J. Pharm. Pharmac., 1975, **27**, 765–770 *Received March* 6, 1975

Effects of hardness on the disintegration time and the dissolution rate of uncoated caffeine tablets

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The effects of hardness on disintegration and dissolution characteristics of uncoated caffeine tablets made at eight different pressure levels were studied. The disintegration times were determined using the J.P. VIII procedure with disks and the dissolution rate measurements were performed with the U.S.P. XVIII procedure (U.S.P. method) and the J.P. VIII disintegration test apparatus (J.P. method). A good correlation between the hardness and the disintegration times was obtained. The dissolution rate constants were determined from the equation of Noyes & Whitney (1897) and a good correlation between the hardness and the dissolution rate constants was obtained. The hardness governed the dissolution over all the stages from tablet to the smallest particles after the breakage by disintegration. The dissolution rates of the J.P. method were greater than those of the U.S.P. method.

The bioavailability of a drug in tablet form is closely associated with the preparation's disintegration time and dissolution rate. Levy (1961) demonstrated, that after the administration of five commercial aspirin tablets to man the *in vivo* absorption of the drug was proportional to the *in vitro* dissolution rate, but not to the disintegration time. Middleton, Davies & Morrison (1964) showed that either disintegration time or dissolution rate can provide a useful estimate of the physiological availability of riboflavin sugar-coated tablets. Symchowicz & Katchen (1968) reported that the plasma concentrations of griseofulvin were correlated with the dissolution rate of this drug from the formulation. Similar conclusions were reached by Fraser, Leach & others (1973) with digoxin preparations.

A good correlation between hardness and disintegration time was obtained by Higuchi, Narsimha Rao & others (1953) for sulphathiazole tablets. Jacob & Plein (1968) found that an increase in hardness resulted in a decrease in the dissolution rate of phenobarbitone tablets but they found no correlation between dissolution rate and disintegration time.

We have undertaken to elucidate the relation between hardness, disintegration time and dissolution rate for eight different uncoated caffeine tablets.

MATERIALS AND METHODS

Materials

All materials were obtained from commercial sources and complied with Japanese Pharmacopoeia VIII (J.P.) requirements.

Preparation of uncoated caffeine tablets

Fifteen g of hydroxypropyl cellulose (HPC) were dissolved in 100 ml of ethanol and mixed uniformly with 485 g of lactose in a mortar. The wet mass was dried at room

temperature until a powdered preparation was obtained. A mixture of caffeine (5% w/w), talc (0·6% w/w), magnesium stearate (1·4% w/w), potato starch (3% w/w) and the lactose containing HPC (90% w/w) was mixed well in an Erweka mixer model KB 15S and then sifted through a No. 60 Japan Industrial Standard (JIS) sieve. The mixture was compressed into 10 mm diameter tablets with an Erweka model EK-O tablet machine. To obtain various hardness levels, eight different compression pressures were used, a hundred tablets being made at each level of the pressure. Hardness was measured by a Monsanto Hardness Tester (Fairchild & Michel, 1961). The tablet weights were all 0·3 g within normal limits.

Disintegration test procedures

The J.P. method of tablet disintegration testing, which is essentially the same as that of the United States Pharmacopeia XVIII was applied to each tablet batch using a Toyama Sangyo model T-2S disintegration test unit. The immersion fluid used in the test was the first fluid in the J.P. method, which contains 2·0 g of sodium chloride and 24 ml of 10% v/v of hydrochloric acid in 1000 ml, the pH being 1·2. Testing was carried out at 37°. The stirring frequency was 32 strokes min^{-1}, amplitude 55 mm. At least six replicate determinations were made.

Dissolution test procedures

The dissolution rate of caffeine from tablets was determined using the U.S.P. rotary basket method (Toyama Sangyo model TR-3S). An aliquot of 1000 ml of the first J.P. fluid was used as the dissolution medium, and the U.S.P. procedure was followed.

The dissolution rate was also measured in the J.P. disintegration apparatus to find the dissolution rate under the same stirring conditions as in the disintegration procedure. This procedure has been arbitrarily called the J.P. dissolution method in the present study. One tablet was placed in one of the six tubes of the basket, and 3 ml of the medium were sampled at measured times, through a pipette plugged with cotton. The same quantity of the medium was added immediately after each sampling to keep the volume of the dissolution medium constant during the course of the test.

The concentration of dissolved caffeine in the medium was determined spectrophotometrically at 270 nm with a Hitachi spectrophotometer, model 124.

RESULTS

Table 1 shows the hardness and disintegration time of the uncoated caffeine tablets made at the eight different compressive pressures with ranges in parentheses. An increase in hardness increased the disintegration time of the preparations. As illustrated in Fig. 1, the regression line of the logarithm of the disintegration time on the hardness, calculated following the method of least squares, was log DT = 0·08046 HD + 1·75963, where DT is the disintegration time and HD is the hardness of the tablet. The correlation coefficient, r, was 0·961.

The dissolution patterns obtained by the U.S.P. method are presented in Fig. 2. All plots are the average of at least three determinations. The curves follow the same pattern in both of the methods, but the dissolution time by the J.P. method is less than that by the U.S.P. method by a significant amount for all the preparations.

The equation for the dissolution of substances proposed by Noyes & Whitney (1897) was

$$dC/dt = k(C_s - C) \quad \ldots\ldots\ldots\ldots \quad (1)$$

Table 1. *Hardness, disintegration time and dissolution characteristics of each uncoated caffeine tablet with the U.S.P. and the J.P. methods.*

Product	Hardness* (kg)	Disintegration time**†	U.S.P. method			J.P. method		
			t_i†§	k_1‡§	k_2‡§	t_i†§	k_1‡§	k_2‡§
A	0·5 (0·4–0·6)	53 (50–55)	137	11·32	43·96	51	17·63	77·86
B	2·5 (2·2–2·8)	115 (106–126)	138	10·98	44·20	62	12·86	65·84
C	2·9 (2·5–3·0)	103 (80–117)	106	10·39	36·12	a	a	a
D	7·0 (6·8–7·5)	208 (205–215)	167	5·48	14·79	a	a	a
E	9·4 (9·3–9·5)	213 (206–226)	202	5·67	31·71	214	6·11	36·25
F	10·5 (10·0–11·0)	601 (593–610)	348	3·04	11·83	a	a	a
G	12·3 (12·0–13·0)	491 (453–528)	397	3·64	17·79	361	4·29	22·90
H	12·9 (12·6–13·1)	675 (655–690)	496	2·24	5·21	a	a	a

* All six tablets were determined by Monsanto Hardness Tester.
** All six tablets were determined by the J.P. VIII procedure.
† Values s.
‡ Values $\times 10^3$ s^{-1}.
§ All values are the mean of three determinations.
a did not determine.

where C_s is the concentration of the solute at saturation, C is the solute concentration at time t, and k is a dissolution rate constant. Equation (1) may be integrated to give

$$\ln C_s/(C_s - C) = kt \quad .. \quad .. \quad .. \quad .. \quad (2)$$

Plots of $\ln C_s/(C_s - C)$ versus t might be expected to yield a straight line with slope k. Such a plot is shown for a tablet with a hardness of 2·5 kg in Fig. 3. Two straight regression lines are obtained in all cases. As indicated in Fig. 3, the time at which the two regression lines intersect is called t_i, the slope of the first being k_1 and that of the second k_2. Values of these are also listed in Table 1.

A linear relation between the hardness and the logarithm of t_i was obtained for both the U.S.P. and the J.P. methods. The equation of these regression lines were $\log t_i = 0{\cdot}04769\ HD + 1{\cdot}98747$ for the U.S.P. method with $r = 0{\cdot}920$ and $\log t_i = 0{\cdot}07372\ HD + 1{\cdot}64173$ for the J.P. method with $r = 0{\cdot}989$.

In the relation of t_i to the disintegration time, the slope of the regression line of the

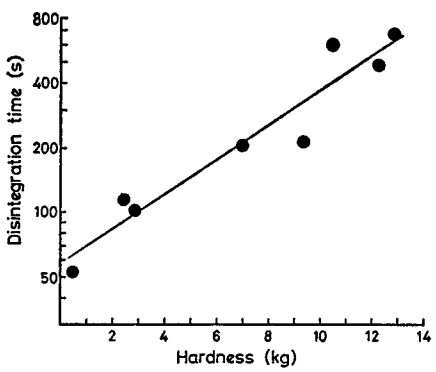

FIG. 1. Effect of hardness on disintegration time of uncoated caffeine tablets. The hardness of each product was determined by Monsanto Hardness Tester. Measurement of disintegration time was carried out by the J. P. method.

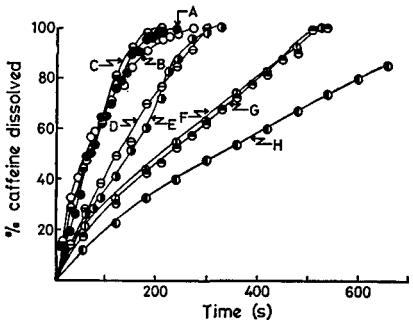

FIG. 2. Dissolution patterns of the uncoated caffeine tablets of different hardnesses employing the U.S.P. method of dissolution test. The dissolution medium used was the first fluid (pH 1·2) of the J.P. disintegration test. All plots are the average of three determinations. A, B, C, D, E, F, G, and H stand for the products in Table 1.

plots obtained by the J.P. method was 0·74 which is closer to 1·0 than is the value of 0·57 for the U.S.P. method.

A linear correlation between hardness and k_1 was also found. In both of the methods k_1 decreased with increasing hardness of the tablets. The regression line for the U.S.P. method is $k_1 = -0{\cdot}00076\ HD + 0{\cdot}01213$ with $r = -0{\cdot}956$, and for the J.P. method $k_1 = -0{\cdot}00108\ HD + 0{\cdot}01619$ with $r = -0{\cdot}977$.

A proportional relation between hardness and k_2 was obtained, the regression line for the U.S.P. method being $k_2 = -0{\cdot}00276\ HD + 0{\cdot}04575$ with $r = -0{\cdot}870$, and for the J.P. method $k_2 = -0{\cdot}00456\ HD + 0{\cdot}07885$ with $r = -0{\cdot}999$.

A similar linear correlation was also found in a plot of k_1 against k_2. The regression lines were $k_1 = 3{\cdot}81624\ k_2 = 0{\cdot}00053$ for the U.S.P. method with $r = 0{\cdot}939$ and $k_1 = 4{\cdot}08558\ k_2 + 0{\cdot}00895$ for the J.P. method with $r = 0{\cdot}992$.

DISCUSSION

Caffeine is a weak base with a pKa value of 0·8 and is fairly well-absorbed from the stomach, obeying the pH-partition hypothesis (Shore, Brodie & Hogben, 1957; Schanker, Shore & others, 1957), therefore it seemed reasonable that the disintegration and the dissolution properties of the tablets should be investigated under simulated stomach conditions. For this reason, the first fluid (pH 1·2) in the J.P. disintegration test was chosen for these experiments.

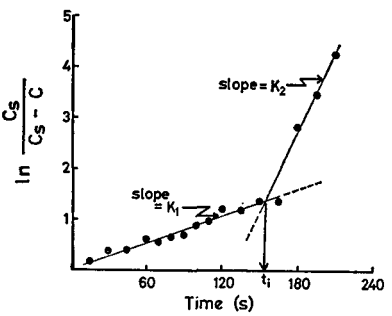

FIG. 3. A plot to determine dissolution rate constants of the uncoated caffeine tablets using the Noyes & Whitney (1897) equation. The figure presents one of three determinations for the tablet B having a hardness of 2·5 kg. Essentially similar curves were obtained for tablets of all hardnesses in both the J.P. and the U.S.P. dissolution test.

In the experiments of Noyes & Whitney (1897), the available surface area of substance for dissolution remained constant during the course of the experiments. However, the dissolution rate constants of an uncoated caffeine tablet changed from k_1, which was relatively small, to k_2, which was much larger than k_1, at a certain time t_i in all the experiments. Applying Fick's law, Brunner (1904) equation (1) may be rewritten as

$$dC/dt = DS/Vh \,.\, (C_s - C) \quad .. \quad .. \quad .. \quad (3)$$

where D is the diffusion coefficient of the solute in the dissolution medium, S is the available surface area for dissolution, V is the volume of dissolution medium and h is the thickness of the diffusion layer. Since D/Vh was constant under the conditions employed in these experiments, it seems that the change from k_1 to k_2 at a time t_i is due to a change in the surface area. An explosive increase in the surface area seemed to occur at time t_i. This was due to breaking of the tablet into small particles.

Although a good correlation between the disintegration time and t_i was observed for all tablets, from the fact that the slopes of the regression lines were not 1·0, it follows that the times were not equal: t_i was less than the disintegration time. Both the pharmacopoeias define the disintegration time as a time after which no particle of tablet remained on the screen of the basket of the disintegration apparatus. It seems reasonable to assume that the tablet broke up at time t_i, but that the resultant particles were not small enough to pass through the screen, and only after a certain time of dissolution had elapsed, or another breakage of the particles into smaller ones had occurred, could the disintegration time be observed. This speculation was supported by the work of Higuchi & others (1953) who found a relation between the disintegration time and the compressional force in sulphathiazole tablets. Thus the factor which changed the dissolution rate constant from k_1 to k_2 would be tablet breakdown. The slope of the regression line obtained by the J.P. method was 0·74 which was closer to 1·0 than that of the U.S.P. method; the difference could be caused by the greater degree of agitation of the dissolution medium.

The inverse correlation between the hardness of the tablet and initial dissolution rate constant, k_1, is due to the fact that, as Higuchi & others (1953) showed, the density of the tablet increased with increasing hardness and, at the same time, the porosity decreased so that the dissolution medium could not penetrate the tablet. The dissolution of the drug occurs only from the surface of the tablet and the rate constant for dissolution would correlate with the hardness of the tablet at this stage of the dissolution. A good correlation was also observed between the hardness and the dissolution rate constant, k_2, which was the rate constant of dissolution of the drug after the breakage of the tablet into small particles.

Wagner & Pernarowski (1971) found that the dissolution rates using the disintegration apparatus were generally greater than those obtained using the U.S.P. method. Saito, Suzuki & others (1974) demonstrated these differences in a comparative dissolution study of commercial tablets using the U.S.P. and the J.P. methods. The differences were thus due to the effectively greater degree of agitation in the J.P method relative to the U.S.P. method.

It is also suggested that the initial hardness of the tablet still influenced the dissolution rate constant of the drug from the disintegrated particles which were small enough to pass through the screen of the basket of the disintegration apparatus, so that the hardness affects the dissolution of the tablet over all the stages of dissolution.

Since the dissolution rate constant is k_1 at $0 \leqq t \leqq t_i$ and k_2 at $t_i \leqq t \leq t_s$, the limited integration equation of equation (1) was written as

$$\int_{C=0}^{C \to C_s} dC/(C_s - C) = \int_{t=0}^{t=t_i} k_1 \, dt + \int_{t=t_i}^{t \to t_s} k_2 \, dt \quad .. \quad .. \quad .. \quad (4)$$

$$[\ln C_s/(C_s - C)]_{C=0}^{C \to C_s} = [k_1 t]_{t=0}^{t=t_i} + [k_2 t]_{t=t_i}^{t \to t_s} \quad .. \quad .. \quad .. \quad (5)$$

where t_s is the time required for 100% of the solute to dissolve. The maximum value of C is $C_s - 0{\cdot}001$, because the values of C and C_s are in practice, the reading of the spectrophotometer, that is, the extinction. The left side of equation (5) may be written as $1n\ C_s/C_s - (C_s - 0{\cdot}001) = 1n\ C_s/0{\cdot}001 = 2{\cdot}303 \log (C_s \times 10^3)$

$$= 2{\cdot}303 \log C_s + 6{\cdot}909 \quad .. \quad .. \quad .. \quad .. \quad (6)$$

Since the right side in equation (5) is the maximum value when the left side is the maximum value, equation (5) may be expressed as

$$6{\cdot}909 + 2{\cdot}303 \log C_s = k_1 t_i + k_2 t_s - k_1 t_i \quad .. \quad .. \quad .. \quad (7)$$

therefore

$$(6{\cdot}909 + 2{\cdot}303 \log C_s - k_1 t_i + k_2 t_i)/k_2 = t_s \quad .. \quad .. \quad .. \quad (8)$$

or

$$[6{\cdot}909 + 2{\cdot}303 \log C_s + t_i (k_2 - k_1)]/k_2 = t_s \quad .. \quad .. \quad .. \quad (9)$$

As mentioned above, t_i, k_1 and k_2 are functions of hardness, so that if the hardness and C_s of the tablets are determined, t_s, k_1 and k_2 will be obtained following the equations derived above. These procedures for obtaining t_s would be useful for performing a quality control of compressed dosage forms of drug.

These observations are valid only for the particular uncoated caffeine tablets prepared in our laboratory. A more extensive investigation is necessary to prove the validity of such observations for all types of formulation.

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