J. Pharm. Pharmacol. 1987, 39: 769–773
Received February 9, 1987

Enhancement of the dissolution rate of a poorly water-soluble drug (tolbutamide) by a spray-drying solvent deposition method and disintegrants

HIROFUMI TAKEUCHI, TETSUROU HANDA AND YOSHIAKI KAWASHIMA*

Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan

The dissolution rate of a poorly water-soluble drug, tolbutamide, was improved by spray-drying a diluted ammonia solution of the drug containing either a low-substituted hydroxypropylcellulose (L-HPC) or partly pregelatinized corn starch (PCS) as disintegrants. With L-HPC the resultant particles were agglomerates of disintegrant with drug on the surface and within the particles, while particles formed with PCS were composed of a single core of PCS on which the drug was deposited. The deposited drug crystals were very fine because the rapid solvent evaporation restricted crystal growth. The spray-dried particles prepared with PCS had a structure similar to that of an ordered mix. The drug dissolution rate from the spray-dried particles was more rapid than that of the powdered drug alone or with disintegrant and could be attributed to separation of the layer of fine drug crystals from the surface of the particles by swelling of disintegrant. PCS enhanced the drug dissolution rate compared with systems using corn starch. The dissolution rate also depended on the drug content of the particles which was higher than that in ordered mixtures or conventional solvent deposition systems. This system described also had the advantage of avoiding the use of organic solvents.

There is a need to improve the dissolution properties of poorly water soluble drugs to ensure good bioavailability. We have found (Takeuchi et al 1987) that spherical solid dispersions containing amorphous tolbutamide prepared by spray-drying with enteric coating polymers or colloidal silica have good dissolution properties.

A solvent deposition system from which micronized drugs are dispersed on a carrier has also been described (Monkhouse & Lach 1972a, b). That system usually involves the evaporation of an appropriate organic solvent containing a drug and a carrier. Johansen & Moller (1978) claimed that a low drug-to-carrier weight ratio was necessary to give sufficiently increasing dissolution rates of a drug. McGinity & Harris (1980) found that both the drug-carrier ratio and the solvent used in preparing the system caused a variance in the drug dissolution profile. Ordered mixes are another system in which very fine drug crystals are adherent to carriers. It has been reported that, by spreading digoxin or hydrocortisone over a lactose surface using frictional pressure, a trituration with a significantly enhanced dissolution rate was produced which was higher than that of other triturations prepared by simple blending or solvent deposition (Ampolsuk et al 1974). Such a system was characterized as a specific example of the use of ordered mixing by Hersey (1974). Recently, McGinity et al (1985) reported that ordered mixes containing 0·25–1·0% griseofulvin with a carrier showed rapid drug dissolution. Nyström & Westberg (1986) and Westberg et al (1986) also reported the enhancement of the dissolution rate of griseofulvin by the use of ordered mixing, showing that highly soluble carrier materials gave an extremely fast dissolution of the drug. However, the drug weight ratio to carrier in ordered mixing is very restricted, since it is necessary that a single layer of fine drug particles is produced on the surface of a carrier in the system.

The present report shows that a spray-drying technique is a promising way to prepare directly spherical particles loaded with fine drug crystals without using the further processes, e.g. crushing and sieving, that are required for conventional solvent deposition or ordered mix systems. It was also found that the use of an efficient disintegrating agent, e.g. partly pregelatinized corn starch (PCS), as the core material of the system gave the resultant particles good dissolution properties even when the drug-excipient weight ratio was high. Furthermore, tablets prepared from the particles showed a high dissolution rate owing to the rapid disintegration caused by the swelling of the core material.

* Correspondence.

MATERIALS AND METHODS

Material

Disintegrating agents, PCS and L-HPC, used as a core material for spray-dried particles were obtained from Asahi Chemical Industry and Shin-Etsu Chemical, respectively. PCS is a physically modified corn starch, partly pregelatinized, that has good swelling and disintegrating properties. L-HPC is a low-substituted hydroxypropylcellulose that is frequently used as a tablet disintegrant. Tolbutamide was a gift from Hoechst, Japan.

Spray-drying technique

A laboratory spray-dryer, with a drying chamber 1·2 m in diameter and equipped with a centrifugal wheel atomizer (Okawara, L12 type) was used. Tolbutamide (20–40 g) was dissolved in 2% aqueous ammonia and the appropriate amount of disintegrant added to the solution. The solution was fed by a roller pump to the spray-dryer for which the temperatures at the inlet and the outlet of the drying chamber were 125 ± 3 °C and 85 ± 2 °C, respectively; the flow rate of the solution was 1000 mL h^{-1}; and the rotation speed of atomizer was 16 500 rev min^{-1}.

Physicochemical properties

The shape and surface topography of the spray-dried product were observed by scanning electron microscopy (Nihon Densi, JSM-T20). The crystallinity of tolbutamide in the spray-dried particles was tested by X-ray diffractometer (Nihon Densi, JDX). The contact angle was measured as described by Takeuchi et al (1987). Tablet hardness was measured by an Erweka hardness tester.

Dissolution studies

The drug dissolution test was performed according to the Japanese Pharmacopoeia X, using disintegration solution No. 2 (pH 6·8) maintained at 37 °C and the paddle at 100 rev min^{-1}. An amount of sample equivalent to 150 mg of tolbutamide was used for each test. The concentration of drug in the solution withdrawn from the dissolution medium was determined spectrophotometrically at 226 nm.

RESULTS AND DISCUSSION

Physicochemical properties of spray-dried product

Fig. 1(a, b) shows scanning electron photomicrographs of original powder of PCS and L-HPC, respectively, presenting the differences in shape and surface topography. The shape of the disintegrant was found to affect the morphology of the spray-dried particles of tolbutamide and disintegrant. When L-HPC was used, the particles were an agglomerate of disintegrant with drug on the surface and inside the particles. With PCS there was a single core of PCS on which the drug was deposited. These structures were confirmed by comparing the size and surface topography of the particles with those of the original disintegrant powders (Fig. 1). Both the crystal form and the crystallinity of tolbutamide in the spray-dried particles was unchanged according to X-ray diffractometry, but the size of the crystals was reduced because rapid solvent evaporation in the spray-drying process restricted crystal growth. The spray-dried particles with PCS had a structure similar to that of an ordered mix, where the very fine drug crystals adhered to the surface of a core material.

The drug-to-core ratio (1 : 1) was much greater than that of the conventional solvent deposition system or ordered mix system in which a monolayer of drug is formed on the surface of the core particle. The thickness of drug layer formed on the surface of the core in the PCS system may be quantitatively evaluated according to equation (1).

$$((a + b)^3 - a^3)(1 - e)d_1/a^3d_2 = n \qquad (1)$$

where a is the radius of core material, b the thickness of drug layer, e porosity of drug layer, d_1 and d_2 the density of drug and core material, respectively, and n the weight ratio of drug to the core material.

Assuming that $d_1 = d_2$ and $e = 0$, equation (1) becomes

$$(a + b/a)^3 = n + 1 \qquad (2)$$

For the spray-dried particles containing the drug and core material in the ratio 1 : 1, the average thickness of drug layer was estimated to be approximately one quarter of the carrier radius by substituting 1 in n of equation (2).

Drug dissolution from the spray-dried particle

It has been demonstrated that the dissolution rate of powdered tolbutamide is slow while that of spray-dried tolbutamide was not noticeably enhanced (Takeuchi et al 1987). However, dissolution rate of the spray-dried particles containing disintegrants was much improved compared with that of the powdered or spray-dried tolbutamide alone (Fig. 2). The rapid dissolution rates were thought to be due to separation of the layer of fine drug crystals from the surface of the spray-dried particles as a result of swelling of disintegrant. Dissolution of drug from the particles with PCS was superior to that from particles with L-HPC. This could be attributed to the difference in structure of the particles, tolbutamide crystals con-

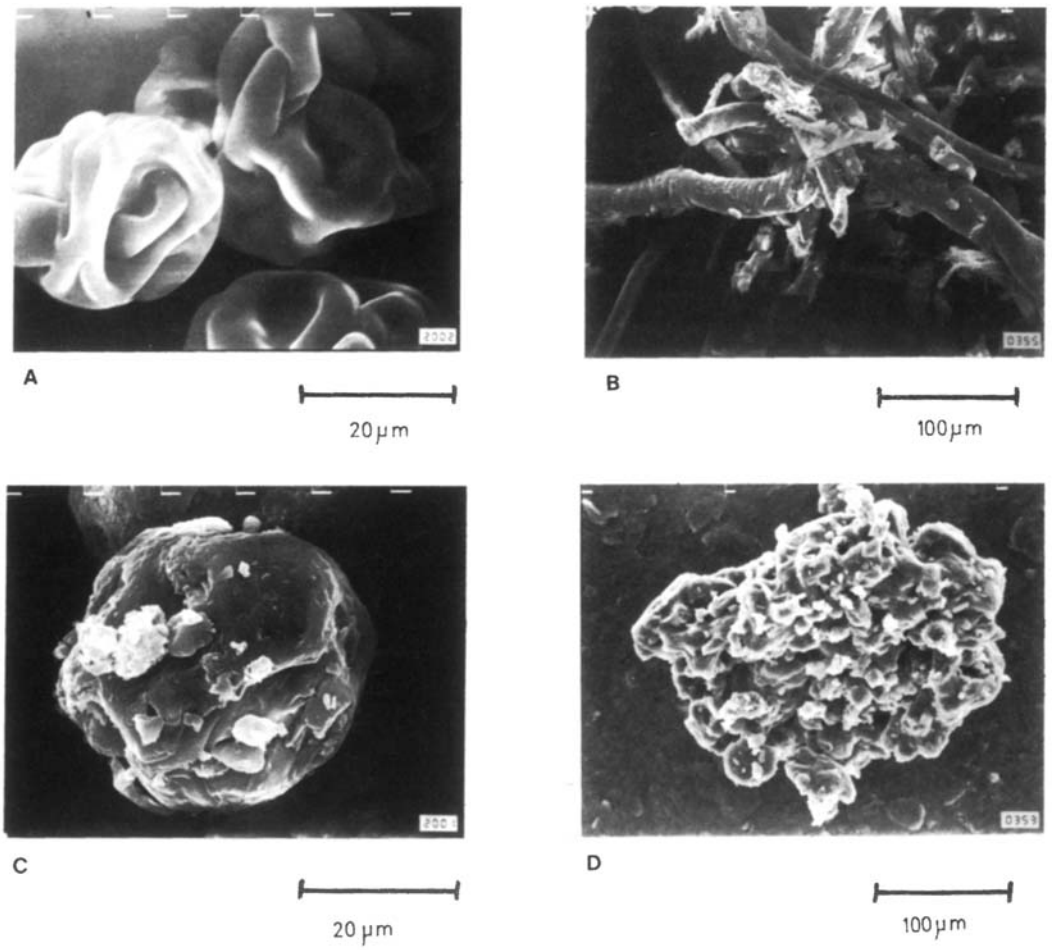

FIG. 1. Scanning electron photomicrographs of original powder of (A) PCS and (B) L-HPC, and spray-dried product with (C) PCS and with (D) L-HPC.

fined in the spray-dried particles with L-HPC not being able to separate from them before the particles disintegrated, while with the particles with PCS all the crystals were localized on the surface of the PCS core.

The dissolution rate decreased with increase in the drug content of the particles (Fig. 3). Takeuchi et al (1987), showed the same trend for spray-dried particles with colloidal silica. In that case, it was concluded that both the increased crystallinity of the drug and decreased wettability with increase in the drug content were responsible for the reduction in drug dissolution rate. But in the spray-dried particles with PCS, tolbutamide was crystallized without amorphism regardless of the drug-to-PCS ratio. It was also found that the spray-dried particles had

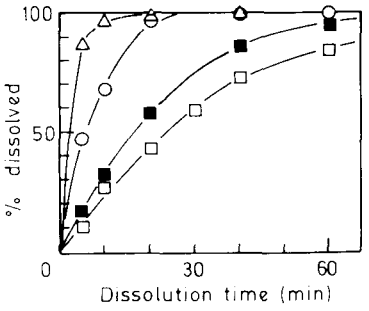

FIG. 2. Drug dissolution patterns of spray-dried tolbutamide with and without disintegrants and powdered tolbutamide in the disintegration solution No. 2 (pH 6·8) specified in the JP X. Key: △, spray-dried particles with L-HPC; ○, spray-dried particles with PCS; ■, spray-dried tolbutamide; □, powdered tolbutamide.

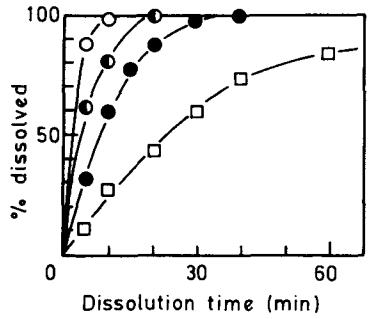

FIG. 3. Effect of drug content of the spray-dried particles on the drug release rate from the particles. Drug: PCS, ○, 1:1; ◐, 2:1; ●, 5:1. □, powdered tolbutamide.

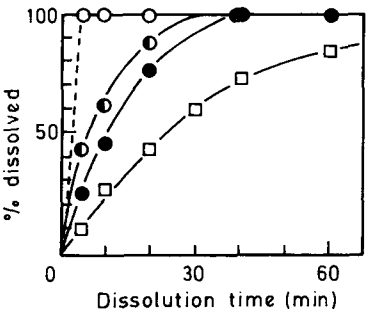

FIG. 4. Effect of drug content of the spray-dried particle on the drug release rate from the tablet prepared from the spray-dried particles. Drug: PCS: ○, 1:1; ◐, 2:1; ●, 5:1. □, powdered tolbutamide.

good wettability, although the contact angle of water to the particles was not determined exactly. The decrease in dissolution rate with increase in drug content was attributed to the increase in the thickness of drug layer formed on the surface of the core material. Coarser discrete particles were produced from the thicker layer of drug separated from the core resulting in a decrease in the surface area of released drug, with a consequent retardation of the dissolution rate. Swelling of the core material, PCS, in the spray-dried particles was also depressed because of the increase in the thickness of the drug layer.

Drug release from a tablet prepared with the spray-dried particles

All spray-dried particles could be directly tableted regardless of the drug-to-disintegrant ratio. The hardness of the tablets (Table 1) also seem to be independent of that ratio. The hardness of tablets of each spray-dried product was greater than that of the physical mixture of drug and disintegrant in the same ratio. There was rapid drug release from the tablets prepared with the spray-dried particles and it depended on the drug-to-disintegrant ratio (Fig. 4). As all tablets disintegrated in the dissolution medium within a few minutes, the release rate was assumed to be determined by the dissolution rate of the spray-dried particles. The release rate was also much greater than that from the tablets prepared from PCS and original powder of tolbutamide (Fig. 5). This relatively slow release was not attributed to the hardness of tablets which disintegrated as rapidly as those prepared from spray-dried particles, rather it was attributed to the larger crystals of tolbutamide in the tablets.

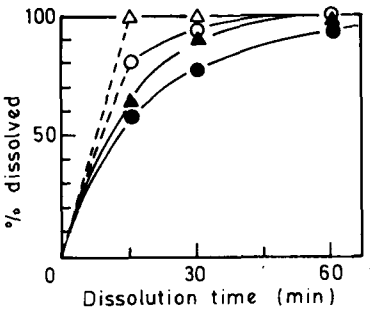

FIG. 5. Comparison of drug release rate from tablets prepared from the spray-dried particles (open symbols) with that from tablets prepared from a physical mixture of the drug and disintegrant (closed symbols). Disintegrant: ○, ●, L-HPC; △, ▲, PCS. Drug: disintegrant is 1:1 in each formulation.

Table 1. Hardness of tablets of spray-dried products and physical mixtures.

Formulation drug: PCS	Hardness (kg)	
	Spray-dried product	Physical mixture
1:1	5·8–7·8	4·2–5·3
2:1	6·8–7·5	3·8–5·0
5:1	4·8–6·3	4·1–5·3

Effect of the type of core material on drug dissolution rate

The usefulness of PCS as a core material for the spray-dried particles was proved by comparison with corn starch, which is a raw material of PCS and is widely used as a disintegrant. Fig. 6 shows the drug release patterns of powdered and tableted spray-dried particles, which indicate that the drug release rate from the spray-dried particles containing corn

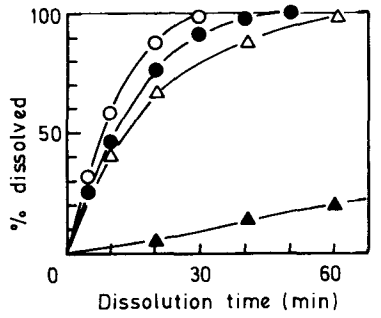

FIG. 6. Comparison of drug release rate from the particles (open symbols) or tablet (closed symbols) of spray-dried tolbutamide with different disintegrants. Disintegrant: ○, ●, PCS; △, ▲, corn starch. Drug : disintegrant is 5 : 1 in each formulation.

starch was slower than that from particles with PCS and also that the tablets containing corn starch did not disintegrate.

Conclusion

A spray-drying technique with solvent deposition markedly improved drug release from particles prepared with PCS as disintegrants. The drug crystals constituting the outer layer of the spray-dried particles were very fine, because crystal growth was limited by the rapid solvent evaporation in the spray-drying process. The amount of drug associated with the particles in this system was higher than that following conventional solvent deposition or an ordered mix system. The particles could be prepared without organic solvent and in a continuous process.

Acknowledgement

The authors thank Prof. A. Otsuka, Maijo University, Nagoya, Japan for the use of the X-ray diffractometer and SEM. We also thank Miss Y. Manabe and Mr W. Nakamoto for technical assistance.

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