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A collaborative study of the in vitro dissolution of phenacetin crystals comparing the flow through method with the USP Paddle method

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Summary

A collaborative in vitro dissolution study has been performed comparing the flow through cell apparatus with the USP Paddle method. The objective was to compare the two methods regarding their suitability for measuring the in vitro dissolution of a drug substance per se. Phenacetin, a sparingly soluble compound was used as the test material. The results indicate that the flow through cell method shows less variation both within and among the laboratories compared with the USP Paddle method. The flow through cell method was also found to generate faster in vitro dissolution rates for phenacetin than those found with the USP Paddle method, probably caused by steeper concentration gradients at the vicinity of the crystals as well as better ability to uniformly wet the phenacetin crystals. Also, the flow through cell method was found to be less dependent on the hydrodynamics and the amount of substance tested in each run, which generated a better overall reproducibility of the in vitro dissolution data. The USP Basket method was tested in one of the laboratories but it was found to give substantially slower dissolution rates than the other two methods showing a high variability between each vessel.

Introduction

Information about the in vitro dissolution characteristics of drug substances per se is important in order to establish the most suitable dosage form design for a given pharmaceutical product. If reliable in vitro dissolution methods can be identified, they may also serve as tools for studying batch to batch variability in order to establish adequate raw material specifications in terms of in vitro dissolution properties.

Several papers have been published describing methods for in vitro dissolution testing of drug compounds. The most common is the rotating disc method (Feld and Higuchi, 1981; Touitou and Donbrow, 1981; Nicklasson et al., 1982; Nicklasson and Magnusson, 1985). This method gives accurate information about solid to liquid mass

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transfer but does not allow any conclusions to be drawn regarding drug dissolution in relation to particle size distribution. Attempts have been made to evaluate dissolution patterns of polydisperse powders (Carstensen and Patel, 1975), applying the well known cube-root law derived by Hixson and Crowell (1931). Other techniques have also been studied for powdered materials such as griseofulvin (Elworthy and Lipscomb, 1969) and phenacetin (Cox and Mulders, 1969), but due to the lack of general experimental standardization in terms of geometry and hydrodynamics, difficulties may arise in routine testing.

The application of an open, infinite sink, flow through cell method may show advantages compared to closed finite sink beaker methods. The geometry of the flow through cells is well defined and cells, particularly designed for studying crystalline or powdered materials, can be easily obtained (Langenbucher et al, 1989). The application of the flow through cell apparatus has been shown (Johansson and Nicklasson, 1986) as a suitable method for studying drug dissolution from aspirin crystals.

The objective of this paper was to investigate the in vitro dissolution of phenacetin crystals using both the flow through cell method and the USP Paddle method. The study was performed in a collaborative manner among five independent laboratories. The Scandinavian collaborative working group on in vitro dissolution testing consists currently of more than five laboratories. In this study one laboratory only participated in additional screening studies and in the overall evaluation of the results. This study is the third performed by the working group and previous results have been published (Nicklasson et al, 1987; Wennergren et al, 1989).

Experimental

Test laboratories

Five different laboratories participated in this collaborative dissolution study (Astra Research Centre AB, Södertälje, Sweden; Draco AB, Lund, Sweden; Gacell Laboratories AB, Malmö, Sweden; Kabi Pharmacia, Solna, Sweden and National Board of Health and Welfare, Dept of Drugs, Uppsala, Sweden.

Benzon Pharma A/S, Hvidovre, Denmark performed in vitro dissolution tests with the USP-XXI Method 1 (Basket method).

Test substance

Phenacetin substance obtained from Apoteksbolaget, Sweden, was used in this study. Density measurements were performed in a Micromeritics multi-volume pycnometer 1305. The phenacetin crystals were fractionated by sieving, and the size fraction 180–250 μm was used for the in vitro dissolution testing. The particle size distribution was determined by a Malvern Master Sizer laser diffraction meter. SEM pictures of phenacetin crystals were taken with a JEOL JSM 25S-II at 70 × magnification before and after being mixed with glass beads. The DSC analysis was performed using a Perkin Elmer DSC 7. The solubility of phenacetin at 37 °C was determined at Astra Research Centre AB. The phenacetin was stored in a desiccator containing silica gel to keep the humidity constant during the experiments.

In vitro dissolution tests

Each laboratory used a flow through apparatus (SOTAX AG Switzerland), equipped with cells specially designed for powders and supplied with dissolution medium by a piston pump. The apparatus has been described thoroughly by Möller (1983). The preparation of the flow through cell was carried out by placing a ruby bead at the bottom of each flow cell and thereafter a bed of glass beads (0.9 g, $\varnothing = 1$ mm). A net (0.2 mm) was then placed on the bed. Phenacetin crystals, 50 or 200 mg, mixed with 4 g of glass beads ($\varnothing = 1$ mm) were then added to each cell. Each cell was filled to maximum volume using additional glass beads. Finally, a net (0.12 mm), a filter (Millipore AP25) and a second net (0.2 mm) were placed at the top of the cells.

The acceptable flow rates were in the range of 16 and 32 ml/min ± 5%, respectively. Deaerated water of 37 ± 0.5 °C was used as dissolution medium. The sampling intervals were 0–5, 5–15, 15–30, 30–60, 60–90 and 90–120 min and the eluate from each cell was collected, weighed and

analysed spectrophotometrically at $\lambda = 244$ nm. All six cell positions were used in the experiments.

A comparative dissolution study was also performed with the USP-XXI Paddle method. 50 and 200 mg of phenacetin crystals were used in the experiments. 900 ml of deaerated water was used as dissolution medium at 37 ± 0.5 °C. The agitation rates used were 50 and 100 rpm. Sample volumes of 5 ml were withdrawn manually, through a Technicon filter, at 5, 15, 30, 60, 90 and 120 min without replacement. The sample sizes chosen (50 and 200 mg) correspond to either 5 or 20% of the saturation value of phenacetin in water at 37 °C. The experiments with a sample size of 200 mg did consequently not conform to sink conditions.

For comparison, one laboratory performed a separate study according to the USP-XXI Basket method, using a SOTAX Dissolutest. The sample size was 50 mg and the agitation rates tested were 50, 100 and 150 rpm. A Millipore filter was placed at the bottom of the basket to prevent the crystals from falling through the net. 900 ml deaerated water was used as dissolution medium at 37 ± 0.5 °C. Samples were taken at 5, 15, 30, 60, 90 and 120 min without replacement.

Results and Discussion

The solubility of phenacetin in water was determined to be 1.2 mg/ml at 37 °C. The DSC analysis showed a melting point of 135.0 °C for the phenacetin batch studied which is in agreement with the literature value (Merck Index, 1989) as well as with the melting point of a high purity NBS standard (National Bureau of Standards). The enthalpy of fusion was determined to be 171 J/g. From the thermal analysis it can be concluded that the phenacetin batch studied is crystalline without any signs of polymorphism. As can be seen in Fig. 1, the particle size distribution is skewed to values higher than the expected range of 180–250 μm most likely because of the presence of rod-shaped crystals. The SEM pictures in Fig. 2a and b indicate that no pronounced damage

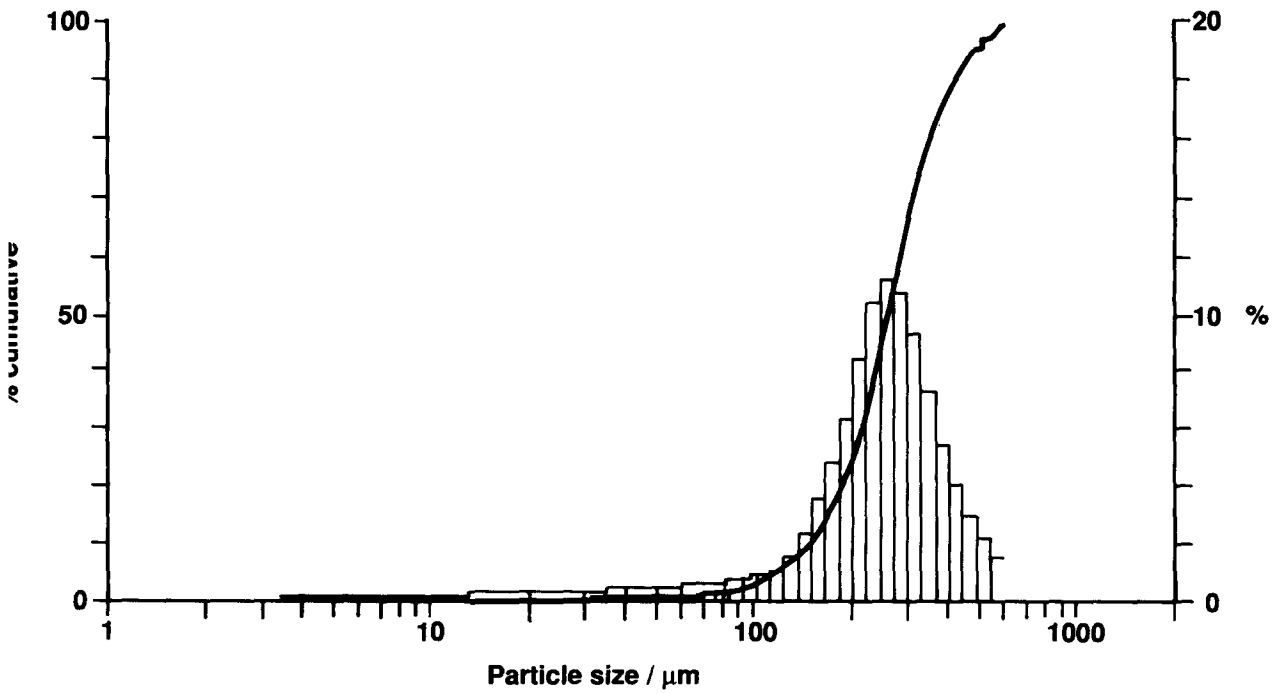

Fig. 1. The particle size distribution of phenacetin, size fraction 180–250 μm. Solid line indicates the cumulative distribution.

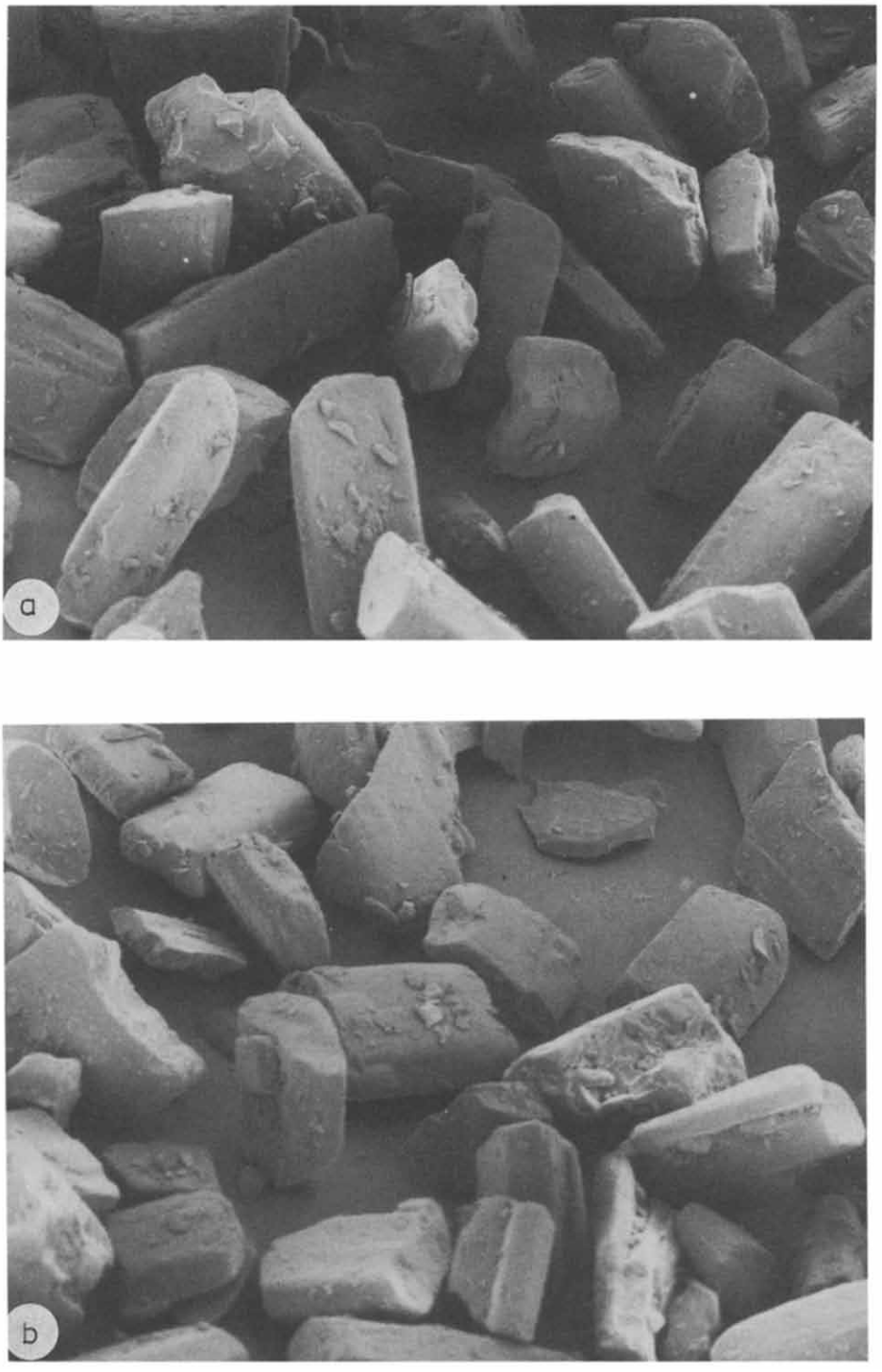

Fig. 2. (a). SEM picture of phenacetin crystals, 180–250 μm, at 70 $\times$ magnification before being mixed with glass beads. (b) SEM picture of phenacetin, 180–250 μm, at 70 $\times$ magnification after being mixed with glass beads.

of the crystals can be observed, caused by the mixing procedure with glass beads during the preparation of the flow through cell.

Table 1 shows the in vitro dissolution data for phenacetin generated by each laboratory using the USP Paddle method. At an agitation rate of 50 rpm using either 50 or 200 mg phenacetin a substantial variability was found in terms of the overall range between all laboratories. This is probably due to insufficient reproducibility of the hydrodynamic conditions in the vessel and due to wetting problems caused by the physical nature of phenacetin. One laboratory (No. 4) experienced experimental difficulties during the weighing procedure which might explain the relatively high end point values. It was generally noticed that crystals were floating on the surface. Four of the laboratories added the phenacetin to the vessels by gently spreading the crystals over the aqueous surface, whereas one laboratory (No. 1) added the whole sample close to the vessel wall. The latter approach seemed to generate a faster dissolution rate. This is probably due to a more intensive hydrodynamic pattern at the periphery of the vessels. It should be noted that this could be of importance when studying a floating formulation.

When the agitation rate was increased to 100 rpm, the ranges for the two sample sizes were as wide as for those found using 50 rpm (see Table 1). However, the coefficient of variation was approximately half of that obtained at 50 rpm probably due to more intense hydrodynamic conditions, higher fluid velocity at the periphery and hence intensive wetting. Thus, the unexpected wide

TABLE 1

Per cent phenacetin dissolved in water at 37 °C, using the USP XXI Paddle method using different sample sizes and different agitation rates (n = 6)

	Time (min)	Laboratory No. ($n = 6$)					Overall range ($n = 30$)	Mean ± c.v. ($n = 30$)	
		1	2	3	4	5			
50 rpm, 50 mg	5	13– 20	9– 10	9–12	8– 14	5– 13	15	10.9	32.6
	15	43– 48	29– 32	25–34	26– 36	21– 28	27	31.5	8.1
	30	77– 86	55– 59	45–59	46– 58	40– 51	46	57.3	22.9
	60	96–101	87– 91	72–91	65– 95	76– 79	36	86.5	10.4
	90	97–100	99–101	84–98	101–104	91– 96	20	97.7	4.4
	120	97–104	101–102	86–99	104–106	94– 98	20	99.8	4.2
100 rpm, 50 mg	5	11– 50	12– 16	21–27	14– 15	7– 24	43	18.4	47.4
	15	31– 70	40– 50	48–59	43– 46	28– 48	42	46.3	10.0
	30	67–103	72– 81	73–83	76– 80	58– 72	45	75.1	11.5
	60	95–102	98–100	94–97	101–103	96– 97	9	98.5	2.7
	90	99–104	99–101	96–99	102–104	100–103	8	100.5	2.2
	120	99–103	99–101	97–99	103–104	100–102	7	100.5	2.1
50 rpm, 200 mg	5	8– 19	6– 8	10–16	6– 7	3– 7	16	8.0	45.0
	15	29– 45	20– 22	24–30	21– 24	14– 19	31	25.5	33.5
	30	54– 71	39– 43	44–48	42– 48	31– 36	40	46.1	24.7
	60	79–103	70– 75	69–75	73– 79	62– 67	41	75.8	14.3
	90	95–100	91– 94	81–90	92– 95	82– 87	19	91.2	5.9
	120	98–102	100–101	85–97	99–101	97– 98	17	97.8	3.8
100 rpm, 200 mg	5	10– 26	12– 14	13–20	10– 13	8– 17	18	13.3	29.8
	15	24– 51	35– 41	35–48	32– 39	27– 32	27	35.3	17.8
	30	42– 72	62– 70	59–72	59– 68	52– 55	30	60.1	12.8
	60	55– 93	95– 99	89–91	78– 90	85– 87	44	90.2	8.9
	90	62–100	100–101	97–98	100–102	95– 98	40	97.7	7.2
	120	69–100	101–102	98–98	102–103	96– 98	34	98.5	6.1

overall ranges in dissolution behavior may be explained by the way that the samples were added to the vessels, which indicate problems when using a beaker method for polydispersed materials.

Table 2 lists the in vitro dissolution data for phenacetin using the flow through cell apparatus. By comparing the results in Table 2 with those in Table 1, it can be seen that during the major part of the dissolution process, the overall variability among the different laboratories was somewhat smaller when using the flow through cell method. A closer examination of the data obtained within each laboratory reveals that narrower ranges were obtained, in general, at each sampling occasion when using the flow through cell apparatus compared to the USP Paddle method. This is also evident from the overall ranges obtained, applying data from all laboratories as well as the overall coefficients of variation, giving support to the assumption that the flow through cell method seems to be a more suitable method for measuring in vitro dissolution from a polydisperse material compared to the USP Paddle method.

Figs 3 and 4 show the mean in vitro dissolution curves for phenacetin crystals using the USP Paddle method and the flow through cell method, respectively. It seems to be obvious from Figs 3 and 4 that the phenacetin dissolution is less dependent on sample size and on hydrodynamic intensity applied when using the flow through cell method than with the USP Paddle method. However, generally higher dissolution rates were obtained with the flow through cell apparatus than with the USP Paddle apparatus implying that

TABLE 2

Per cent phenacetin dissolved in water at 37 °C, using the flow through method using different sample sizes and different agitation rates (n = 6)

	Time (min)	Laboratory No. (n = 6)					Overall range (n = 30)	Mean ± c.v. (n = 30)	
		1	2	3	4	5			
16 ml/min, 50 mg	5	28– 33	30– 33	34–40	28– 33	26– 31	14	32.4	13.7
	15	60– 64	68– 83	76–81	61– 71	61– 68	23	69.2	10.5
	30	78– 84	91– 96	90–93	84– 92	79– 89	18	87.0	6.3
	60	92– 96	97–100	92–95	96– 99	92– 99	8	95.8	2.6
	90	96– 98	98–100	92–95	98–100	97–100	8	97.7	2.1
	120	98– 99	98–100	92–95	98–100	98–100	8	98.1	2.2
32 ml/min, 50 mg	5	36– 43	46– 58	55–59	40– 51	38– 47	23	47.2	14.9
	15	68– 82	86– 92	90–95	77– 90	74– 84	27	83.4	8.4
	30	85– 95	97–100	98–99	91– 98	94– 98	15	95.7	3.7
	60	97–102	99–100	98–99	94–101	101–102	8	99.1	1.9
	90	99–102	99–100	98–99	95–101	101–102	7	99.3	1.7
	120	99–102	99–100	98–99	95–101	101–102	7	99.5	1.7
16 ml/min, 200 mg	5	23– 32	17– 29	27–33	24– 34	31– 34	17	27.9	17.8
	15	57– 70	44– 70	59–73	56– 76	72– 79	35	65.2	13.5
	30	81– 90	70– 92	82–91	80– 94	92– 96	26	87.3	7.1
	60	91– 96	88– 99	96–98	95–100	98–100	12	96.8	2.8
	90	96– 99	94– 99	98–98	97–102	99–101	8	98.1	2.4
	120	98–100	97–100	98–98	98–102	99–101	11	99.2	1.3
32 ml/min, 200 mg	5	42– 49	27– 50	48–52	29– 50	45– 47	25	45.3	12.6
	15	86– 92	70– 93	91–93	71– 93	90– 91	23	88.7	6.2
	30	96– 99	94–100	96–98	97–102	97– 99	8	97.9	1.7
	60	99–100	100–100	97–98	97–103	99–100	6	99.3	1.2
	90	99–100	100–100	97–98	100–103	99–100	6	99.5	1.2
	120	99–100	100–100	97–98	100–103	99–100	6	99.5	1.2

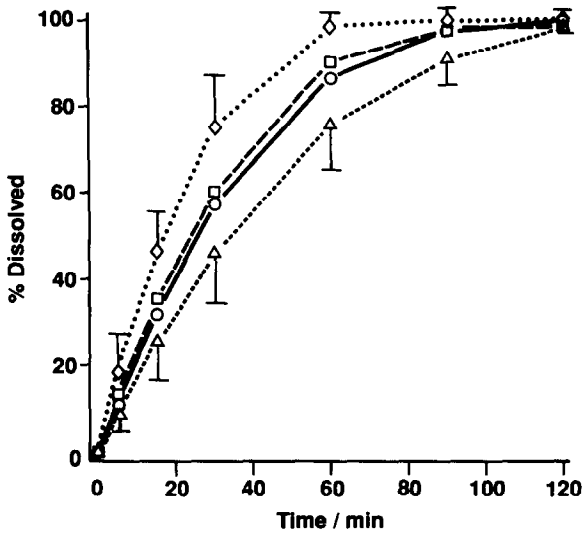

Fig. 3. Per cent phenacetin dissolved vs time in water at 37 °C, using the USP XXI Paddle method. Mean curves based on results from five laboratories ($n = 30$). (○———○) 50 rpm, 50 mg; (△------△) 50 rpm, 200 mg; (◇·····◇) 100 rpm, 50 mg; (□-----□) 100 rpm, 200 mg. Bars denote the standard deviation.

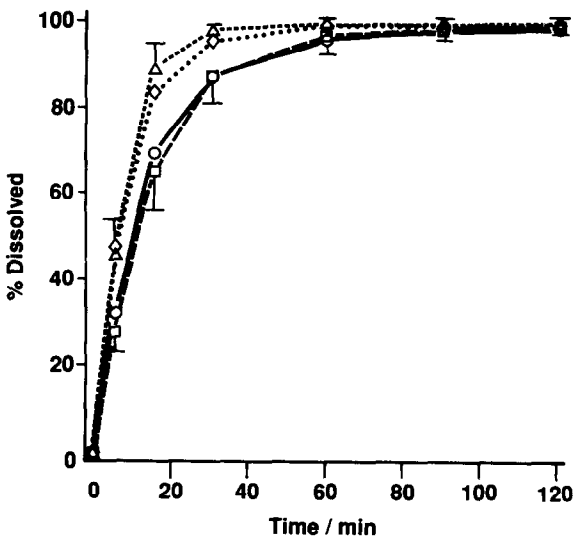

Fig. 4. Per cent phenacetin dissolved vs time in water at 37 °C using the flow through cell apparatus. Mean curves based on results from five laboratories ($n = 29$). (○———○) 16 ml/min, 50 mg; (□-----□) 16 ml/min, 200 mg; (◇·····◇) 32 ml/min, 50 mg; (△------△) 32 ml/min, 200 mg. Bars denote the standard deviation.

variabilities between the two methods at the same sampling times are not fully comparable due to difference in hydrodynamic intensities and patterns as well as wetting of the phenacetin crystals.

For the flow through cell using equal flow rates similar in vitro dissolution rates were obtained irrespective of the amount of sample used. This was not seen when using the USP Paddle method at the same agitation rate. Such a discrepancy might be explained by more efficient hydrodynamic conditions in the flow through cell apparatus compared to what might be present for the USP Paddle apparatus. Using the flow through method high local drug concentrations in the

TABLE 3

One Way Analysis of Variance considering dissolution of phenacetin after 15 and 30 min in water using the USP XXI Paddle method and the flow through cell method (the degrees of freedom between groups are 4 and within groups are 25)

	Agitation rate/flow rate	Sample size (mg)	Time = 15 min			Time = 30 min		
			SS between	SS within	*F*-ratio	SS between	SS within	*F*-ratio
USP Paddle	50 rpm	50	429	7.61	56.4	1 142	16.2	70.5
		200	472	9.00	52.5	875	11.1	78.9
	100 rpm	50	394	55.7	7.08	246	46.5	5.30
		200	110	28.4	3.87	241	30.4	7.95
Flow through cell	16 ml/min	50	323	10.0	32.3	174	7.54	23.0
		200	288	42.6	6.74	110	26.3	4.16
	32 ml/min	50	243	31.2	7.77	54.1	5.48	9.88
		200	26.5	31.1	0.850	2.23	2.72	0.820

TABLE 4

Calculated mean β and τ values according to the Weibull distribution (dissolution of phenacetin in water using the USP Paddle method and the flow through cell method at different agitation rates and sample sizes; the values within brackets denote the 95% confidence interval)

	Agitation or flow rate	Sample size	β	τ (min)
USP-Paddle method	50 rpm,	50 mg	1.2 [1.0; 1.4]	34 [23.4; 44.6]
	100 rpm,	50 mg	1.1 [0.9; 1.3]	22 [18.0; 26.0]
	50 rpm,	200 mg	1.2 [1.0; 1.4]	43 [30.6; 55.4]
	100 rpm,	200 mg	1.1 [0.9; 1.3]	31 [24.8; 37.2]
Flow through method	16 ml/min,	50 mg	0.76 [0.61; 0.91]	13 [8.3; 17.7]
	32 ml/min,	50 mg	0.72 [0.45; 0.99]	7.2 [4.0; 10.4]
	16 ml/min,	200 mg	0.88 [0.77; 0.99]	16 [12.0; 20.0]
	32 ml/min,	200 mg	0.74 [0.47; 1.01]	7.4 [6.0; 8.8]

vicinity of the phenacetin crystals will be reduced. This is probably explained by a more efficient maintenance of sink conditions due to its experimental set-up and supply of fresh solvent. In the case of the USP Paddle method practical problems were observed in terms of insufficient dispersion and wetting of the phenacetin crystals.

Statistical analysis on the dissolution data obtained after 15 and 30 min testing was performed by a one-way analysis of variance and the results are shown in Table 3. It should be emphasized that a better analysis of the data would have resulted if time comparisons of given percentages dissolved could have been conducted. However, Table 3 shows that the sum of squares is higher between than within the different laboratories for both dissolution methods, except when using the flow-through cell apparatus with a sample size of 200 mg and a flow rate of 32 ml/min. This indicates that both techniques are operator and/or apparatus dependent. As might be expected, the difference in the sum of squares will decrease as one approaches 100% dissolved and at this level, no reflection in the terms of technique differences can be seen.

The in vitro dissolution data can be transformed into a linear curve by means of the Weibull transformation (Langenbucher, 1976; Christensen et al, 1989), by applying the following equation:

$$R(t) = 1 - \exp\left[-(t/\tau)^{\beta}\right] \quad (1)$$

where $R(t)$ represents the accumulated release at time t; τ is a scale parameter; the time at which 63.2% has been dissolved, less the lag time; and β denotes a shape parameter representative of the slope, and hence an index of the dissolution rate.

Table 4 shows that there is no statistically significant difference among the slopes (β) obtained by the USP Paddle method. Likewise there is no statistically significant difference among the slopes (β) obtained by the flow through method. However, the slopes for the USP Paddle method and the flow through method are not equal. Since the dissolution rate of the flow through method is faster, the β value is smaller for the flow through method compared to the USP Paddle method. By comparing the absolute values of the confidence intervals for both methods, the USP Paddle method appears to generate a wider range than the flow through method indicating that the results generated by the latter method compare favourably with the reproducible results from the USP Paddle method. However, if the relative values of the confidence intervals were comparable, it is probable that no difference would appear among the ranges.

For comparison but not within the scope of this collaborative study, one laboratory made an additional test using the USP Basket method at various agitation rates. The sample size was 50 mg phenacetin. As can be seen in Fig. 5, much slower in vitro dissolution rates were obtained compared

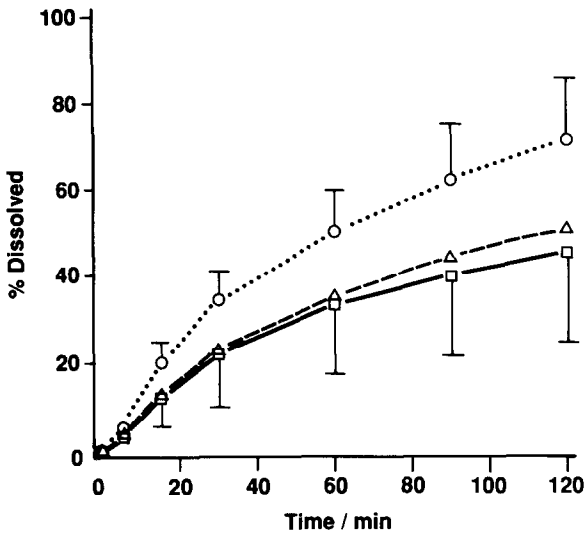

Fig. 5. Per cent phenacetin dissolved vs time in water at 37 °C using the USP XXI Basket method. Mean curves based on results from one laboratory ($n = 6$). Sample size, 50 mg; (□———□) 50 rpm; (△------△) 100 rpm; (○·····○) 150 rpm. Bars denote the standard deviation.

to the results shown in Figs 3 and 4. The agitation dependency does not seem to be pronounced between 50 and 100 rpm, but at 150 rpm a significant increase in the dissolution rate was obtained. Since the Basket method is generally recommended for disintegrating solid dosage forms, the authors would like to raise some doubts about the applicability of this approach particularly if one is investigating a poorly soluble drug compound. It was found that the Basket method did not generate adequate liquid flow past the surface of the crystals, which resulted in the formation of aggregates inside the basket. The aggregates subsequently adhered to the basket walls.

Conclusions

The results from this third Scandinavian collaborative study support previous data that the flow through cell apparatus is a suitable alternative to the USP Paddle method for dissolution testing. When studying the in vitro dissolution properties for drug compounds per se, the flow through cell apparatus may be an even better method when it comes to data reproducibility and conformity. The flow through cell apparatus proved to be less dependent on hydrodynamic intensity compared to the USP Paddle method. Since the flow through cell apparatus operates under more efficient sink conditions, since fresh solvent is constantly supplied, a faster drug release was in general observed. The flow through method gave more efficient wetting of the crystals and showed less dependence upon the sample sizes, when compared to the USP Paddle method.

The flow through cell apparatus is available commercially and hence is not restricted to specialized laboratories. It can be obtained in standardized geometrical forms. The Scandinavian collaborative working group therefore encourages new and extended applications in this field, particularly in cases where there might be a scientific rationale for using this alternative method instead of the compendial finite sink condition methods.

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