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A collaborative in vitro dissolution study using the flow-through method

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Summary

A collaborative in vitro dissolution study has been performed in 4 laboratories using the flow-through method at various hydrodynamic conditions. The USP XXI salicylic acid calibrator tablet was used as test formulation. The results obtained by the flow-through method were compared with data generated using the compendial USP XXI paddle method. The flow-through method was found to produce reproducible and corresponding dissolution data both within and among the different laboratories. It can be concluded that the flow-through method does not produce larger variations, expressed in terms of ranges of amount dissolved at various times, compared to the paddle method. In fact, at some flow conditions, smaller variations were obtained with the flow-through method compared to the paddle method. This was confirmed by the coefficients of variation for the time to dissolve 20, 50, and 80% of the salicylic acid. The coefficient of variation was also found to decrease with increasing hydrodynamic intensity for both dissolution methods. The use of deaerated dissolution medium was found to be a critical experimental factor and the need for a proper pretreatment of the medium must be emphasized.

Introduction

Dissolution testing has become an important tool in solid dosage form development and quality control. However, even if in vitro dissolution testing cannot replace in vivo bioavailability assessment, it gives the formulator valuable biopharmaceutical information in a dosage form design program. Several dissolution methods have been described (Braun and Walker, 1969; Langenbucher and Rettig, 1977; Needham et al., 1978; Rothe and Schellhorn, 1977; Simmons et al., 1980; Tingstad et al., 1973; Weintraub and Gibaldi, 1970) and some of them have been improved over the past 20 years in order to meet world-wide standardization procedures (Cox et al., 1978; Hanson, 1982; United States Pharmacopeia, 1985). For the latter ones, i.e. the official compendial methods, practical aspects on dissolution testing have been revealed and the importance of using standardized experimental conditions for producing reproducible results has been emphasized

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(Cartwright, 1979a; Cox and Furman, 1984; Hanson, 1982).

The compendial methods, described in different pharmacopeias, can be regarded as closed system-stirring methods which operates under finite sink conditions. However, another approach would be to operate under infinite sink conditions by applying an open flow-through system. In order to make adequate biopharmaceutical interpretations in a formulation design program, various in vitro dissolution test conditions must be investigated. Thus, application of both closed and open systems will increase the fundamental understanding in terms of in vitro dissolution properties of a given solid dosage form. In a joint report from the section for control laboratories and the section of industrial pharmacists of the F.I.P. both these alternatives were recommended as meaningful alternatives for a dissolution test (Möller et al., 1981). The application of the flow-through dissolution method has been shown in several papers (Herzfeldt, 1980; Langenbucher, 1969; Langenbucher and Rettig, 1977; Möller, 1983; Möller, 1985; Posti and Speiser, 1980; Tingstad and Riegelman, 1970; Tingstad et al., 1972; Tingstad, 1978). This method introduces an important aspect on dissolution testing since it solves the problem of sink conditions when investigating poorly soluble compounds by continuously exposing the formulation with a flow of fresh solvent (Hanson, 1982; Langenbucher and Rettig, 1977).

Several comparative evaluations of various dissolution apparatuses have been conducted (Baichwal et al., 1985; Carstensen et al., 1978; Möller, 1985; Needham and Luzzi, 1974; Ogata et al., 1979; Prasad et al., 1983; Smith et al., 1985). The precision obtainable with compendial dissolution testing apparatus has been studied (Thakker et al., 1980; Lea et al., 1985) as well as the systematic errors associated with a given compendial dissolution method (Cox and Furman, 1982; Cox et al, 1982 and 1983b; Cox and Furman, 1984). Large systematic errors were found among laboratories that contributed data from which the USP acceptance ranges for the official calibrator tablets were derived (Cox et al., 1983a). However, even if the sources of these errors were found to be unknown, the authors emphasized that the USP suitability test cannot ensure correct equipment operation. Different sources of variation during a collaborative study of in vitro dissolution tests have been examined and factors such as vibration, analytical procedures, design of the dosage form tested etc. were found to be of significant importance for the outcome of the tests when using the USP basket method (Cartwright, 1979b).

In the present study, different laboratories have been investigated the dissolution rate from a standard tablet formulation (USP XXI salicylic acid calibrator tablets) using the flow-through dissolution method. The aim of this collaborative study is to investigate the application of the flow-through method at different hydrodynamic conditions and to compare the results obtained from each laboratory in order to evaluate the inter-laboratory variations when using this dissolution test method. The results obtained by using the flow-through method are also compared with corresponding data generated by using the USP XXI paddle method.

Materials and Methods

Test laboratories

Five different pharmaceutical and analytical laboratories participated in this collaborative dissolution study (Astra Alab AB, Södertälje, Sweden; Draco AB, Lund, Sweden; AB Hässle, Mölndal, Sweden; Ferring AB, Malmö, Sweden; Ferrosan AB, Malmö, Sweden).

Test formulation

USP dissolution calibrator tablets lot H, non-disintegrating type, containing salicylic acid were used as test formulation (USP-NF Reference Standards, Rockville, U.S.A.).

In vitro dissolution tests

A flow-through apparatus (SOTAX AG, Switzerland) with cells of a diameter of 12 mm i.d., supplied with dissolution medium by a piston pump were used in all experiments. The apparatus has been described thoroughly by Möller (1983).

Prior to the dissolution experiments, it was agreed by the collaborators to follow the operating

conditions specified by the USP-NF Reference Standards for non-disintegrating calibrator tablets, i.e. preparation of the dissolution medium (pH 7.4, 37 °C), handling of the tablets prior to the experiments and concentration measurements of salicylic acid using spectrophotometry at 296 nm. It was also agreed that dissolved gases should be removed sufficiently prior to testing and that the flow rate through the dissolution cells should be kept constant within ±1 ml/min during the experiments. Six tablets were tested at each run using flow rates of 8, 16 and 50 ml/min respectively. During each run, fresh dissolution medium was pumped through each cell and the eluate was collected in separate fractions during different time periods, i.e., 0–5, 5–10, 10–15, 15–20, 20–30, 30–45, 45–60, 60–90, 90–120, 120–180, and 180–240 min or until the tablets were completely dissolved. The tablets were positioned directly onto a bed of 2.5 g of glass beads (0.75–1.00 mm) thus filling up the conical part at the bottom of each cell.

A separate dissolution study was performed on the salicylic acid tablets using the USP XXI paddle method. The same experimental conditions were used as mentioned above for the flow-through apparatus regarding dissolution medium, handling of the tablets prior to the experiments and analytical performance. Two agitation conditions were tested, 50 and 100 rpm, using 6 individual tablets at each run.

Results and Discussion

Fig. 1 shows the mean curves of the amount of salicylic acid dissolved vs time obtained in each laboratory using the flow-through method at a flow rate of 16 ml/min. Laboratory nos. 4 and 5 deviate significantly from the other ones as can be seen from the two lower curves. It was concluded later on that these two laboratories didn't remove dissolved gases properly before the test. The consequences of dissolved gases and air in the dissolution medium has been thoroughly outlined by Hanson (1982). In a paper by Cox et al. (1983b), results obtained with the USP XX paddle method using prednisone tablets were found to be influenced by the concentration of air in the dissolution medium. The reproducibility was also markedly improved when the air concentration in the medium was accurately controlled at the beginning of the test. Consequently, laboratory no. 4 changed the procedure for removing dissolved gases in the medium. A second test was performed at 16 ml/min and, as can be seen in Fig. 1, a corresponding dissolution rate profile was obtained compared to laboratories nos. 1-3. Laboratory no. 5 was not able to conduct a second test with properly deaerated medium and data generated by this laboratory are therefore omitted in the following presentation. The results shown in Fig. 1 for laboratories 4 and 5, thus, demonstrate the need for a careful pretreatment of the dissolution medium in order to remove any dissolved air or gases before a dissolution test is performed with the flow-through method.

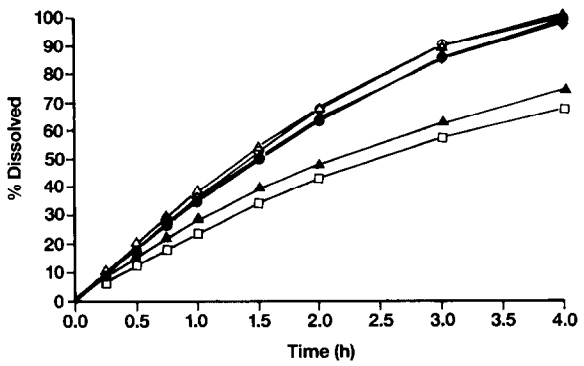

Fig. 1. Percent salicylic acid dissolved vs time at pH 7.4 using the flow-through method at 16 ml/min. Mean curves, USP-calibrator tablets, Lot H; ○, laboratory 1; ●, laboratory 2; ◇, laboratory 3; △, laboratory 4; ▲, laboratory 4 without deaerated medium; □, laboratory 5 without deaerated medium.

Table 1 shows the ranges of amount of salicylic acid dissolved at 16 ml/min as a function of time for each laboratory. The intralaboratory variation is small. The largest range obtained at 6 individual runs in a laboratory is not more than 8% (see laboratory 2 after 3 h run). Furthermore, the overall maximum difference, i.e. the difference between the largest and the smallest amount dissolved at a given sampling time among all laboratories, was also found to be not more than 8%, see Table 1 after 2 and 3 h run. This indicates that the

TABLE 1

Percent salicylic acid dissolved at pH 7.4 (range, n = 6) using the flow-through method, 16 ml/min, 37 °C

Time (h)	Laboratory no.				Maximum difference * (%)
	1	2	3	4	
0.25	8– 10	9– 10	8–10	9– 10	2
0.5	18– 19	17– 19	16–19	19– 21	5
0.75	27– 28	26– 28	24–29	29– 30	6
1.0	35– 37	34– 37	33–37	37– 38	5
1.5	51– 54	48– 53	48–53	54– 55	7
2.0	66– 69	61– 67	62–66	66– 68	8
3.0	88– 91	83– 91	83–86	87– 90	8
4.0	101–101	99–102	98–99	100–101	3

* Between all laboratories ($n = 24$).

TABLE 3

Percent salicylic acid dissolved at pH 7.4 (range, n = 6) using the flow-through method, 50 ml/min, 37 °C

Time (h)	Laboratory no.			Maximum difference * (%)
	2	3	4	
0.25	16– 18	15– 16	15–16	3
0.5	31– 34	30– 31	28–30	6
0.75	45– 49	44– 45	40–43	9
1.0	57– 62	55– 57	50–55	12
1.5	78– 82	75– 79	65–74	17
2.0	94– 98	90– 95	77–86	21
3.0	99–103	100–100	89–96	14

* Between all laboratories ($n = 18$). Laboratory no 1 didn't conduct a test at this flow rate.

flow-through method at 16 ml/min is capable of producing uniform and reproducible dissolution results with small intra- and inter-laboratory variations when using the USP salicylic acid calibrator tablets.

Tables 2 and 3 show the amounts of salicylic acid dissolved (range) as a function of time using both a lower (8 ml/min) and a higher (50 ml/min) flow rate. At 8 ml/min, somewhat larger ranges were found after a few hours dissolution time compared to at 16 ml/min (see Table 2). However, during the first hours of release, a relatively small overall maximum difference was obtained which is comparable to the ranges found at 16 ml/min. Low variations were also found during the first hour of release at 50 ml/min (Table 3). After 1.5–2 h release time, a somewhat higher variation can be seen.

Fig. 2 shows the mean dissolution curves for salicylic acid obtained by means of the USP XXI paddle method at 50 rpm. By comparing the mean curves in Fig. 2 by those shown for the same laboratories in Fig. 1, one may conclude that the flow-through method at 16 ml/min generates more corresponding interlaboratory results than the USP paddle method when using the salicylic acid calibrator tablets. Tables 4 and 5 summarize the numerical results obtained at both agitation conditions with the paddle method. It is quite interesting to compare the overall maximum difference

TABLE 2

Percent salicylic acid dissolved at pH 7.4 (range, n = 6) using the flow-through method, 8 ml/min, 37 °C

Time (h)	Laboratory no.				Maximum difference * (%)
	1	2	3	4	
0.25	4– 7	4– 6	4– 6	4– 9	5
0.5	11–14	9–12	9–13	9–16	7
0.75	18–21	13–18	13–19	16–22	9
1.0	26–28	18–24	17–25	21–29	12
1.5	37–41	28–36	26–36	29–35	15
2.0	48–52	39–46	35–47	37–42	17
3.0	66–72	59–65	51–67	50–54	22
4.0	81–88	74–81	67–82	60–65	28

* Between all laboratories ($n = 24$).

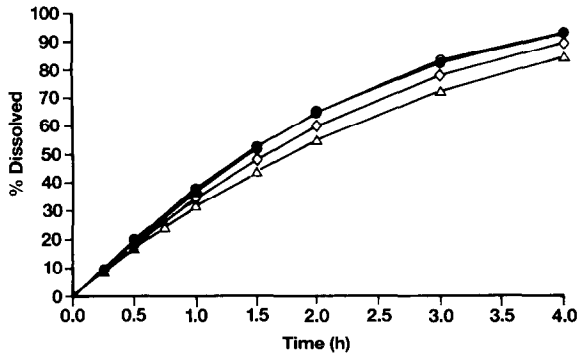

Fig. 2. Percent salicylic acid dissolved vs time at pH 7.4 using the USP XXI paddle method at 50 rpm. Mean curves USP-calibrator tablets, Lot H; ○, laboratory 1; ●, laboratory 2; ◇, laboratory 3; △, laboratory 4.

as well as the intralaboratory ranges obtained by this compendial dissolution method with the ranges given in Tables 1–3 for the flow-through method at the same sampling times. At 50 rpm, similar or somewhat higher ranges are found compared to the flow-through method at a flow rate of 8 ml/min. Similar ranges are also obtained with the paddle method at 100 rpm and the flow-through method at 50 ml/min. However, the flow-through method at a flow rate of 16 ml/min obviously produces significantly smaller ranges both between and among the laboratories compared to the USP XXI paddle method at either 50 or 100 rpm.

TABLE 4

Percent salicylic acid dissolved at pH 7.4 (range, n = 6) using the USP XXI Paddle method, 50 rpm, 37 °C

Time (h)	Laboratory no.				Maximum difference * (%)
	1	2	3	4	
0.25	8–11	8– 11	–	8–11	3 **
0.5	16–23	18– 25	16–20	15–21	10
1.0	31–45	31– 46	30–37	28–33	16
1.5	43–62	44– 62	42–51	39–53	23
2.0	54–76	56– 73	52–64	50–64	26
3.0	74–93	76– 90	70–83	65–80	28
4.0	88–99	89–100	84–93	76–89	24

* Between all laboratories ($n = 24$).
** $n = 18$.

TABLE 5

Percent salicylic acid dissolved at pH 7.4 (range, n = 6) using the USP XXI Paddle method, 100 rpm, 37 °C

Time (h)	Laboratory no.				Maximum difference * (%)
	1	2	3	4	
0.25	10–13	11– 13	–	9–10	4 **
0.5	21–26	24– 26	21– 24	18–20	8
1.0	38–47	41– 46	37– 43	34–37	13
1.5	53–62	56– 61	51– 59	48–52	14
2.0	66–74	67– 74	63– 74	60–65	14
3.0	85–91	84– 92	81– 93	77–86	16
4.0	96–99	95–102	91–100	88–97	14

* Between all laboratories ($n = 24$).
** $n = 18$.

A somewhat different picture of the situation is illustrated in Table 6. Instead of comparing ranges of amount dissolved at various times, Table 6 shows the coefficient of variation for the time to dissolve 20, 50, and 80% of salicylic acid at various test conditions. The coefficient of variation has a tendency to become smaller at higher flow rates for the flow-through method and at more intense stirring rates for the paddle method. The reproducibility is accordingly also better at higher flow rates and at a more intense stirring. It also seems to be easier to obtain a better reproducibility over a wide range of flow rates (16–50 ml/min) for the flow-through method than with the paddle method at 50 or 100 rpm. An explanation to this is that the flow pattern in the vicinity of the solid/liquid interface is an important factor that governs the mass transport. At low flow rates, when the flow is semilaminar, the pattern is easily disturbed by irregularities on the surface of the tablet, eccentric positioning of the tablet and variations of the flow rate with time (Wennergren et al., 1986). At higher flow rates, with semiturbulent or turbulent flow, the sensibility of the flow pattern is less pronounced.

Conclusions

The flow-through method at 16 ml/min was found to produce the most consistent dissolution results between 4 different laboratories using the USP XXI salicylic acid calibrator tablets as test formulation.

The coefficients of variation for the time to dissolve 20, 50, and 80% indicated a better reproducibility over a wide range of flow rates for the flow-through method than with the paddle method at 50 or 100 rpm. For both methods, however, a lower coefficient of variation was obtained at higher hydrodynamic intensities. The use of deaerated dissolution medium was found to be a critical experimental factor for the flow-through method. If the medium is not properly deaerated, a significant reduction of the salicylic acid dissolution rate was obtained.

The data presented in this study for salicylic acid calibrator tablets thus give support to the application of the flow-through method as an alternative to the compendial USP XXI paddle method in a dosage form design program. However, further similar studies are needed in order to

TABLE 6

Coefficient of variation (n = 6) for the time to dissolve 20, 50, and 80% of salicylic acid obtained by each laboratory using either the flow-through method or the USP XXI paddle method

	Flow-through method			USP XXI Paddle method	
	8 ml/min	16 ml/min	50 ml/min	50 rpm	100 pm
20%					
Lab 1	5	3	–	13	8
Lab 2	11	4	4	12	4
Lab 3	12	8	1	9	6
Lab 4	31	5	5	13	4
50%					
Lab 1	2	2	–	13	7
Lab 2	6	4	3	12	4
Lab 3	9	4	1	8	6
Lab 4	3	1	4	11	3
80%					
Lab 1	3	1	–	9	4
Lab 2	3	4	2	7	3
Lab 3	6	2	2	8	6
Lab 4	–	1	5	7	4

support the adoption of the flow-through method as an alternative compendial method for dissolution testing. The authors therefore look forward, with great interest, to future publications by other laboratories comparing the flow-through method with already accepted compendial methods at various experimental conditions.

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