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Effect of drug content and drug particle size on the change in particle size during tablet compression

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Three size fractions for each of three poorly soluble drugs were compressed into 10 mm diameter tablets of four different dilution ratios. The compression was carried out on a physical testing instrument at four compression levels of 49·0, 98·1, 196·2 and 294·3 MN m^{-2}. The effect of drug content and drug particle size on the change in particle size during tableting was examined by the determination of the dissolution rate for disintegrated tablets. A linear relation was obtained when plotting ln(T80%) versus drug content. There was a critical particle size where the phenomena of cleavage and bonding during tableting balanced each other, but this varied with drug content.

Recently Kitamori & Makino (1979) found it possible to elucidate the change in particle size in a tablet during compression by comparing the dissolution rate for disintegrated tablets with that for suspensions or granules containing the same amounts of drug.

The purpose of this paper is to investigate the effect of drug particle size and drug content on the pressure-dependent dissolution of tablets by the method reported.

MATERIALS AND METHODS

Materials

Three poorly soluble drugs, chloramphenicol (Takeda Chemical Ind., Ltd), phenacetin (acetophenetidine) (Yamamoto Kagaku Co.), and prednisolone (Uclaf Inc., France) were used. The crystalline material used as such is termed "coarse" powder the hammer-milled material is termed "regular" powder and the recrystallized material is termed "fine" powder. The recrystallization was effected by pouring a solution of the drug in a water-soluble solvent into water. The mean particle sizes of drugs for logarithmic size distribution were obtained from data derived from a series of measurements of 200 particles by means of an optical micrometer (Table 1).

Lactose (D.M.V., Holland) used as a diluent and hydroxypropyl cellulose (HPC-L, Nihon Soda Co.) used as a binder were both of J.P. grade.

Method of preparation

Lactose was employed to adjust the drug content to 1, 10, 30 and 50%. The binder was used at 3% by weight of dry base in the final granules.

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Table 1. Mean particle sizes (μm) of three size fractions of each drug.

	Coarse	Regular	Fine
Chloramphenicol	150	26·5	1·0
Phenacetin	120	26·0	7·5
Prednisolone	—	25·0	≈1·0

The wet granulation method used to make granules was as described by Kitamori & Makino (1979) as was compression of granules without disintegrants and the pressures used (49·0, 98·1, 196·2, 294·3 MN m^{-2}).

Dissolution rate measurement

The dissolution profiles were obtained by a modification of the U.S.P. method described by Kitamori & Makino (1979) using the same amounts as in that paper.

RESULTS AND DISCUSSION

The dissolution curve of a tablet is usually S-shaped in the presence of disintegration factors. As we reported in the previous paper, dissolution profiles are basically similar for both disintegrated tablets and for granules since dissolution occurs simultaneously from discrete particles produced after disintegration. Thus, a change in particle size alone can effectively be distinguished by this method.

All the dissolution data of granules before compression and disintegrated tablets are summarized in Table 2. T50% and/or T80% (the time necessary for 50 and/or 80% dissolution) were employed to represent each dissolution pattern.

Table 2. Dissolution data (T50% and T80% min) of granules and disintegrated tablets (compressed at 98·1 MN m^{-2}) of three poorly soluble drugs at four levels of drug content (1, 10, 30, and 50%).

		Granules								Disintegrated Tablet (98·1 MN m^{-2})							
		1%		10%		30%		50%		1%		10%		30%		50%	
		T50	T80	T50	T80	T50	T80	T50	T80	T50	T80	T50	T80	T50	T80	T50	T80
Chloramphenicol	C*	2·0	4·3	2·0	4·2	1·8	4·2	1·8	3·8	0·8	2·5	0·8	2·3	0·5	1·8	0·5	1·8
	R**	0·5	0·8	0·5	0·8	0·5	0·8	0·5	0·8	0·5	0·8	0·5	0·8	0·5	0·8	0·8	1·0
	F***	0·7	1·0	0·8	1·0	0·8	1·0	0·8	1·0	0·5	1·0	0·5	1·0	0·5	1·0	0·5	1·0
Phenacetin	C	6·0	13·0	6·0	13·0	6·0	13·0	6·0	13·0	1·7	5·3	2·2	6·0	2·5	6·5	3·5	8·0
	R	1·2	3·3	1·0	3·2	1·2	3·2	1·2	3·3	0·7	2·0	1·0	2·2	1·0	2·3	1·7	4·2
	F	0·7	1·0	0·8	1·0	0·8	1·0	1·0	1·7	0·5	1·0	0·5	1·0	1·3	3·0	2·0	5·7
Prednisolone	C																
	R	2·2	9·0	2·2	9·5	2·2	9·5	2·2	9·5	1·2	3·8	1·0	4·5	1·5	5·5	2·5	10·5
	F	0·5	0·8	0·5	0·8	1·0	2·2	1·4	2·6	0·7	1·0	0·7	1·0	0·8	1·5	1·5	4·5

* Coarse powder ** Regular powder *** Fine powder

Effect of drug content

Fig. 1 shows the change in dissolution rate (T80%) against the content of the drug in a disintegrated tablet for the three particle size fractions. The tablets were compressed at 98·1 MN m^{-2}. There is little or no effect of compression pressure on the 1 and 10% formulations for all three particle size fractions. However, the dissolution rate slows with the 30 and 50% drug formulations of phenacetin and prednisolone. Also the smaller the particle size of the drug, the more severely does the drug content affect the dissolution.

A linearity obviously exists for ln(T80%) versus drug content for three size fractions of phenacetin (Fig. 2). The deviation of the plot for the 1% formulation of fine phenacetin is probably due to the limitation of the dissolution rate measurement since fine phenacetin may dissolve completely within 1 min. The effect of drug content on dissolution can be interpreted as follows; lactose particles between drug particles inhibit the drug aggregation due to compression stress. Therefore, the lower the drug content, the less effect the compression pressure exerts on the aggregation or rebonding.

Effect of initial particle size

Fig. 3 shows the effect of the compression pressure on the dissolution rate (T80%) of the disintegrated tablets of phenacetin. In Fig. 3c it is seen that an increase in compression pressure causes no fragmentation or aggregation of fine drug particles at 1 and 10%. At 30 and 50%, however, the dissolution rate is significantly slowed by increase in compression pressure. This suggests aggregation of fine particles occurred during compression. With coarse phenacetin crystals (Fig. 3a), the dissolution rate increases with increase in compression pressure over the entire concentration range. It can be assumed that fragmentation is the predominant phenomenon during compression in this instance. However, rebonding appears to occur, since the

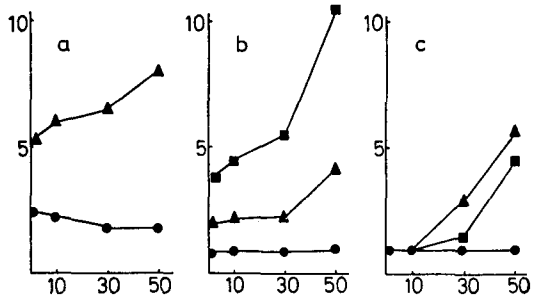

FIG. 1. Effect of the drug content on the dissolution rate of disintegrated tablets (compressed at 98·1 MN m^{-2}) of chloramphenicol (●), phenacetin (▲) and prednisolone (■). a—coarse powder, b—regular powder and c—fine powder. Ordinate: T80% (min). Abscissa: drug content (%).

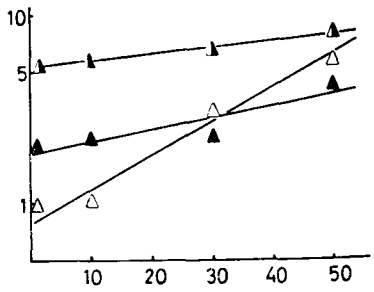

FIG. 2. Ln(T80%) versus drug content for three size fractions of phenacetin. △—coarse powder, ▲—regular powder and △—fine powder. Ordinate: T80% (min). Abscissa: drug content (%).

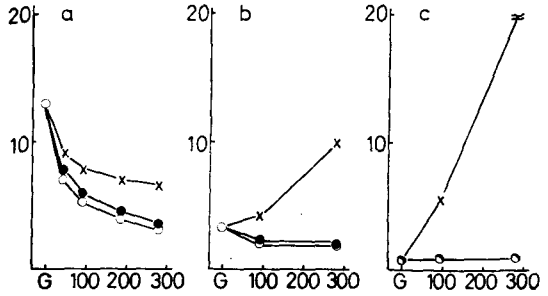

FIG. 3. Effect of compression pressure on the dissolution rate for disintegrated phenacetin tablets of different drug content. a—coarse powder, b—regular powder and c—fine powder. ○—1% of drug content. ●—10% of drug content. ×—50% of drug content. Ordinate: T80% (min). Abscissa: compression pressure (MN m^{-2}).

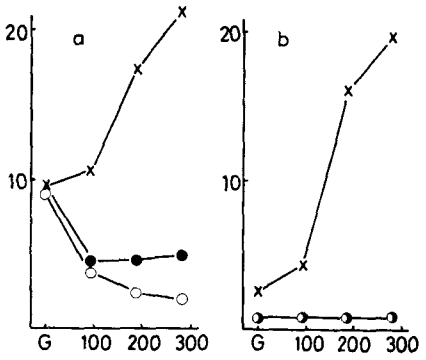

FIG. 4. Effect of compression pressure on the dissolution rate for disintegrated prednisolone tablets of different drug content. a—regular powder and b—fine powder. ○—1% of drug content. ●—10% of drug content. ×—50% of drug content. Ordinate: T80% (min). Abscissa: compression pressure (MN m^{-2}).

relative increase in dissolution rate with an increase in compression pressure in the 50% drug formulation is smaller than with the 1 and 10% formulations as shown in Fig. 3a. Regular powder of phenacetin behaves intermediately. In the 1 and 10% formulation the dissolution rate increases slightly with increase in compression pressure. At 30 and 50%, however, the dissolution rate decreases with an increase in compression pressure.

Fig. 4 shows the effect of the compression pressure on the dissolution rate of the disintegrated tablets of prednisolone. The effect of compression pressure on the dissolution behaviour is almost the same as with phenacetin.

Carless & Sheak (1976) have stated that there is a critical size where the phenomena of bonding and cleavage balance each other. In our results coarse phenacetin crystals were crushed as the compression pressure increased in the 30 and 50% formulations, and regular and fine powders aggregated as the compression pressure increased. Therefore, it is clear that there must be a critical particle size where the effects of crushing and bonding cancel each other. However, the equilibrium particle size varies with the drug content. When the drug content is low, the critical particle size whould be small since the particle cleavage is predominant, while when the drug content is high, the critical particle size would become larger since the rebonding phenomenon is no longer negligible.

The preparation initially containing fine particle size drug does not always dissolve more rapidly than the preparation initially containing coarse drug. The large particles will be broken down under stress to fill the voids, while the small drug particles will be forced together. Thus the drug content and compression pressure to be applied must be considered in order to maximize dissolution behaviour when formulating a tablet of a poorly soluble drug.

REFERENCES

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