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A collaborative study of the in vitro dissolution of acetylsalicylic acid gastro-resistant capsules comparing the flow-through cell method with the USP paddle method

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Abstract

A collaborative in vitro dissolution study was performed comparing the Flow-through cell (FTC) method with the USP Paddle method. The objective was to compare the two methods regarding their suitability for changing the pH of a dissolution medium and for measuring the in vitro dissolution of a gastro-resistant dosage form. Aspirin, a gastro-irritant substance in an enteric-coated, multiple-unit dosage form, was used as the test material. The results show that the FTC method gives comparable results compared with the Paddle method. The FTC method is also more convenient to use for shifting the pH from an acidic condition at pH 1.2 to a pH of 6.8. The effect of different ionic strengths of the dissolution media on dissolution rate results was observed for the test product by using the FTC method. © 1997 Elsevier Science B.V.

Keywords: Dissolution testing; Flow-through method (FTC); Flow cell; USP Paddle method; Acetylsalicylic acid (Aspirin); Collaborative study; Gastro-resistant capsules; pH-change; Ionic strength

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1. Introduction

The Scandinavian collaborative dissolution group (SCDG) on in vitro dissolution testing has previously reported on the use of the Flow-through cell method (FTC) (Nicklasson et al., 1987; Wennergren et al., 1989; Nicklasson and Langenbucher, 1990; Nicklasson et al., 1991) and the method has subsequently been introduced in the USP and Ph. Eur. This previous work by the SCDG has focused on the comparison of the two different techniques of dissolution testing on USP dissolution calibrator tablets and drug substances per/se in order to study the inter- and intravariability of the dissolution data of the different participating laboratories. It could therefore be of interest to study more specifically the data obtained by the FTC method (USP) for products with an established USP Apparatus I or II method.

One of the advantages of the FTC method is the possibility of changing the pH during experiments. For enteric-coated products, acid resistance is tested by pH-shift experiments, and the general drug-release standards for enteric coated formulations described in the USP are Basket and Paddle methods. In this methods the dissolution medium is 0.1 M HCl for 2 h. The pH is then changed to 6.8 by adding a 0.2 M trisodium phosphate solution. Adjusting the pH with NaOH or HCl may be necessary. Here, the FTC method, which readily allows a change of pH during the dissolution test, while keeping the ionic strength of the 2 pH levels the same, could be an alternative method for enteric coated dosage forms.

The aim of the present investigation was to compare the FTC method with the Paddle method by exploring the applicability of the FTC method for enteric coated dosage forms using the same dissolution media. Applicability being defined as convenience, an easy shift of pH, and variation between and within different laboratories.

2. Experimental

2.1. Test laboratories

A total of six different laboratories participated in this collaborative dissolution study: Astra Draco AB, Lund, Sweden; Astra AB, Södertälje, Sweden (represented by Astra Läkemedel AB and Astra Arcus AB); Gacell Laboratories AB, Malmö, Sweden; Pharmacia and Upjohn, Inc., Stockholm, Sweden; The Medical Products Agency, Uppsala, Sweden, and Nycomed Pharma Research and Development, Roskilde, Denmark.

3. Test formulation

Aspirin (Reumyl® 500 mg, Astra; Batch RK719) gastro resistant capsules were used as the test formulation.

The test formulation was chosen on the basis that the drug should be well-known and easy to analyse, criteria met by acetylsalicylic acid. According to the focus on dose-dumping problems for controlled-release compositions, it was an advantage that Reumyl® was a multiple-unit, enteric coated, gastro-resistant capsule.

3.1. Test equipment/apparatus

3.1.1. Paddle method (USP 23)

A total of two laboratories used a Sotax AT6 (Sotax AG, Switzerland) and the other laboratories used a Dissolutest (Prolabo, France).

3.1.2. FTC method (USP 23)

Each laboratory used the standard FTC system consisting of the Sotax CE6 dissolution-testing apparatus (Sotax AG, Switzerland) with six cells and the CY6D piston pump.

3.1.3. Calibration status

The laboratories calibrated their Paddle apparatus concerning temperature and agitation. In addition, three of the six laboratories also used the USP calibration tablets.

The FTC method was by all laboratories calibrated concerning temperature and flow rate measurements.

3.2. Dissolution media

The laboratories used different deaeration

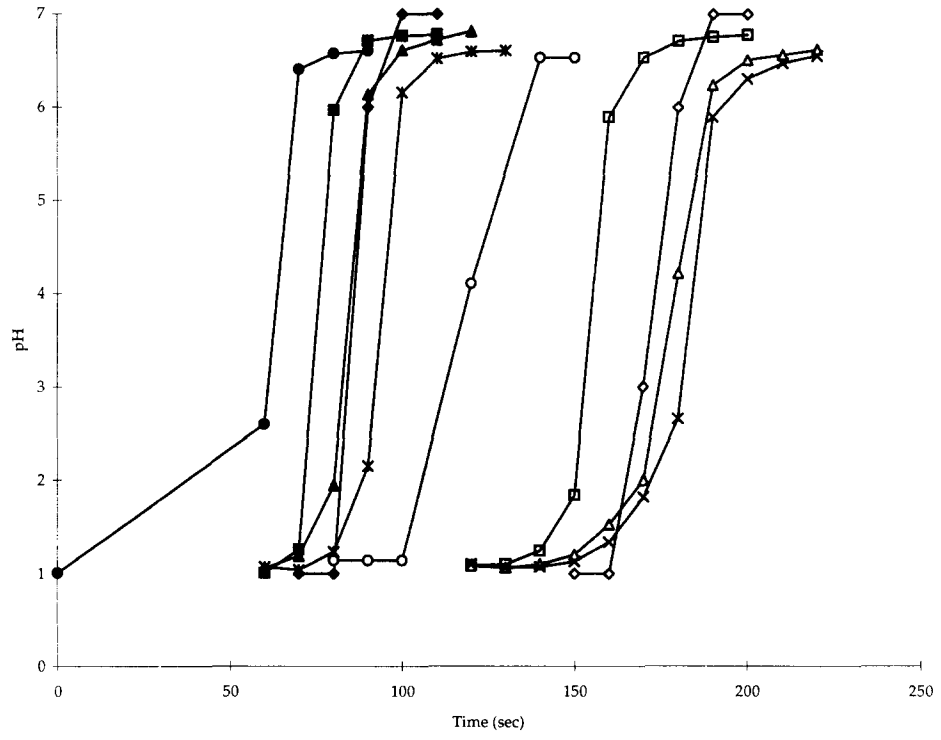

Fig. 1. Time for pH to change from pH 1.2 to 6.8 with the FTC method at 8 ml/min (open and cross symbols) and 16 ml/min (filled and star symbols) for five of the participating laboratories.

methods: heating, helium degassing, ultrasonification and vacuum filtration.

3.2.1. Paddle method

The dissolution medium was prepared according to USP method A. A volume of 750 ml of 0.1 M HCl was used for 2 h, and 250 ml of 0.2 M Na_3PO_4 was then added. The resulting pH of 7.1–7.2 was adjusted with 2 M HCl to pH 6.8. The resulting ionic strength at pH 6.8 was 0.22.

3.2.2. FTC method

The dissolution medium for the first 2 h in the FTC experiments was 0.1 M HCl. In order to have identical dissolution conditions with the same ionic strength at pH 6.8, it was necessary to prepare the dissolution medium with the same concentration of HCl and trisodium phosphate as for the Paddle experiments. Thus, for a 1000 ml medium, 750 ml of 0.1 M HCl was mixed with 250 ml of 0.2 M Na_3PO_4 and adjusted to pH 6.8 with 2 M HCl.

The experiments were widened to study the effect of the ionic strength on the dissolution rate of aspirin from the Reumyl® capsules since three laboratories did not change medium pH according to USP method A. Instead they changed from 0.1 M HCl to the ordinary phosphate buffer of pH 6.8 (USP) with a lower ionic strength ($\mu = 0.10$) compared to the Paddle tests ($\mu = 0.22$). The ionic strength experiments ($\mu = 0.10$) were performed at flow rates of 8, 12 and 16 ml/min by three laboratories ($n = 3$). These three laboratories also performed one more experiment each at flow rates of 8, 12 and 16 ml/min so that four paralells (n = 4) were obtained in the FTC experiments at the higher ionic strength($\mu = 0.22$).

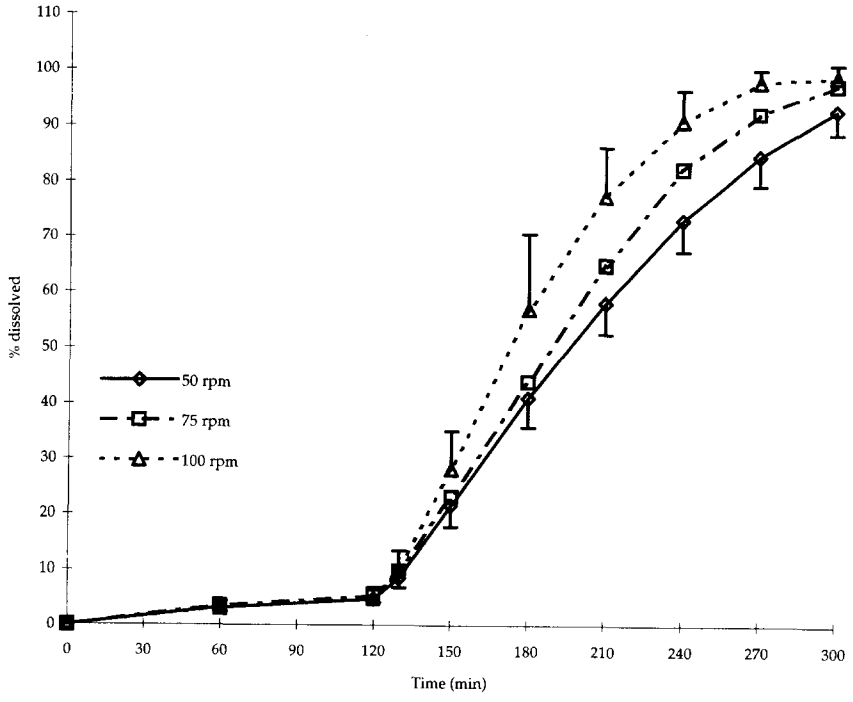

Fig. 2. Percent aspirin of labelled amount dissolved versus time using the Paddle method at 37°; pH 1.2 for 120 min and buffer pH 6.8 with an ionic strength of 0.22 μ for 180 min (120–180 min). Mean curves based on results from six laboratories ($n = 36$). Bars denote the S.D.

3.3. In vitro dissolution test procedure

The pellet content of six Reumyl® capsules was studied in each experiment ($n = 6$). To avoid interference from the capsule shell during ultraviolet detection, only the pellets were investigated.

3.3.1. Paddle method

The comparative studies with the Paddle method were performed at stirring rates of 50, 75 and 100 rpm, respectively. The experiments were conducted according to the procedure described in the USP.

At the sampling times, 60, 120, 130, 150, 180, 210, 240, 270 and 300 min, 10 ml was withdrawn with a pipette fitted with a Technicon filter. At 60 and 120 min only, the withdrawn aliquot was replaced with 10 ml of 0.1 M HCl to ease the pH shift procedure at 120 min keeping the volume fixed at 750 ml. The withdrawn aliquots after 120 min was judged to not influence on the dissolution process of acetylsalicylic acid and they were therfore not replaced.

3.3.2. FTC method

The powder cell with a diameter of 12.0 mm was used in all the experiments. The pellets were placed on a bed of approximately 1 g of 1 mm glass beads. The flow rates used for the experiments were 8, 12 and 16 ml/min ± 5%, respectively. Millipore AP25 filters (Millipore, USA) were used to filter the eluate during the test. Eluate from each cell was collected and weighed for the following periods: 0–60, 60–120, 120–130, 130–150, 150–180, 180–210, 210–240, 240–270 and 270–300 min.

The ability of the FTC system to change the dissolution medium and thus the pH during the experiments was evaluated separately at each laboratory by measuring pH as a function of time from the moment when the medium was changed. The duration of the pH shift took about 1–3 min, depending on the tube length and the flow rate (Fig. 1). The individual pH-change time for the laboratories was thereafter applied so that the pH was 6.8 at time 120 min.

Table 1
Percent aspirin of labelled amount dissolved from Reumyl®, gastro resistant capsules 500 mg, using the Paddle method

	Time (min)	Laboratory no. ($n = 6$)						Overall range ($n = 36$)	Mean ($n = 36$)	±S.D.
		1	2	3	4	5	6			
50 rpm	60	2–4	3–4	2–3	1–3	3–5	3–3	4	3	0.7
	120	4–6	5–6	4–5	3–5	4–7	5–5	3	4	0.7
	130	7–9	8–9	7–10	6–8	10–13	8–9	7	8	1.7
	150	17–22	21–23	17–25	15–22	23–35	19–23	8	22	3.9
	180	33–40	41–46	31–47	29–42	42–56	38–44	27	41	5.3
	210	51–60	57–64	45–65	43–59	60–72	54–62	29	58	5.5
	240	67–78	70–76	60–81	57–73	77–85	67–76	21	73	5.7
	270	81–90	82–87	72–93	71–85	87–94	79–85	19	84	5.2
	300	92–98	90–95	81–95	82–92	94–99	88–96	18	93	4.2
75 rpm	60	3–4	2–4	4–5	2–3	3–4	4–4	3	4	0.7
	120	5–6	4–6	6–6	4–5	5–6	5–6	2	5	0.7
	130	9–10	7–9	9–13	8–9	10–14	10–11	7	10	1.8
	150	23–26	18–20	20–21	20–22	25–33	23–27	15	23	3.9
	180	44–52	36–38	34–39	38–43	48–58	45–52	22	44	6.5
	210	65–76	54–57	51–60	57–63	71–80	66–77	29	65	8.1
	240	84–97	71–77	66–78	74–81	89–94	82–95	31	82	8.8
	270	96–101	85–90	69–8	88–93	98–102	93–100	33	92	7.3
	300	99–102	92–96	87–97	96–99	98–105	86–103	19	97	4.3
100 rpm	60	3–4	3–4	3–4	3–4	0–0	3–4	4	3	1.4
	120	5–6	5–6	5–6	6–7	0–2	5–7	7	5	1.9
	130	10–21	8–10	10–11	10–11	4–6	13–14	17	10	3.2
	150	27–42	24–27	24–26	24–26	20–22	36–44	24	28	6.9
	180	54–72	50–57	46–52	46–50	44–48	77–91	47	57	13.6
	210	76–89	74–85	69–79	66–71	67–71	84–94	28	77	8.7
	240	91–98	90–98	85–93	82–89	82–86	95–100	18	91	5.5
	270	98–102	96–101	97–99	93–98	96–100	95–98	8	98	2.2
	300	99–102	98–101	98–103	97–100	98–101	92–98	11	99	2.2

Different agitation rates were used, 0–120 minutes in 0.1M HCl thereafter 120–300 minutes in buffer pH 6.8 with an ionic strength of 0.22.

A typical experimental procedure including change of the dissolution medium, can be described as follows: the experiment started with the pumping of 0.1 M HCl. After 117–119 min the pump and the timer are stopped and the inlet tube of the piston pump is moved from the 0.1 M HCl solution to the pH 6.8 buffer solutions. The pump and the timer are restarted and at 120 min the pH of the medium passing the pellets should be 6.8.

3.4. Analysis

The principle of the analysis was that acetylsalicylic acid is hydrolysed to salicylate by the addition of NaOH.

A 2 ml aliquot of the sample was mixed with 3 ml of 1 M NaOH. After 1 min 15.00 ml water was added before spectrophotometric analysis at 296 nm. Salicylic acid was used as the reference standard and was treated identically.

3.5. Calculations and statistical methods

The amount of aspirin dissolved was calculated as a percentage of the labelled amount. Corrections were made for loss of the volume in the Paddle method due to the fact that sampling was performed without replacing the volume in the pH 6.8 buffer solution.

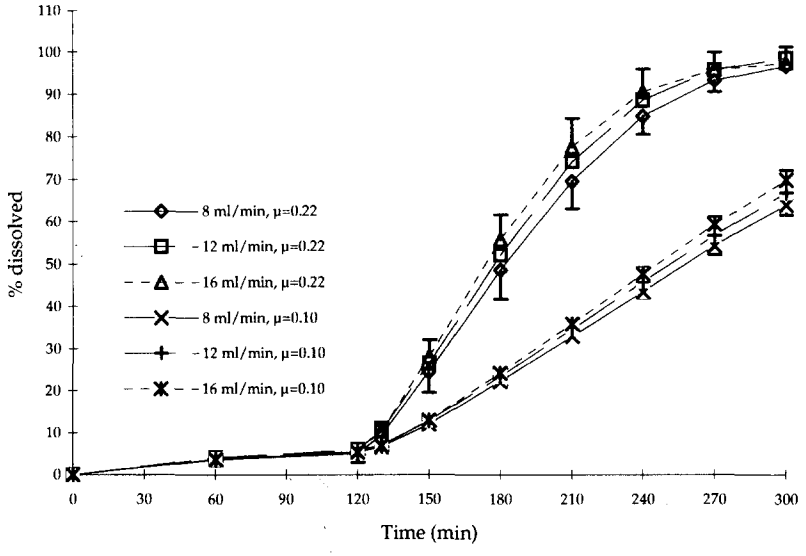

Fig. 3. Percent aspirin of labelled amount dissolved versus time using the FTC method at 37°; pH 1.2 for 120 min and buffer pH 6.8 with 2 different ionic strengths (0.22 and 0.10 μ) for 180 min (120–300 min). Mean curves based on results from four ($n = 24$, open symbols) and three ($n = 18$, cross symbols), laboratories, respectively. Bars denote the S.D.

Descriptive statistics, including mean values, overall range and standard deviations, were calculated for the in vitro dissolution data.

The in vitro dissolution data was transformed into a linear plot by means of the Weibull transformation (Langenbucher, 1976 and Christensen et al., 1989), by applying the following equation:

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

where $R(t)$ represents the accumulated amount released at time t, τ is a scale parameter: the time at which 63.2 % has been dissolved, less the lag time (120 min), and β denotes a shape parameter representative of the slope, and hence an index of the dissolution rate.

In order to investigate possible differences between the profiles and the techniques, a traditional t-test was used to compare τ and β. Variance between and within the laboratories was studied comparing the τ values by ANOVA one-way analysis of variance. For both tests statistical significance was declared for an outcome of $P \leq 0.05$.

4. Results and discussion

Fig. 2 and Table 1 show the average percentage of aspirin dissolved as a function of time with the Paddle technique, using data generated by all laboratories under the given hydrodynamic conditions ($n = 36$). The profiles are somewhat separated where the agitation rate of 100 rpm has caused a faster dissolution rate than 75 and 50 rpm, respectively. The τ values of the mean profiles for 75 and 100 rpm and 50 and 100 rpm were compared using a t-test and it was shown that τ was significantly separated in both cases.

Fig. 3 and Table 2(a) show the in vitro dissolution data for aspirin capsules generated by four laboratories ($n = 24$) using the FTC method. It can be seen that the flow-rate influenced only to a small extent the release rate of aspirin from the pellets and that the three profiles are similar. However, according to the t-test, τ was significantly separated for flow rates of 8 and 16 ml/min, but not for flow rates of 12 and 16 ml/min.

Table 2
Percent aspirin of labelled amount dissolved from Reumyl®, gastro resistant capsules 500 mg, using the FTC method at different flow rates

	Time (min)	Laboratory no. ($n = 6$)						Overall range ($n = 24$)	Mean ($n = 24$)	±S.D.
		1	2	3	4	5	6			
(a)										
8 ml/min	60	3–4		3–4	2–3	4–4		2	3	0.7
	120	4–6		5–6	3–3	6–6		3	5	1.2
	130	7–11		8–9	6–7	11–12		6	9	2.0
	150	19–27		21–23	24–24	27–29		10	24	2.7
	180	36–52		40–44	51–52	50–54		18	48	5.0
	210	56–74		57–63	74–75	71–76		20	70	6.7
	240	72–89		74–79	89–90	86–90		18	85	6.4
	270	90–97		84–90	94–97	94–97		13	93	4.3
	300	95–99		91–96	95–98	96–100		9	96	2.6
12 ml/min	60	3–5	4–4	4–4		3–5		2	4	0.6
	120	4–7	6–7	5–6		5–7		3	6	1.0
	130	9–12	9–11	10–11		10–12		2	10	1.0
	150	25–29	23–25	28–29		25–28		6	27	2.1
	180	51–57	43–49	56–57		50–54		14	52	4.4
	210	72–78	63–71	78–80		72–75		17	74	5.1
	240	87–91	79–87	90–93		88–91		14	88	4.0
	270	94–96	89–97	95–97		98–100		11	96	2.8
	300	95–97	94–100	96–98		102–105		11	98	3.2
16 ml/min	60	3–4		4–5		4–5	2–3	3	4	0.8
	120	5–6		6–7		6–7	3–5	4	6	1.4
	130	10–12		11–13		10–13	6–9	5	10	2.1
	150	28–30		30–34		20–31	22–25	12	28	4.0
	180	55–59		60–65		48–59	46–50	19	56	5.9
	210	76–83		82–86		70–81	64–71	22	78	6.7
	240	90–96		90–96		84–95	76–86	20	90	5.3
	270	97–101		92–97		90–101	83–94	18	96	4.2
	300	98–102		92–97		92–103	87–98	15	97	3.8

(b)	Time (min)	Laboratory no. ($n = 6$)			Overall range ($n = 18$)	Mean ($n = 18$)	±SD
8 ml/min	60	3–4	3–3	4–4	1	4	1.4
	120	5–6	4–5	6–6	2	5	0.7
	130	6–7	5–6	7–7	2	6	0.7
	150	11–13	11–12	12–13	2	12	0.7
	180	21–23	21–23	21–24	3	22	0.9
	210	31–34	32–34	31–35	4	33	1.2
	240	42–45	42–44	40–46	6	43	1.5
	270	52–56	52–55	49–58	9	54	2.0
	300	62–66	62–65	58–67	9	64	2.3
12 ml/min	60	3–6	3–4	4–5	3	4	0.7
	120	5–9	4–5	5–7	5	6	1.2
	130	6–10	5–6	7–8	5	7	1.3
	150	12–16	11–12	12–14	5	13	1.2
	180	23–27	22–23	22–25	5	23	1.3
	210	35–38	32–35	31–36	7	34	1.6
	240	46–50	45–47	41–47	9	46	2.3
	270	58–62	54–58	50–57	12	56	3.0
	300	68–72	64–69	58–64	14	67	3.4

Table 2 (continued)

	Time (min)	Laboratory no. ($n = 6$)						Overall range ($n = 18$)	Mean ($n = 18$)	±S.D.
		1	2	3	4	5	6			
16 ml/min	60		3–4		3–4		4–4	1	3	0.4
	120		4–5		4–6		6–6	2	5	0.5
	130		5–7		6–7		7–8	2	6	0.6
	150		11–13		12–14		14–15	3	12	0.7
	180		22–24		23–25		25–26	3	24	0.9
	210		34–35		35–37		36–38	4	35	1.1
	240		45–47		46–49		48–50	4	47	1.3
	270		56–58		58–60		60–63	4	58	1.5
	300		66–69		68–71		70–73	5	69	1.7

In Table 2(a), 0–120 min in 0.1 M HCl thereafter 120–300 min in buffer pH 6.8 with an ionic strength of 0.22.
In Table 2(b), 0–120 min in 0.1 M HCl thereafter 120–300 min in buffer pH 6.8 with an ionic strength of 0.10.

Fig. 3 also illustrates the effect on dissolution rate when using buffers with different ionic strengths in the FTC method. The dissolution data is given in Table 2(b). A faster release is obtained with the buffer prepared according to the prescription for the Paddle experiments ($\mu = 0.22$), while the buffer with the lower ionic strength ($\mu = 0.10$) produces a significant slower release from the aspirin capsules. This illustrates the importance of controlling the ionic strength in in vitro dissolution experiments. Using the FTC method, it is possible to perform pH shifts without changing the ionic strength in contrast to the Paddle method.

Table 3(a) lists the mean τ and β values calculated for the experiments performed with the ionic strength of 0.22. It can be seen that the shape factor, β, is the same for data generated by the FTC technique. For the Paddle results, the shape factor, is significantly separated at 75 and 100 rpm. The shape factor is identical for the Paddle 100 rpm results and results from the FTC technique, indicating that the dissolution process seems to be the same for both techniques.

The scale parameter, τ (time taken to reach 63.2% dissolved), is considered to be equal using ANOVA for results obtained by the Paddle 100 rpm method and the FTC technique with flow rates of 12 and 16 ml/min. This means that the FTC method at flow rates of 12 and 16 ml/min produces in vitro dissolution results which are comparable to those generated by the Paddle method at 100 rpm for Reumyl® gastro-resistant capsules 500 mg.

Table 3(b) lists the mean τ and β values calculated for the experiments performed with the ionic strength of 0.10 in the FTC method. The shape factor obtained is the same at all three flow rates and is also the same as the shape factor calculated from dissolution profiles at the higher ionic strength. However, the time taken to 63.2% is dissolved, τ, is longer at the lower ionic strength. These results indicate that the difference in ionic strength influences only the dissolution rate and not the dissolution process.

Table 4 shows the results from the one-way ANOVA analysis of τ for the combinations of method and agitation rate/flow rate. It can be seen that there is a significantly greater variation between the laboratories compared with the variation in the results within the laboratories. The mean square between laboratories, is generally greater for the Paddle method than the FTC method. This can also be seen in Tables 1 and 2. The results show that the FTC method generates as reproducible data for the aspirin gastro-resistant pellet capsule as the Paddle method.

The practical experience gained from these comparative experiments is that it takes time to achieve the pH shift in the Paddle method, and

Table 3
Calculated mean τ and β values ± S.D. according to the Weibull distribution

	Agitation rate/flow rate	Laboratory no.						Mean ± S.D.
		1 ($n=6$)	2 ($n=6$)	3 ($n=6$)	4 ($n=6$)	5 ($n=6$)	6 ($n=6$)	
(a)								
	τ (min)							
								($n=36$)
Paddle	50 rpm	103 ± 7.8	99 ± 4.8	100 ± 16.2	113 ± 12.6	90 ± 9.0	103 ± 6.0	101 ± 11.6
	75 rpm	82 ± 4.8	105 ± 4.2	110 ± 16.2	97 ± 4.8	70 ± 5.4	83 ± 5.4	91 ± 15.4
	100 rpm	64 ± 8.4	73 ± 4.8	78 ± 3.6	83 ± 3.6	81 ± 2.4	47 ± 3.6	71 ± 13.3
								($n=24$)
FTC	8 ml/min	84 ± 10.32		97 ± 3.36	74 ± 0.54	77 ± 1.68		83 ± 10.5
	12 ml/min	73 ± 2.88	87 ± 4.62	70 ± 0.78		79 ± 2.58		77 ± 7.3
	16 ml/min	76 ± 11.6		62 ± 1.44		73 ± 6.96	83 ± 5.16	74 ± 10.4
	β							
								($n=36$)
Paddle	50 rpm	1.5 ± 0.05	1.5 ± 0.04	1.4 ± 0.03	1.5 ± 0.1	1.2 ± 0.09	1.4 ± 0.04	1.4 ± 0.10
	75 rpm	1.5 ± 0.07	1.5 ± 0.03	1.4 ± 0.20	1.4 ± 0.0	1.3 ± 0..06	1.4 ± 0.04	1.4 ± 0.11
	100 rpm	1.4 ± 0.15	1.6 ± 0.03	1.5 ± 0.05	1.4 ± 0.1	1.5 ± 0.05	1.6 ± 0.10	1.5 ± 0.11
								($n=24$)
FTC	8 ml/min	1.5 ± 0.04		1.5 ± 0.03	1.6 ± 0.007	1.3 ± 0.012		1.5 ± 0.11
	12 ml/min	1.5 ± 0.02	1.5 ± 0.02	1.5 ± 0.01		1.4 ± 0.02		1.5 ± 0.05
	16 ml/min	1.5 ± 0.02		1.5 ± 0.01		1.5 ± 0.08	1.5 ± 0.06	1.5 ± 0.05
(b)								
	τ (min)							
								($n=18$)
FTC	8 ml/min		185 ± 4.0		181 ± 2.6			
	12 ml/min		168 ± 3.0		172 ± 4.2		188 ± 7.8	176 ± 10.2
	16 ml/min		163 ± 2.9		173 ± 3.5		165 ± 2.0	167 ± 5.0
	β							
								($n=18$)
FTC	8 ml/min		1.5 ± 0.02		1.5 ± 0.01			
	12 ml/min		1.5 ± 0.02		1.5 ± 0.01		1.4 ± 3.1	1.5 ± 0.04
	16 ml/min		1.5 ± 0.01		1.5 ± 0.01		1.5 ± 0.02	1.5 ± 0.8

In Table 3(a), dissolution of Reumyl® 500 mg in buffer solution pH 6.8 with an ionic strength of 0.22, using the Paddle method and the FTC method at different agitation rates/flow rates.
In Table 3(b), dissolution of Reumyl® 500 mg in buffer solution pH 6.8 with an ionic strength of 0.10, using the FTC method at different flow rates.

that the time needed is different for different vessels. For the FTC method, the pH of the medium is adjusted and ready before the shift, and the time to change the pH from 1.2 to 6.8 is the same for all the cells. The FTC method is also more applicable when it comes to pH shift when it is necessary to keep the ionic strength constant from one pH to another.

5. Conclusions

It can be concluded that the use of the FTC method for the gastro-resistant formulation investigated, results in similar in vitro dissolution results compared to the official USP 23 Paddle method. However, based on the reported experiments, the FTC method seems to generate data in

Table 4
One-way ANOVA for τ considering dissolution of Reumyl® 500 mg in buffer solution pH 6.8, using the USP Paddle method and the FTC method

	Agitation rate/flow rate	MSS between	MSS within	*F* ratio	*P*
Paddle	50 rpm	0.09203	0.02827	3.3	0.015
	75 rpm	0.37802	0.01767	21.4	0.000
	100 rpm	0.30472	0.00628	48.5	0.000
FTC	8 ml/min	0.16978	0.00836	20.3	0.000
	12 ml/min	0.09747	0.00258	37.8	0.000
	16 ml/min	0.12951	0.01516	8.5	0.001

For the Paddle method d.f. = 5 and 30 between groups and within groups, respectively. Similarly for the FTC method d.f. = 3 and 20, respectively.

a more convenient way. The results of this study also confirm the fact that it is possible to compare data generated by different laboratories with equipment of the same type from different manufactures.

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