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Evaluation of changes in drug particle size during tableting by measurement of dissolution of disintegrated tablets

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Three poorly soluble drugs (chloramphenicol, phenacetin and prednisolone) were compressed into tablets of 10% drug content on a physical testing instrument at three different compression pressures. The dissolution profiles were determined by a modification of the U.S.P. method for drug suspensions, granules before compression, disintegrated and intact tablets. By comparison of the dissolution rates for disintegrated tablets with those for granules before compression, or suspensions, it is possible to separate the change in particle size during compression from the pressure-dependent dissolution behaviour of intact tablets. A comparative measurement of dissolution for disintegrated tablets with that for granules provides a useful method for elucidating the particle bonding or cleavage within the tablet during compression.

The effect of the compression pressure on the dissolution of drugs from tablets has been widely studied (Levy et al 1963; Ganderton et al 1967; Polderman & Braakman 1968; Van Oudtshoorn et al 1971; Hirshorn & Kornblum 1971; Khan & Rooke 1976). However, the results are confusing. Levy et al (1963), for example, reported that increasing precompression pressure caused an increase in rate of dissolution of salicylic acid from tablets. With tablets of a quinazolinone compound, Hirshorn & Kornblum (1971) found a decrease in dissolution rate with increasing compression pressure. More complex relations between dissolution rates of drugs from tablets and compression pressure were noted by Ganderton et al (1967) and Polderman & Braakman (1968).

Smith et al (1971) suggested that one of the more logical interpretations of these data was in terms of the dependency of dissolution upon changes in particle size or specific surface area during tablet compression. Thus, when particle bonding is predominant during compression, dissolution rate should slow and when particle cleavage is predominant, dissolution rate should increase. Their observation was that the ratio of bonding to cleavage would not be linearly related to the compression force.

Their interpretation is essentially true, but simplified, because the effect of disintegration rate on the tablet dissolution was not taken into account and disintegration time is also a factor in tablet dissolution.

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Tablet dissolution has been suggested as being a sequential process of the disintegration of tablets into granules or primary particles and the dissolution of drugs from them (Wagner 1971). Thus, the compression pressure effect on the dissolution of an intact tablet consists of the change effected by compression on disintegration time and on the state of particles (bonding or cleavage). The effect of disintegration time cannot easily be separated from the dissolution profile of an intact tablet. The measurement of the dissolution profile of tablets without interference from disintegration factors would clarify some changes in the state of particles induced in a tablet by compression pressure.

The purpose of this paper is to demonstrate through the dissolution test for disintegrated tablets that it is possible to separate the change in the particle state during compression from the pressure-dependent dissolution behaviour of tablets.

MATERIALS AND METHODS

Materials

Three poorly soluble drugs of different water solubilities were chosen (mean particle sizes): chloramphenicol (26·5 μm) (Tekada Chemical Ind.), phenacetin (acetophenetidine) (26·0 μm) (Yamato Kagaku Co.), and prednisolone (25·0 μm) (Uclaf Inc., France). Lactose (D.M.V., Holland) used as a diluent and hydroxypropyl cellulose (HPC-L, Nihon Soda Co.) used as a binder were of J.P. grade respectively.

Method of preparation

Lactose was employed to adjust the intragranular drug content to 10%. The binder was always used at 3% by weight of dry base in the final granules.

Each drug was mixed with lactose and moistened with aqueous HPC-L solution in a mortar. The moistened powder was massed with a pestle so that the particle size of drug would not be altered, and passed through a 32-mesh sieve. The granules were then dried in a vacuum (55°C) and passed again through a 32-mesh sieve.

Compression of granules without disintegrants and lubricants was carried out on a physical testing instrument (Autograph IS-5000, Shimazu Seisakusho Ltd.) with 9 mm flat-faced punches and die. Before each compression, the die wall and punch faces were dusted with magnesium stearate powder as a lubricant. Granules weighing 250 mg were compressed at each time at a constant strain rate of 5 mm min^{-1}. Tablets were compressed at three pressure levels: 98·1, 196·2 and 294·3 MN m^{-2}.

One tablet each for phenacetin and prednisolone, and two tablets for chloramphenicol were disintegrated in 3 ml of water before the dissolution measurement.

Suspensions were prepared in 10 ml of 1% aqueous solution of HPC-L and contained 250 mg of each drug powder. These were agitated with a ultrasonic probe for 3 min and subjected to the dissolution test.

Dissolution rate measurement

The dissolution profiles of intact and disintegrated tablets as well as drug suspensions and granules were measured by a modification of the U.S.P. method. A magnetic stirrer was used to agitate the dissolution medium instead of the rotating basket of the U.S.P. method. The agitation rate was regulated to 300 rev min^{-1} by a tachometer generator (Toyo Seisakusho Co.). Samples were assayed continuously by monitoring their characteristic uv absorbance with the aid of a proportioning pump and were then returned to the flask at a flow rate of approximately 2·9 ml min^{-1}. One litre of distilled water maintained at 37°C was used as the dissolution medium.

Respective amounts of samples, corresponding to 50 mg of chloramphenicol, 25 mg of phenacetin and prednisolone, were used in the dissolution studies for drug suspensions, granules, and disintegrated and intact tablets. Apparent sink conditions were maintained throughout the dissolution test since the quantity of drug used was less than one tenth of its solubility.

RESULTS

All the dissolution data for drug suspensions, granules before compression, disintegrated tablets and intact tablets are summarized in Table 1. T50% and/or T80% (the time necessary for 50 and/or 80% dissolution) were employed to represent each dissolution rate. Examples of dissolution profiles for drug suspensions, granules, disintegrated tablets, and intact tablets of phenacetin are given in Fig. 1. The change in dissolution rate (T80%) with increasing compression pressure for the three drugs is shown in Fig. 2.

Table 1. The dissolution data (time in min) for drug suspensions, granules before compression, disintegrated tablets, and intact tablets (compressed at 98·1 MN m^{-2}) of three poorly soluble drugs.

Drug suspensions		Granules before compression		Disintegrated tablets		Intact tablets	
T50	T80	T50	T80	T50	T80	T50	T80
Chloramphenicol							
0·5	0·8	0·5	0·8	0·5	0·8	7·5	11·5
Phenacetin							
1·0	3·0	1·0	3·2	1·0	2·2	8·7	12·5
Prednisolone							
2·2	8·0	2·2	9·5	1·0	4·5	11·0	15·8

DISCUSSION

Dissolution behaviour of drug suspensions and granules before compression

Granules before compression and suspensions of the three drugs show no significant difference in their dissolution rates (Fig. 1, Table 1). This in-

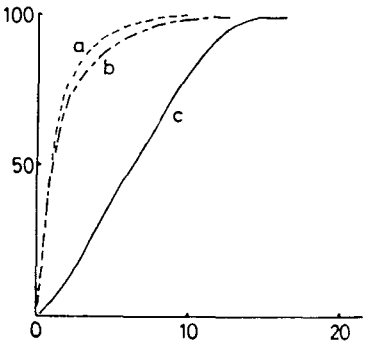

FIG. 1. The dissolution profiles (ordinate: % dissolved) for drug suspensions, granules before compression, disintegrated tablets, and intact tablets of phenacetin. Abscissa: time (min). a—disintegrated tablets, b—suspensions and granules before compression, c—intact tablet having disintegration time of 11·3 min.

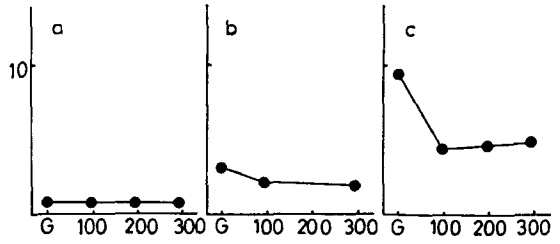

FIG. 2. The effect of compression pressure on the dissolution rate of disintegrated tablets of three poorly soluble drugs. a—chloramphenicol, b—phenacetin, c—prednisolone. Ordinate: T80% (min). Abscissa: compression pressure (MN m^{-2}).

dicates that the particle size of drugs in the granules did not change during granulation. The fact also indicates that the disintegration process of granules is negligible. Drug particles in granules are readily wetted during the dissolution test since the hydroxypropyl cellulose binder acts as a wetting agent. The rate of disintegration of granules slows with high concentration of hydroxypropyl cellulose as a binder, because of this it was used at 3% by weight of dry base in the final granules (Machida & Nagai 1974).

Dissolution behaviour of disintegrated and intact tablets

Change in particle size distribution during compression have been studied by Cid & Jaminet (1971), Khan & Rhodes (1975) and Carless & Sheak (1976). Disintegrated tablets were used in their studies for the determination of change in particle size produced by the compression process. We carried out dissolution tests on disintegrated tablets to exclude disintegration factors from the effect of compression pressure on the dissolution behaviour of tablets. The dissolution test for an intact tablet can evaluate an overall pressure effect on tablet dissolution. However, the evaluation of the compression effect on the particles alone is impossible by measuring dissolution of intact tablets, since their dissolution profile includes disintegration factors which are also pressure-dependent. Thus, change in particle size during compression can only be clarified by the comparative measurement of dissolution of disintegrated tablets with granules.

The dissolution profile of a tablet was S-shaped probably due to the influence of the disintegration rate of the tablet. On the other hand, the disintegrated tablet showed the same basic shape profile as that of drug suspensions or granules (Fig. 1). The disintegration rate of granules can also be negligible in this case. Tablets were broken and 32-mesh granules were subjected to the dissolution test. The same result was obtained as with the disintegrated tablets. This fact indicates that the disintegration rate of granules is negligible. It was therefore confirmed that the dissolution method with broken tablets, thereby eliminating the disintegration factors, is effective as a tablet dissolution test.

Change in particle size during compression

The difference in particle size before and after compression can be observed by comparing the dissolution profiles for drug suspensions or granules with those for disintegrated tablets but not with those of intact tablets. From Fig. 1 and Table 1 it is seen that the dissolution rate for disintegrated tablets of chloramphenicol does not differ from that of its suspensions. On the other hand, the dissolution rates for disintegrated tablets of phenacetin and prednisolone are more rapid than those of suspensions. These results mean that, from the point of view of dissolution, a change occurred in particle size during compression of phenacetin and prednisolone but not of chloramphenicol. However, the measurement of dissolution for intact tablets does not reveal whether the change in particle size in tablets during compression has occurred, since the dissolution profiles for intact tablets are different from those of suspensions due to the interference of disintegration factors.

The change in dissolution rate (T80%) of disintegrated tablets with increasing compression pressure for all drugs is shown in Fig. 2. The dissolution rate for disintegrated tablets of chloramphenicol remains constant with increasing compression pressure but for phenacetin and prednisolone the dissolution rate increased initially with application of compression pressure but there was practically no change after.

The phenomena of bonding and cleavage during compression could be considered to occur in these experiments. The result for chloramphenicol may indicate either that an overall change is insignificant, i.e., a dynamic equilibrium of bonding and cleavage is established or that the particle size change during compression cannot be detected by measurement of dissolution. Although the initial particle size of all drugs is about the same, the less the solubility of drugs, the greater the change in dissolution rate when the compression pressure was applied.

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