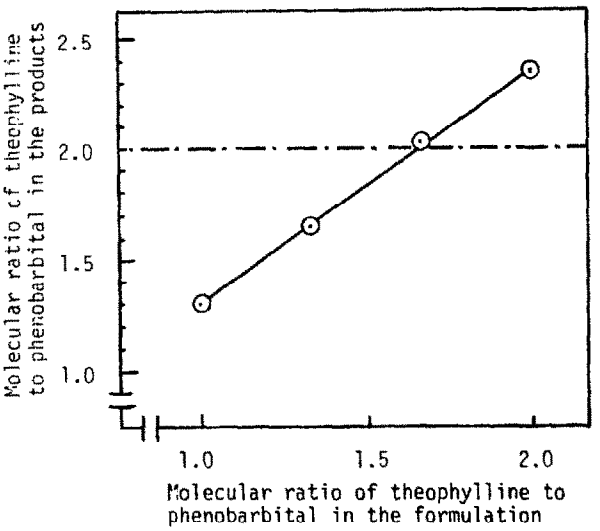

Fig. 5. Relationship between molecular ratio of theophylline to phenobarbital in the spray-dried products and that in the formulation of the slurry (·–·–·, represents ratio in the molecular complex).

The effect of formulation of the ammonium hydroxide slurry on the complex formation was examined by varying the amounts of theophylline and phenobarbital contained in the formulation as shown in Fig. 5. A linear correlation between the molecular ratio of theophylline-to-phenobarbital contained in the spray-dried products and that in the formulation was found. When adjusting the molecular ratio of theophylline-to-phenobarbital to 1.67 in the formulation, only the theophylline–phenobarbital complex was obtained as confirmed by the fact that IR spectra and X-ray diffraction patterns of the products coincided with those (see Figs. 2 and 3) of the

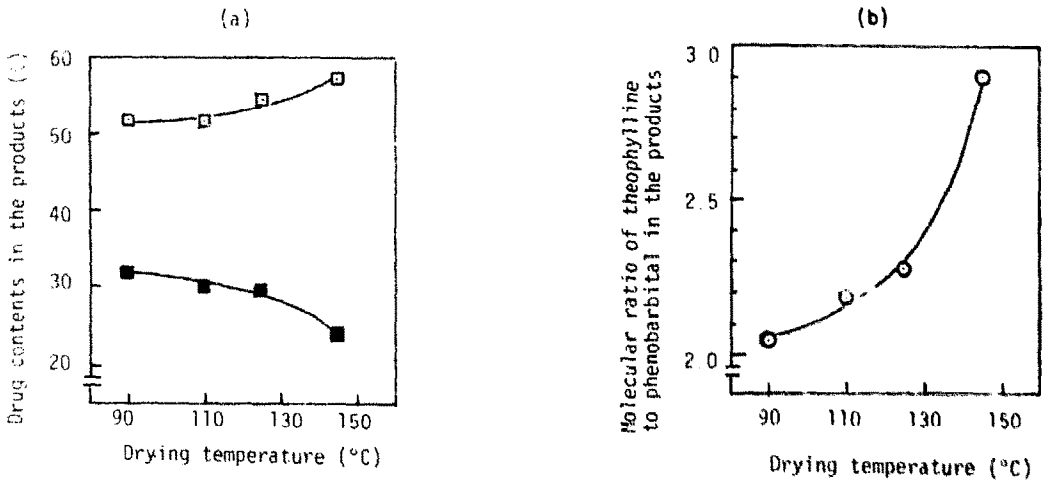

Fig. 6. The effect of drying temperature on drug contents in the spray-dried products from ammonium hydroxide slurry. (a) Drug contents in the products (%): ⊡ = theophylline, ■ = phenobarbital; (b) molecular ratio of theophylline to phenobarbital in the products.

reference complex. When the molecular ratio of theophylline to phenobarbital in the formulation was less or greater than 1.67, the resultant products were the mixture of the molecular compound and phenobarbital or theophylline, respectively, as confirmed by IR spectra and X-ray diffraction analysis.

It was also found that temperature in the drying chamber affected the molecular ratio of theophylline to phenobarbital in the products as seen in Fig. 6. The theophylline content of the spray-dried products increased slightly, while the phenobarbital content decreased with increasing drying temperature (Fig. 6a). As a result, the molecular ratio of theophylline to phenobarbital in the products increased exponentially with the drying temperature (Fig. 6b). When raising the drying temperature, the difference between the temperature in the drying chamber and melting point of phenobarbital decreased, resulting in increasing the amount of phenobarbital melt adhering to the drying chamber wall.

As mentioned above, the formulation factors and manufacturing conditions can be controlled in such a way that the complex could be largely avoided while obtaining the desired spray-dried physical mixture of phenobarbital and theophylline.

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