J. Pharm. Pharmacol. 1991, 43: 79–82
Received October 8, 1990

In-vitro Dissolution Properties of Indomethacin Extended-release Capsules

TETSUO KOMURO, CHIKAKO YOMOTA AND TOSHIO KIMURA

Drug Division, National Institute of Hygienic Sciences, Osaka Branch, Hoenzaka 1-1-43, Chuo-ku, Osaka 540, Japan

Abstract—In-vitro dissolution properties of indomethacin extended-release capsules, from samples available on the Japanese market, have been investigated using a continuous flow, column-type dissolution apparatus and the results compared with those obtained by the paddle and the rotating basket methods. A plot of the percent of drug dissolved against the square root of time gave a straight line with the flow-through method but not with the paddle or the rotating basket methods. The results suggest an advantage of the flow-through method over the other two methods when extended-release products are tested by in-vitro dissolution.

The USP paddle and the rotating basket methods for assessing the dissolution of solid dosage forms are known to have weaknesses and several modifications have been sugested (Langenbucher 1969, 1981; Withey 1971; Möller et al 1981; Prasad et al 1983; Shenouda et al 1986). Another apparatus in use is the flow-through device (Baun & Walker 1969; Langenbucher 1969; Tingstad & Riegelmann 1970), which has been described by several authors (Möller et al 1981; Gould 1983; Möller 1983; Tingstad et al 1985; Nicklasson et al 1987; Wennergren et al 1989).

We have already shown that the flow-through method is superior to the paddle and the rotating basket methods in in-vitro quality control procedures because of its better discrimination between commercial brands of conventional nitrazepam solid dosage forms (Komuro et al 1987). In the present study, we have applied the flow-through method to extended-release capsules of indomethacin and investigated in-vitro dissolution properties of the products obtained from eight commercial brands available on the Japanese market. We have also compared the results with those obtained using the paddle and the rotating basket methods (JP XI).

Materials and Methods

Materials

Eight commercially available extended-release capsules (Spansule type) of indomethacin were used as follows ME: Proarisin, Maeda Yakuhin K.K., MR: Indomethacin SP, Maruko Seiyaku K.K., MK: Mikametan-R, Mikasa Seiyaku K.K., NP: Salinac SR25, Nihon Kayaku K.K., RR: Inmetan-SR25, Rorer Japan Inc., SM: Inteban SP, Sumitomo Pharmaceuticals Co. Ltd., TA: Inderanic-TR, Taiyo Yakuhin Kogyo K.K., ZN: Indomethacin TR25, Zensei Yakuhin Kogyo K.K. Each capsule (25 mg of indomethacin) contained two or three kinds of granules having different dissolution rates. The chemicals used were of analytical reagent grade and were used without further purification.

Correspondence to: T. Komuro, Drug Division, National Institute of Hygienic Sciences, Osaka Branch, Hoenzaka 1-1-43, Chuo-ku, Osaka 540, Japan.

In-vitro dissolution studies

A schematic diagram of the continuous-flow dissolution apparatus used in the flow-through method is shown in Fig. 1. The dissolution cell (C) consisted of a 50 mm long plastic cylinder with an inner diameter of 16 mm and a volume of 10 mL. The capsule under test was placed in the vertically mounted dissolution cell (C), on a thin cotton filter (F_b) which permits fresh test solution to enter easily from the bottom. The upper end of the cell was closed by another thin cotton filter (F_u) which filtered the test solution and prevented the removal of undissolved particles. The test solution was pumped by means of a persistaltic pump from a reservoir maintained at 37 ± 0.5°C to the dissolution cell. The dissolution cell was also maintained at 37 ± 0.5°C. Flow rates used were 3·4, 5·9, 8·5 and 16·4 mL cm^{-2} min^{-1}. The drift of the flow rate 6 h after the beginning of the dissolution test was within 2%. The dissolution test was replicated at least three times for each sample. The eluate from the cell was collected at 10 min intervals for the first hour and at 30 min intervals for the following 5 h and the amount of indomethacin released was determined by UV absorbance at 320 nm (Shimadzu spectrophotometer UV-160, Japan).

The dissolution tests using the rotating basket and the paddle methods were carried out according to JP XI specifications at 50, 100 and 200 rev min^{-1} using an automated six-channel dissolution tester (Toyama Sangyo Co. Ltd, Japan) controlled by computer.

The dissolution medium used was a 0·05 M phosphate buffer, pH 6·8 (the second solution used for the disinte-

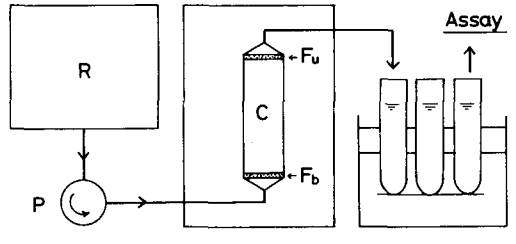

FIG. 1. Schematic diagram of the flow-through apparatus. C: dissolution cell, P: pump, R: reservoir for test solution, F_u and F_b: filters.

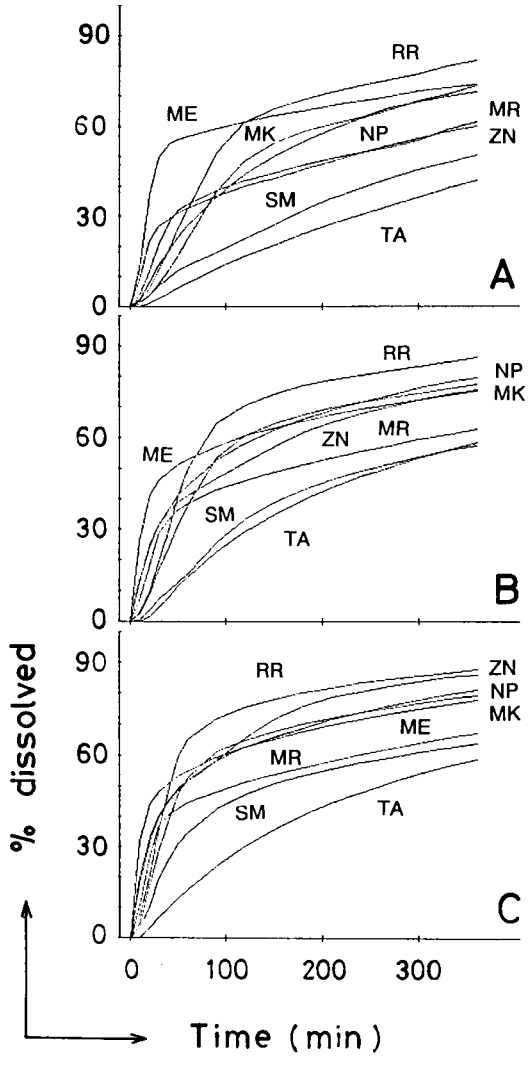

FIG. 2. Dissolution profiles of indomethacin extended-release capsules using the flow-through, the rotating basket or the paddle methods. A: the flow-through method at 5·92 mL cm^{-2} min^{-1}, B: the rotating basket method at 100 rev min^{-1}, C: the paddle method at 100 rev min^{-1}. Test solution: 0·05 M phosphate buffer, pH 6.8, 900 mL.

gration test in JPXI). For the paddle and the rotating basket methods 900 mL of the fresh dissolution medium was used.

Results

Results of dissolution studies are shown in Fig. 2. Higuchi plots (percent of drug dissolved against the square root of time (Higuchi 1963)) of the same data are shown in Figs 3, 4 and 5.

Discussion

For testing the diffusion controlled-release mechanism of the extended-release preparations, the flow-through method can be used because it is a comparatively mild method, and mechanical disintegration of granules does not need to be considered. With this method, a linear dissolution profile was

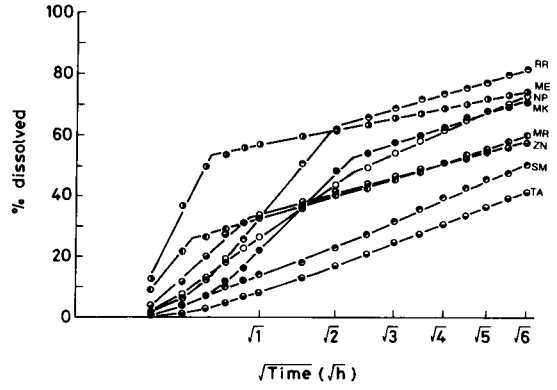

FIG. 3. Dissolution profiles of indomethacin extended-release capsules using the flow-through method. Test conditions are the same as in Fig. 2. Each point is the mean of three experiments.

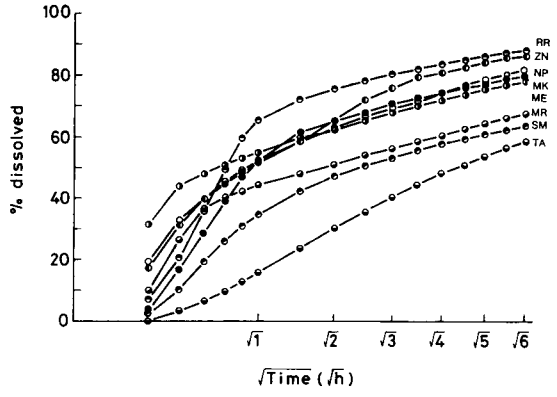

FIG. 4. Dissolution profiles of indomethacin extended-release capsules using the paddle method. Test conditions are the same as in Fig. 2. Each point is the mean of three experiments.

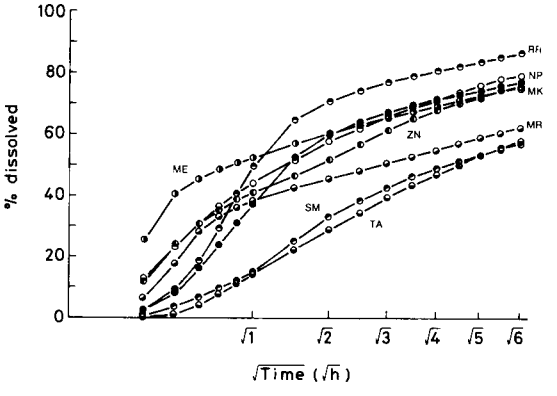

FIG. 5. Dissolution profiles of indomethacin extended-release capsules using the rotating basket method. Test conditions are the same as in Fig. 2. Each point is the mean of three experiments.

clearly obtained (Fig. 3). The paddle or the rotating basket methods remain useful to test the extended-release mechanism if their mechanical destructive forces are taken into consideration since disintegration of granules will change the dissolution profiles of the preparations.

To check for disintegration of granules, a paddle method

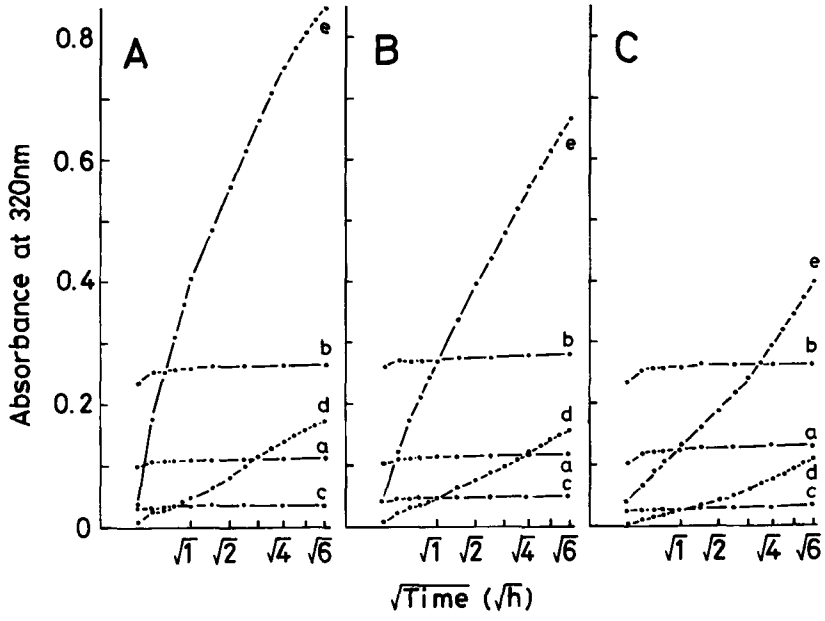

FIG. 6. Dissolution profiles of indomethacin from fractionated granules based on size and colour using the paddle (A), the rotating basket (B) or the flow-through (C) methods. Test conditions are the same as in Fig. 2. White granules—a: < 500 μm, b: 500–590 μm, c: > 590 μm. Yellow granules—d: < 500 μm, e: > 590 μm.

at 100 rev min^{-1}, for example, would be useful because of its stronger mechanical destructiveness. All preparations should show the first-order release profiles according to the diffusion-controlled mechanism whatever the testing method used. In fact, some preparations (e.g. samples ME, TA) could pass both tests, that is, similar dissolution profiles were observed with linearity at the extended-release stage by the paddle method as well as by the flow-through method. However, some preparations (e.g. SM, ZN) were mechanically disintegrated by the agitating paddle (Fig. 4), and curvilinear profiles were observed with more than 50% of active ingredient released within 60 min. This suggests disintegration of granules.

Statistical testing for linearity was not done because not all preparations were curvilinear in the paddle and the rotating basket methods (Figs 4, 5) nor did they always disintegrate under the mild flow-through conditions. In addition, it is known that for drugs undergoing diffusion-controlled release, linearity could not always be obtained after the percentage of drug dissolved had increased above 70–80%. The slope of the dissolution curve becomes less steep and apparently linear, as often observed in the paddle and the rotating basket methods at 100, as well as 200, rev min^{-1} because of the initial drug release (Fig. 6).

The hypothesis that non-linearity may be due to initial disintegration of the extended-release granules was tested as follows. A sample (ZN) was selected and the granules packed into the capsule were fractionated into five kinds of granules based on size and colour. The drug dissolution properties of these granules were compared using the three dissolution testing methods as shown in Fig. 6. Extended-release granules, d and e, showed a linear relationship between the percent of drug dissolved and the square root of time with the use of the flow-through method but not with the paddle and the rotating basket methods.

The change in the slope of the dissolution curve observed in the extended-release granules about 2 h after the beginning of the dissolution test, may be related to a change in the dissolution mechanism as described by Stamm & Tritsch (1988), or could be due to the internal structure of the

Table 1. Correlation in the dissolution profiles of eight different capsules between different flow rates or revolution speeds.

Time (min)	Flow-through method						Paddle method			Rotating basket method		
	A:B	A:C	A:D	B:C	B:D	C:D	E:F	E:G	F:G	E:F	E:G	F:G
60	0·947	0·937	0·941	0·865	0·882	0·936	0·810	0·368	0·785	0·908	0·368	0·491
120	0·949	0·974	0·957	0·953	0·928	0·962	0·824	0·416	0·785	0·933	0·416	0·438
180	0·953	0·970	0·952	0·958	0·946	0·945	0·817	0·378	0·733	0·941	0·378	0·381
240	0·956	0·952	0·935	0·949	0·943	0·910	0·828	0·326	0·694	0·945	0·326	0·332
300	0·958	0·953	0·903	0·935	0·924	0·876	0·824	0·270	0·650	0·939	0·270	0·291
360	0·958	0·949	0·848	0·924	0·940	0·820	0·810	0·227	0·608	0·935	0·227	0·255

Figures are square values of the correlation coefficients based on the plots of the percent of drug dissolved at a given time for each of the eight capsules at a certain flow rate (or revolution speed) versus percent of drug dissolved at the same time for the corresponding capsule at another flow rate (or revolution speed). A: 3·4, B: 5·9, C: 8·5, D: 16·4 mL cm^{-2} min^{-1}. E: 50, F: 100, G: 200 rev min^{-1}.

granules. Swelling of the granules may be also related to the phenomena as this changes the surface area presented to the test solution (Fouli et al 1983).

We also compared the difference in the dissolution profiles under different experimental conditions using the same dissolution method. Dissolution tests were compared statistically according to Spearman's rank correlation test and it was found that the flow-through method and the rotating basket method were almost correlative but the flow-through method and the paddle method ranked the preparations in different order. Consideration of the results of Fig. 6 together with the different rank order suggests that the difference between the methods is due to the varying properties or fragilities of granules. For example, comparison of the dissolution profiles of eight capsules from different brands in the flow-through method showed good correlation for any two flow rates studied (Table 1), but poor results in the cases of the paddle and the rotating basket methods.

In the present study, we have applied the flow-through method to the evaluation of indomethacin extended-release capsules in-vitro and showed its usefulness for quality control. This method was found to be useful in evaluating all dosage forms (Möller 1983), and is described in the European and French Pharmacopoeias (Möller 1989). Therefore, the flow-through method is expected to be an alternative compendial method for dissolution testing in Japan.

References

Baun, D. C., Walker, G. C. (1969) Apparatus for determining the rate of drug release from solid dosage form. J. Pharm. Sci. 58: 611–616

Fouli, A.M., El-Sayed, A. A., Badawi, A. A. (1983) Release of drugs from microcapsules of methacrylate polymers. Int. J. Pharm. 14: 95–102

Gould, P. L. (1983) Methods of following drug release from controlled release dosage forms. Br. Polymer J. 15: 172–176

Higuchi, T. (1963) Mechanism of sustained-reaction medication. J. Pharm. Sci. 52: 1145–1149

Komuro, T., Hasegawa, R., Isaka, H. (1987) Investigation on the dissolution test of nitrazepam uncoated tablets by the flow-through method. The 107th Annual Meeting of Pharmaceutical Society of Japan, Kyoto

Langenbucher, F. (1969) In vitro assessment of dissolution kinetics: description and evaluation of a column-type method. J. Pharm. Sci. 58: 1265–1272

Langenbucher, F. (1981) Possible improvements of the USP XX dissolution test standards. Pharm. Ind. 43: 136–139

Möller, H. (1983) Dissolution testing of different dosage forms using the flow-through method. Ibid. 45: 617–622

Möller, H. (1989) Conference of International Harmonization of Pharmaceutical Quality. Tokyo

Möller, H., Boer, Y., Cabana, B. E., Eijkel, G., Johnson, C. A., Phillips, G. F., Bentejac, R., Boss, J., Dibberrn, H. W., Jones, T. M., Langenbucher, F., Nyiredy, S., Simioni, L., Tingstad, J. E., Wahlgren, S. (1981) Guidelines for dissolution testing of solid oral products. Pharm. Ind. 43: 334–343

Nicklasson, M., Wennergren, B., Lindberg, J., Persson, C., Ahlgren, R., Palm, B., Pettersson, A., Wenngren, L. (1987) A collaborative in vitro dissolution study using the flow-through method. Int. J. Pharm. 37: 195–202

Prasad, V. K., Shah, V. P., Hunt, J., Purich, E., Knight, P. (1983) Evaluation of basket and paddle dissolution methods using different performance standards. J. Pharm. Sci. 72: 42–44

Shenouda, L. S., Adams, K. A., Alcorn, G. J., Zoglio, M. A. (1986) Evaluation of a modified paddle method for dissolution testing. Drug Dev. Ind. Pharm. 12: 1227–1239

Stamm, A., Tritsch, J. C. (1988) Some considerations on the liberation of drugs from inert matrices. In: Rubinstein, M. H. (ed.) Pharmaceutical Technology, Controlled Drug Release. Vol. I Ellis Horwood, New York, pp 54–63

Tingstad, J. E., Riegelmann, S. (1970) Dissolution rate studies I: Design and evaluation of a continuous flow apparatus. J. Pharm. Sci. 59: 692–696

Tingstad, J., Gropper, F., Lachman, L., Shami, E. (1985) Dissolution rate studies II: modified column apparatus and its use in evaluating of isosorbide dinitrate tablets. Ibid. 61: 1985–1990

Wennergren, B., Lindberg, J., Nicklasson, M., Nilsson, G., Nyberg, G., Ahlgren, R., Persson, C., Palm, B. (1989) A collaborative in vitro dissolution study: comparing the flow-through method with the USP paddle method using USP prednisone calibrator tablets. Int. J. Pharm. 53: 35–42

Withey, R. J. (1971) The kinetics of dissolution for a non-disintegrating standard substrate. J. Pharm. Pharmacol. 23: 573–582