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A comparison of the dissolution rates of caffeine tablets in a rotating-basket with those in a Sartorius dissolution tester

SHIKIFUMI KITAZAWA*, IKUO JOHNO, TOKUZO MINOUCHI, YOKO ITO AND JUTARO OKADA

Department of Pharmacy, Kyoto University Hospital, Kawara-cho, Shogoin, Sakyo-ku, Kyoto, Japan

Uncoated caffeine tablets of four different hardnesses were tested for dissolution rate by the Sartorius (S.S. method) and by the rotating basket method of the U.S.P. XVIII. In both methods the dissolution rate decreased with increasing hardness, and the rate obtained with the S.S. method was always less than that by the U.S.P. method. This result cannot be explained as being due only to the difference in the volume of dissolution medium. Also it was difficult to ensure that the characteristic changes in the process of dissolution paralleled the curves obtained from a plot of % caffeine dissolved *vs* time. Accordingly, the dissolution rate constants were calculated from the slope of each straight line in a plot of ln $W^{\infty}/(W^{\infty} - W)$ *vs* time.

Without correlation of *in vitro* with *in vivo* data, the dissolution profiles of solid dosage forms obtained by dissolution testing are of use only for formulation or quality control. Efforts have therefore been directed towards the design of a tester that would give conditions more akin to those in the gastrointestinal tract (Nelson, 1958; Souder & Ellenbogen, 1958; Levy, 1963; Baun & Walker, 1969; Langenbucher, 1969; Gibaldi & Weintraub, 1970). On the other hand the United States Pharmacopeia adopted an *in vitro* method devised by Pernarowski, Woo & Searl (1968) which uses a rotary basket.

Another type of dissolution tester which was named the Sartorius Simulator (S.S. method) has been reported by Stricker (1969, 1970, 1971). *In vitro* dissolution profiles using this method were reported by several investigators (Saito, Suzuki & others, 1974; Kitazawa, Maeda & others, 1975b). However, significant differences in the results obtained between the U.S.P. method and S.S. method were not apparent in plots of the percentage of an active ingredient dissolved against time which is the usual way of presenting such results.

Previously Kitazawa, Johno & others, (1975a; 1977) have described another method of treating the results of dissolution measurements. This allows elucidation the differences in dissolution profiles and additional dissolution information may be obtained.

MATERIALS AND METHODS

Dosage form

The dosage form used was uncoated caffeine tablets prepared as described by Kitazawa & others (1975a). Hydroxypropylcellulose (HPC) (15 g) were dissolved in 100 ml of ethanol and mixed well with lactose (485 g) in a mortar. The wet mass was dried at room temperature until a thoroughly powdered preparation was obtained. To this was added caffeine (5% w/w), talc (1·6% w/w), magnesium stearate (0·4% w/w), and potato starch (3% w/w). The whole was mixed in an Erweka mixer model KB 15S and then passed through a 60-mesh Japan Industrial Standard (JIS) sieve. The true density of this uniformly mixed preparation was 1·57 g cm^{-3}, as measured with a Beckman air comparison pycnometer model 930 (Beckman-Toshiba Ltd.).

The mixture was compressed into 10 mm diameter tablets with an Erweka model EK-0 tablet machine. To obtain various degrees of tablet hardness, four different compression pressures were used and approximately 100 tablets were made at each pressure. Hardness was determined using a Monsanto Hardness Tester. The weights of the tablets were all 0·3 g within the normal range of the J.P. (VIII) (0·3 ± 0·015 g) and their densities were significantly greater than 1·0 at all hardnesses.

Dissolution test procedures

U.S.P. method. The rotary basket method of the U.S.P. (XVIII) was followed, using a Toyama Sangyo model TR-3S at a rotational speed of 150 rev min^{-1}. One tablet was placed in the basket, and 3 ml of the medium was sampled at given times through a pipette plugged with cotton-wool (Saito & others, 1974). A replacement quantity of the medium was added immediately after each sampling to keep the volume of the dissolution medium constant during the experiment. The dissolution medium was

* Correspondence.

1000 ml of the disintegration measurement solution of the J.P. (VIII) (an aqueous solution containing 2·0 g of sodium chloride and 24 ml of 10% v/v hydrochloric acid in 1000 ml, pH 1·2). Testing was at 37°.

Modified rotary basket method (M.R.B. method). The method of the U.S.P. was followed, but with modifications in the volume of the dissolution medium and in the size of the container for the dissolution medium. A tablet was placed in the rotary basket of the type used in the U.S.P. method; the position of the basket was adjusted so that it was wholly immersed in 100 ml of the dissolution medium in a beaker equipped with two glass baffles, the width of the baffles being about 20% of the beaker diameter. The sample volume was 2 ml; other procedures were the same as those of the U.S.P. method.

Sartorius Simulator method (S.S. method). A Sartorius dissolution tester, model SM 167 51, was used. Glass beads and 100 ml of the disintegration measurement solution of the J.P. were placed in the solution chamber, and after the temperature reached 37°, testing was started. The sampling volume and the sampling interval were 2 ml and 1 min respectively, and all of the samples in the fraction collector were analysed spectrophotometrically.

At least three replicate determinations were made in all cases, concentrations of dissolved caffeine in the medium being determined spectrophotometrically at 270 nm.

Determination of the dissolution rate constants of the tablets

The dissolution rate constants of the tablets were determined by the methods used by Kitazawa & others, (1975a; 1977) applying the Noyes & Whitney equation (1897b). Plots were made of $\ln W^{\infty}/(W^{\infty}-W)$ against time, W being the weight dissolved at any time and W^{∞} the eventual final amount dissolved.

RESULTS

The dissolution profiles obtained with three kinds of dissolution testers for tablets having a hardness of 2·9 kg is shown in Fig. 1. The dissolution rate in the U.S.P. method was the fastest and that of S.S. method was the slowest. Plots of $\ln W^{\infty}/(W^{\infty}-W)$ versus time for the results illustrated in Fig. 1 to obtain the dissolution rate constants are shown in Fig. 2a: each graph is made up of two straight lines.

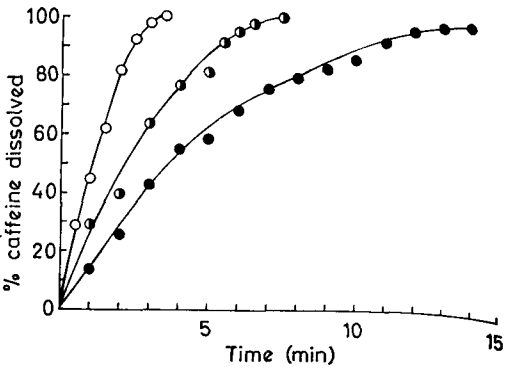

FIG. 1. Dissolution patterns of uncoated caffeine tablets having a hardness of 2·9 kg employing three kinds of dissolution testers. The dissolution medium used was the first fluid (pH 1·2) of the J.P. disintegration test. ○—U.S.P. method, ◑—M.R.B. method, ●—S.S. method.

As was concluded previously by Kitazawa & others (1975a), the initial straight line corresponded to the stage when dissolution was occurring from the surface of the tablet and the final straight line corresponded to dissolution from the surfaces of particles of disintegrated tablet. The slopes of these lines give the dissolution rate constant of caffeine in the corresponding stage and the intersection indicates the disintegration time of the tablet.

The initial dissolution rate in the U.S.P. method was faster than that in the S.S. method, and the disintegration time of the tablet was longer in the S.S. method than in the U.S.P. method, in which disintegration occurred at about 2 min. On the other hand, the correlation of the intersection to the disintegration was not seen with the S.S. method, since the container for the dissolution medium is not transparent like that of the U.S.P. method. However, from earlier evidence (Kitazawa & others, 1975a), a possible estimate of about 10 min for the disintegration of the tablet could be deduced for the S.S. method.

A possible reason for the time difference might be the difference in the volume of the dissolution medium; the U.S.P. method uses 1000 ml while the S.S. method uses 100 ml. Therefore, the U.S.P. method was used but with a volume of 100 ml of medium, to form the M.R.B. method.

The effect of the decrease in the volume of medium was seen in the rates of both the initial and the final stages of the dissolution. The disintegration time was reduced as shown in Fig. 2a, but there was still a difference between the M.R.B. and the S.S. methods.

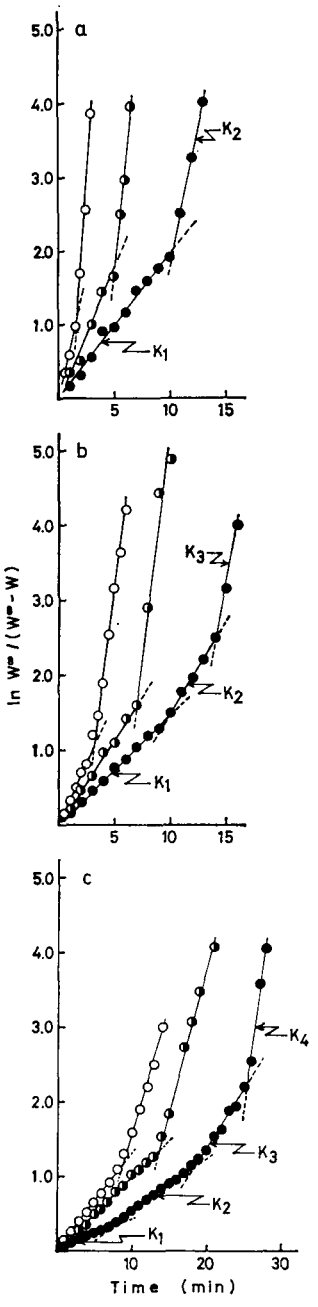

FIG. 2. Characteristic change in dissolution of uncoated caffeine tablets having hardnesses of 2·9 kg (a), 7·0 kg (b), and 12·9 kg (c) using three kinds of dissolution testers. The data are plotted using the correlation of Kitazawa & others (1975a; 1977). The slope of each straight line indicates the dissolution rate constant in the corresponding stage. -○—U.S.P. method. -◑—M.R.B. method. -●—S.S. method.

Disintegration curves for the tablet having a hardness of 7·0 kg are illustrated in Fig. 2b, but here the S.S. method gave three straight regression lines with two intersections. Essentially similar dissolution profiles were obtained for tablets with a hardness of 10·5 kg. The first intersection observed at about 10 min in the dissolution curve of the S.S. method could correspond to the breakdown of the tablet into two or three lumps, the surface area not being increased explosively. A slight increase in the surface area of the tablet during the dissolution process was also observed when tablets of 12·9 kg in hardness were assessed by the S.S. method, and three intersections with four straight regression lines were observed (Fig. 2c).

The number of intersections apparently increased with increasing hardness of the tablets in the S.S. method and each intersection did not always indicate the so-called disintegration time defined by the J.P. disintegration test, but it may be correlated with its probable mode of breakdown. On the other hand, in both the U.S.P. and the M.R.B. methods a decrease in dissolution rate at both stages and prolongation of the disintegration time were observed as tablet hardness increased in agreement with Kitazawa & others (1975a).

A summary of the results obtained in a series of experiments was presented in Table 1.

DISCUSSION

Much has been published on the dissolution of active ingredients from compressed dosage forms. In some cases (Levy & Sahli, 1962; Nelson, 1962; Gibaldi & Weintraub, 1968), an attempt has been made to keep the surface area, S, constant in which case the dissolution rate, with a sufficient volume of solvent to maintain sink conditions, becomes zero order. In other instances (Levy & Hollister, 1964; Wagner, 1969), the Noyes & Whitney equation (1897a), which contains the surface area for dissolution as a variable, was used. Our results were based on an equation (Kitazawa & others, 1975a; 1977) derived from the Noyes & Whitney equation without the surface area (1897b). The reason for this was that, the tablets having been prepared in the same size of die, all had the same diameter. Although the thickness varies with change in compression pressure, measurement showed the thickness of all tablets was 2·9 $\pm$ 0·1 mm. Thus the initial surface area available for dissolution was identical for all tablets, and it was therefore not necessary to include it as a variable.

In Table 1, the effect of hardness on the dissolution

Table 1. *Hardness and dissolution characteristics of each caffeine tablet with S.S., M.R.B. and U.S.P. methods*

Hardness (kg)	S.S. method					M.R.B. method			U.S.P. method**		
	K_1*§	K_2*§	K_3*§	K_4*§	N.I.†	K_i*‡	K_f*‡	N.I.†	K_i*‡	K_f*‡	N.I.†
2·9	21·18 (50·58)	71·76	—	—	1	38·88	120·06	1	62·34	216·72	1
7·0	14·52 (9·66)	24·18	76·08 (51·90)	—	2	21·42	89·64	1	32·88	88·74	1
10·5	7·97 (8·17)	16·14	66·30 (50·16)	—	2	14·52	70·14	1	18·24	70·98	1
12·9	5·16 (1·80)	6·96	12·12 (5·16)	61·50 (49·38)	3	12·42	53·70	1	13·44	31·26	1

All values are the mean of at least three determinations.
Number in parentheses suggests the difference in the dissolution rate constant at each intersection.
* Values ($\times 10^{-2}$, min^{-1}).
** The data were quoted from our previous study (Kitazawa & others, 1975a).
† Number of intersections of straight lines obtained from the ln $W^{\infty}/(W^{\infty}-W)$ versus time plot.
‡ The K_i and K_f suggest the initial and the final dissolution rate constants, respectively.
§ Each dissolution rate constant corresponds to those in Fig. 2.

rate was evident in all three methods and in both the initial and final dissolution phases. Thus the Kitazawa method is applicable in such experiments.

In comparing the results obtained with the U.S.P. method and M.R.B. method, the effect of the difference in volume of medium on the dissolution rate was apparent especially at low degrees of hardness. In fact, the volume of the dissolution medium is a more important factor than the efficacy of the stirring. But when the M.R.B. and the S.S. methods are compared, all the differences are attributable to the different method of agitation, since the dissolution medium volumes are the same.

The multiple intersections of straight lines observed in the S.S. method may be correlated with the tablet hardness and with its probable mode of breakdown and consequent increase in surface area. Attrition by the glass beads could cause initial breakage into large fragments before disintegration into the constituent granules, and at each fragmentation stage the area would change, and so too the dissolution rate constant. Such changes become apparent only when the Kitazawa method of plotting is used.

REFERENCES

BAUN, D. C. & WALKER, G. C. (1969). *J. pharm. Sci.*, **58**, 611–616.
GIBALDI, M. & WEINTRAUB, H. (1968). *Ibid.*, **57**, 832–835.
GIBALDI, M. & WEINTRAUB, H. (1970). *Ibid.*, **59**, 725–726.
KITAZAWA, S., JOHNO, I., ITO, Y., TERAMURA, S. & OKADA, J. (1975a). *J. Pharm. Pharmac.*, **27**, 765–770.
KITAZAWA, S., MAEDA, A., ITO, Y. & OKADA, J. (1975b). *Yakugaku Zasshi*, **95**, 872–878.
KITAZAWA, S., JOHNO, I., MINOUCHI, T. & OKADA, J. (1977). *J. Pharm. Pharmac.*, **29**, 453–459.
LANGENBUCHER, F. (1969). *J. pharm. Sci.*, **58**, 1265–1272.
LEVY, G. (1963). *Ibid.*, **52**, 1039–1046.
LEVY, G. & HOLLISTER, L. E. (1964). *Ibid.*, **53**, 1446–1452.
LEVY, G. & SAHLI, B. A. (1962). *Ibid.*, **51**, 58–62.
NELSON, E. (1958). *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 292–299.
NELSON, E. (1962). *Chem. Pharm. Bull. (Tokyo)*, **10**, 1099–1101.
NOYES, A. A. & WHITNEY, W. R. (1897a). *Z. Physik. Chem.*, **23**, 689.
NOYES, A. A. & WHITNEY, W. R. (1897b). *J. Am. chem. Soc.*, **19**, 930–934.
PERNAROWSKI, M., WOO, W. & SEARL, O. (1968). *J. pharm. Sci.*, **57**, 1419–1421.
SAITO, T., SUZUKI, S., NUMBU, N. & NAGAI, T. (1974). *Yakuzaigaku*, **34**, 143–151.
SOUDER, J. C. & ELLENBOGEN, W. C. (1958). *Drug Stand.*, **26**, 77–83.
STRICKER, H. (1969). *Pharm. Indust.*, **31**, 794.
STRICKER, H. (1970). *Arzneimittel-Forsch.*, **20**, 391–396.
STRICKER, H. (1971). *Pharm. Indust.*, **33**, 446–454.
WAGNER, J. G. (1969). *J. pharm. Sci.*, **58**, 1253–1257.