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A collaborative in vitro dissolution study: comparing the flow-through method with the USP paddle method using USP prednisone calibrator tablets

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Summary

A collaborative in vitro dissolution study has been performed in 5 laboratories using the flow-through method with different cell types and at various hydrodynamic conditions. The USP disintegrating prednisone calibrator tablets have been used as a test formulation The results obtained by the flow-through method were compared with data generated using the USP XXI paddle method. The flow-through method was found to produce reproducible and corresponding dissolution data both within and between the different laboratories. It was found that the linear flow rate in the flow-through cells is a fundamental parameter for the dissolution rate of the formulation. There was a conformity in dissolution rate between cells with different diameters when applying the same linear flow rate of the dissolution medium using the flow-through method. At low flow rates the flow-through method was found to be a sensible instrument to establish differences in the disintegration properties between the various prednisone tablets examined.

Introduction

In vitro dissolution testing is essential in modern drug delivery research. A fundamental understanding about various factors that can influence drug release from a dosage form is of utmost importance. Hence, the demands on in vitro dissolution technologies capable of reflecting subtle physical properties of formulations will increase in the near future.

It is, thus, important to evaluate new in vitro dissolution methods and compare their ability to generate reproducible data compared to the already existing compendial methods.

The present study is a continuation of a collaborative work within a Swedish group of pharmaceutical laboratories with the purpose of evaluating the flow-through method as a complement to already existing compendial methods (Nicklasson, et al., 1987).

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The dissolution rate from USP disintegrating prednisone calibrator tablets has been studied with the flow-through method to map out the characteristics of the method and to compare these dissolution data with data obtained using the USP-XXI paddle method.

Five different independent laboratories participated in the study.

Materials and Methods

Test laboratories

Five different Swedish laboratories participated in this collaborative study (Astra Alab AB, Södertälje; Draco AB, Lund; Ferring AB, Malmö; Gacell Laboratories AB, Malmö; National Board of Health and Welfare, Dept. of Drugs, Uppsala).

Test formulation

USP dissolution calibrator tablets, Lot H, disintegrating type, containing 50 mg prednisone were used as test formulation (USP-NF Reference Standards, Rockville, MD, U.S.A.).

Dissolution tests

The flow-through apparatus, supplied with dissolution medium via a piston pump, was used in all the experiments. Exactly the same type of equipment (Sotax AG, Switzerland) was used within all laboratories. The apparatus has been thoroughly described (Möller, 1983; Deutscher Arzneimittel Codex, 1983; Notes techniques Pro Pharmacopoea Française, 1986), and Fig. 1 shows some drawings on the cells used in the current study. Two types of cells were used having a diameter of 12.0 and 22.6 mm. The designs of the cells are shown in Fig. 1. This particular design of the 12.0 mm cell was chosen since it is considered to be suitable for a dosage form like prednisone tablets which disintegrate into fine particles during the dissolution process. The filters and filterhead of this type of 12.0 mm cell is considered to handle small particulate systems in a pertinent way.

Before dissolution testing, the laboratories had to make a study on the variation of the flow rate between each cell for each particular flow-through apparatus. The laboratories had to comply with ± 0.5 ml/min of the nominal flow rate. The flow rate within each single cell among all laboratories was allowed to vary between $\pm 4\%$ of the nominal flow rate in order to consider the test to be valid for further applications.

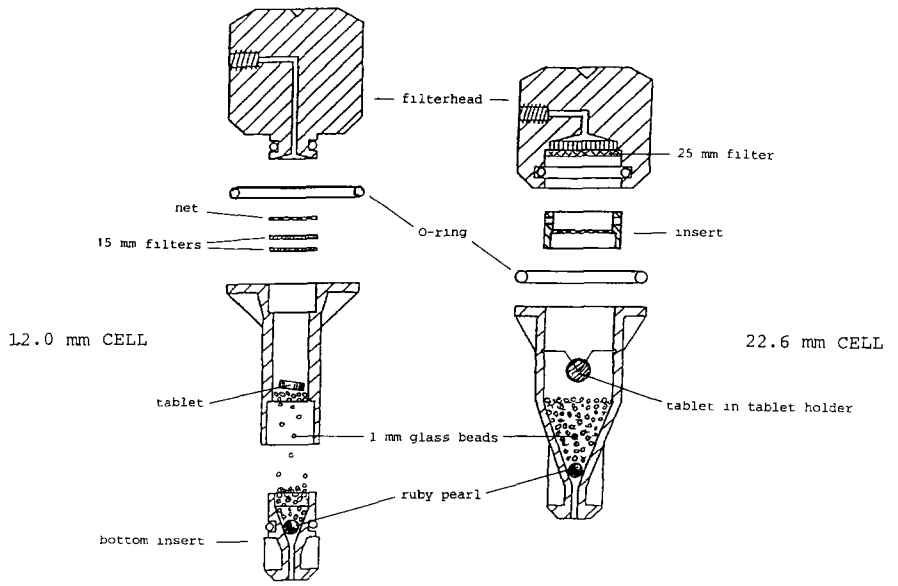

Fig 1 Drawings of the different flow through cells used in the study including the positions for glass beads, filters and tablets

Six tablets were tested in each run. For the 12.0 mm cell, flow rates of 9 and 16 ml/min were applied. The flow rate used for the 22.6 mm cell was 32 ml/min to give the same linear flow rate as compared to the 12.0 mm cell with a flow rate of 9 ml/min.

All eluate from each cell was collected and weighed for the time periods: 0–10, 10–30, 30–60, 60–120 and 120–240 min. The concentration of prednisone in the eluate was determined after filtration through a 0.45 μm Millex SLHV filter (Millipore, U.S.A.).

For the 12.0 mm cell, the tablet was positioned on the bed of 1 mm glass beads (2.5 g, filling up the conical part at the bottom of the cell). For the 22.6 mm cell, the tablet was put in a tablet holder above the bed of 1 mm glass beads (8 g filling up the conical part at the bottom of the cell); see Fig. 1.

A separate study was performed with the USP-XXI paddle method at stirring rates of 50 and 100 rpm using 6 tablets in each run.

10 ml of dissolution medium was withdrawn manually and immediately filtered through a 0.45 μm Millex SLHV filter. Sampling was made after 10 and 30 min and after 1, 2, and 4 h.

As prescribed in USP-NF Reference Standards, the laboratories used deaerated water of 37 °C and measured the concentration of prednisone spectrophotometrically at 242 nm.

All tablets used in this study were weighed and the amount of prednisone dissolved as a function of time was normalized against the tablet weight and the prednisone content of the tablet, i.e. mg/g tablet (determined on 10 tablets by one of the laboratories). As a check, each laboratory made at least one determination of the prednisone content of the tablet batch (mg/g tablet). All laboratories used prednisone (Roussel Uclaf) USP assay 99.5% on dry product (titirmetrical determination) dispensed from the same container as a reference standard.

It is well-known that prednisone tablets may be sensitive to exposure to humidity (Hanson and Hanson, 1979). Prior to the experiments, the tablets from a number of containers were combined in a new container and stored in this container for one week before dispensing and distribution to the participating laboratories. This precaution was made with the purpose of obtaining a homogeneous content of moisture in the tablets to obtain similar physical properties of the individual tablets.

Results and Discussion

In Fig. 2, the average percentage of prednisone dissolved as a function of time is presented using data generated by all laboratories at the given hydrodynamic conditions ($n = 30$).

Conforming results were obtained with the flow-through method using cells with a diameter of 12.0 mm and a flow rate of 9 ml/min compared to the situation when 22.6 mm cells and a flow rate of 32 ml/min were used. This is explained by the fact that, for the the experimental conditions described, the linear flow rate of the medium is about the same in both cells (6.3 cm/min). The hydrodynamic conditions will, therefore, be similar and the dissolution rate of

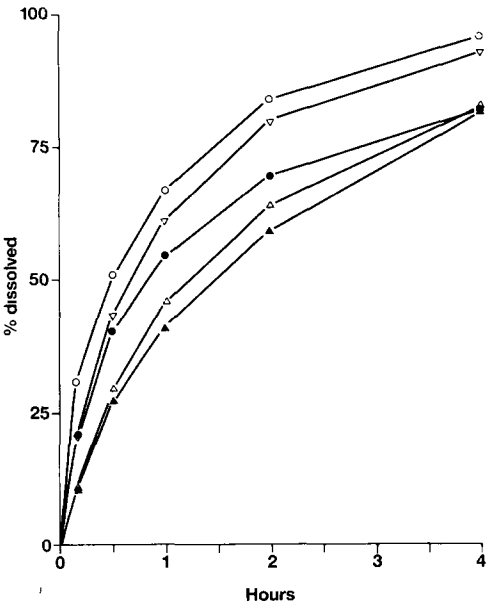

Fig. 2. Per cent prednisone dissolved as a function of time in water at 37 °C. Mean values from all laboratories ($n = 30$ for each curve). USP calibrator tablets Lot H, 50 mg (△) flow through 9 ml/min. 12 mm cell (▽) flow through 16 ml/min. 12 mm cell (▲) flow through 32 ml/min. 22.6 mm cell (●) USP paddle 50 rpm (○) USP paddle 100 rpm.

TABLE 1

Percent prednisone dissolved using the flow-through method, 9 ml/min, 12 0 mm cell, USP calibrator tablets, lot H, 50 mg

Time/h	Laboratory no.					Maximum difference/%
	1	2	3	4	5	
0 17	9–14	12–15	9–12	10–11	8–12	7
0.50	28–34	28–33	24–30	29–34	22–30	12
1.00	45–50	43–46	41–45	46–54	38–46	16
2 00	65–70	60–63	56–63	67–73	57–63	17
4.00	85–87	78–81	76–85	84–93	77–82	17

TABLE 2

Percent prednisone dissolved using the flow-through method 32 ml/min, 22 6 mm cell, USP calibrator tablets, lot H, 50 mg

Time/h	Laboratory no.					Maximum difference/%
	1	2	3	4	5	
0.17	10–13	8–11	10–12	7– 11	12–14	7
0 50	26–30	22–26	24–33	17– 27	27–30	16
1.00	40–46	37–40	37–49	27– 42	41–43	22
2 00	59–65	56–57	55–65	42– 61	58–61	24
4 00	79–84	78–81	74–80	82–101	75–80	27

the tablets should also be similar provided that sink conditions are maintained. The solubility of prednisone in water was determined to be 0.19 g/l at 37 °C (0.12 g/l at 23 °C).

As can be seen in Fig. 2, the overall impression is that a higher linear flow rate in the flowthrough cells generates a faster dissolution rate of prednisone. This phenomenon can also be seen for the USP XXI paddle where a more intensive stirring rate generates a faster dissolution of the prednisone.

Comparison of the flow-through method with the USP XXI paddle method indicates that it is possible to obtain conforming dissolution profiles at certain hydrodynamic conditions. The dissolution profile obtained using flow-through cells of 12.0 mm in diameter at 16 ml/min falls within the range between the dissolution profiles obtained with the USP XXI paddle method at 50 and 100 rpm, respectively.

Tables 1 and 2 show that the flow-through method generates consistent data for the prednisone tablets. The results thus confirm that it is

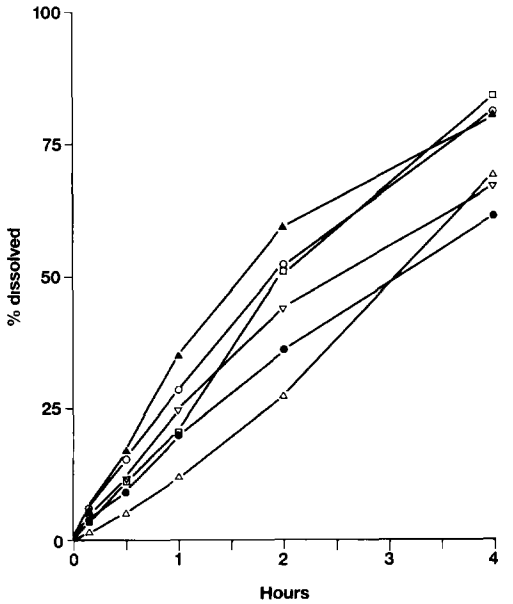

Fig. 3. Percent prednisone dissolved as a function of time in water at 37 °C using the flow-through method at a flow rate of 9 ml/min. Cell diameter = 12 mm. Each curve represents one tablet in different flow cells. USP calibrator tablets Lot H, 50 mg; (▲), (○), (□), (▽), (●), (△) tablets 1–6.

TABLE 3

Percent prednisone dissolved using the flow-through method, 16 ml/min, 12 0 mm cell, USP calibrator tablets, lot H, 50 mg

Time/h	Laboratory no.					Maximum difference/%
	1	2	3	4	5	
0 17	17–22	21–23	22–26	14– 17	23–25	12
0.50	37–45	41–44	44–47	35– 38	45–52	17
1.00	52–61	56–62	57–63	57– 64	60–69	18
2.00	67–76	72–81	77–83	86– 92	73–84	25
4.00	81–91	90–97	92–97	96–100	82–95	19

TABLE 4

Percent prednisone dissolved using the USP XXI paddle method, 50 rpm, USP calibrator tablets, lot H, 50 mg

Time/h	Laboratory no.					Maximum difference/%
	1	2	3	4	5	
0.17	21–23	21–23	18–24	17–22	21–25	8
0.50	40–41	41–42	38–41	37–40	40–42	6
1 00	54–55	54–57	52–57	52–55	54–58	6
2.00	68–69	69–72	67–73	68–72	68–74	7
4.00	80–82	80–84	81–84	80–86	80–85	6

TABLE 5

Percent prednisone dissolved using the USP XXI paddle method, 100 rpm, USp calibrator tablets, lot H, 50 mg

Time/h	Laboratory no.					Maximum difference/%
	1	2	3	4	5	
0.17	29–31	28–30	35–38	29–30	29–30	10
0 50	50–52	50–53	52–61	50–51	49–51	11
1 00	66–68	64–66	68–72	67–68	65–67	9
2.00	84–85	79–82	84–91	84–85	83–84	11
4 00	96–98	92–94	93–98	97–99	94–97	8

TABLE 6

S D s after 30 min dissolution testing (% dissolved), USP calibrator tablets, lot H, 50 mg

	Laboratory no.					All tablets from all laboratories
	1	2	3	4	5	
Flow-through method						
12 0 mm diam						
9 ml/min	1.9	1 7	2 2	2 1	3 4	3.1
16 ml/min	2.6	0 93	1.4	0 93	2 4	4 7
Flow-through cells						
22.6 mm diam						
32 ml/min	1 7	1 3	3 6	3.8	0.82	3.1
USP XXI-paddle method						
50 rpm	0.42	0.60	1.2	1.4	1 1	1 4
100 rpm	0.61	1 2	3 4	0 42	1.8	2 1

possible to compare data generated by different laboratories but with equipment of the same type.

Residues of non-disintegrated tablets were, in some cases, observed even after 4 h testing. The presence of residues is, in most of the cases, reflected by deviating results. A possible explanation to poor disintegration may be that the shearing forces acting on the tablets are small in the flow-through cells at this low linear flow rate (6.3 cm/min). The USP XXI paddle method gives a more even disintegration of the tablets with the stirring rates applied in this investigation. The shearing forces on tablets in the flow-through cells originate mainly from the pulsation of the flow caused by the piston pump. It seems as if the flow-through method is a sensitive test method stressing the formulation behavior which may be needed for discriminating quality control.

In one run, using 12.0 mm cells and a flow rate of 9 ml/min, the 6 tablets showed remarkable different disintegration behavior and these differences between the tablets gave diverging dissolution profiles (Fig. 3).

Tables 3–5 show that the USP XXI paddle method generated somewhat more consistent results between the laboratories than the flow-through method. For the flow-through method, using 12.0 mm cells at a flow rate of 16 ml/min, the total range between all laboratories ($n = 30$) was found to be 17% after 30 min testing. For the USP XXI paddle method, the corresponding values were 6% and 11% at 50 and 100 rpm, respectively. It should be pointed out that the ranges obtained in this study for the USP XXI paddle method are low, taking into consideration that the USP states suitability ranges leave alone for Lot H 18% (31–49% dissolved) and 23% (41–64% dissolved) at 50 and 100 rpm, respectively ($n = 6$).

Table 6 shows the standard deviations obtained for the flow-through method and the USP XXI paddle method. The S.D.s for the USP XXI paddle method were found to be low in this study (1.4 and 2.1% dissolved) in comparison with previous collaborative studies on prednisone tablets (standard deviations ranging from 2.6 to 7.0% dissolved; Haaland and Grostic 1985; Cox and Furman, 1984).

In comparison with a previous collaborative study on salicylic acid non-disintegrating tablets (Nicklasson et al., 1987), the S.D.s obtained in this study for the flow-through method are higher for prednisone tablets, i.e. 4.7% ($n = 24$) at 16 ml/min using 12.0 mm cells, compared to 1.0% ($n = 24$) for salicylic acid tablets at corresponding conditions. The USP XXI paddle method showed similar S.D.s for both prednisone tablets and salicylic acid tablets at 100 rpm, i.e. 2.1% and 2.4%, respectively. The USP XXI paddle method showed even lower S.D.s for the prednisone tablets than for the salicylic acid tablets at 50 rpm, i.e. 1.4% for prednisone and 2.6% for salicylic acid (Nicklasson et al., 1987).

Complementary work at Draco showed that the flow-through method at low linear flow rates (i.e. a volume flow rate of 9 ml/min using 12.0 mm cells) may be an instrument to discriminate between physical differences even among tablets from different containers of the same batch of tablets (Table 7).

Containers Nos. 1 and 2 were opened immediately before the experiments. Container No. 3 is the container with combined tablets used in the collaborative study (c.f. Materials and Methods).

Measurements were made after 30 min on the collected eluate from each flow-through cell and on filtered samples from the USP XXI paddle vessels.

TABLE 7

Using the flow-through method at low flow rates as an instrument to discriminate between differences in physical properties among different containers of the same lot of prednisone tablets Comparison between the flow-through method at a higher flow rate with the USP XXI paddle method at 50 rpm

	Cont. 1	Cont 2	Cont 3 *
Flow-through method, 9 ml/min, 12 mm cells	20 3 (17 0–25.9)	24 8 (21 5–28 4)	31 3 (28.3–33.7)
Flow-through method, 16 ml/min, 12 mm cells	41.5 (38 8–45 8)	40.1 (38 5–41 0)	42 2 (37 4–45 2)
USP XXI paddle method, 50 rpm	40.8 (38 7–42 9)	40 4 (39 5–42.0)	40 5 (40.0–41 1)

Percent dissolved after 30 min (mean value for 6 tablets), range given within brackets USP prednisone calibrator tablets 50 mg, lot H disintegrating type

* Tablets from the common container used in the collaborative study

At high linear flow rates (corresponding to a volume flow rate of 16 ml/min in 12.0 mm cells), conforming results were obtained with tablets taken from all 3 containers. Conformity was achieved also between the flow-through method and the USP XXI paddle method for the higher flow rate and 50 rpm, respectively.

Differences in the nominal flow rate between the flow through cells will give rise to variations in the observed dissolution rates within a single run.

A supplementary investigation was, therefore, made at Draco regarding the sensitivity of the dissolution rate due to small variations of the nominal flow rate in the flow-through cells.

Measurements were made at flow rates of 6 and 12 ml/min using the 12.0 mm cell and at 21 and 43 ml/min using the 22.6 mm cell. Six tablets were used in each run.

The results show that a change in flow rate of 1 ml/min at 9 ml/min (12.0 mm cell) caused a change of about 4% dissolved substance after 30 min testing. At 32 ml/min (22.6 mm cell) the corresponding change was found to be about 0.5% dissolved.

A statistical evaluation of the deviations from the nominal flow rates that actually occurred during the experiments showed that this could only account for a minor part of the variation in the observed dissolution rates that was obtained in this collaborative study (c.f. Materials and Methods). This holds true for all flow rates used (see Tables 1–3).

Conclusions

It can be concluded that, for the flow-through method, the linear flow rate of the dissolution medium in the cells is a fundamental parameter to consider. When using the USP disintegrating prednisone tablets as a test formulation, the same linear flow rate generated conforming dissolution profiles, independent of the cell diameters tested.

The consistent results between the 5 laboratories show that a higher linear flow rate generates a faster dissolution of prednisone.

It is possible to define a certain flow rate for the flow-through method which will generate similar dissolution profiles compared to the USP XXI paddle method.

The flow-through method may be valuable as an alternative dissolution method capable of generating reproducible results for disintegrating tablets if the flow rate is properly chosen.

At low flow rates the flow-through method may even be a discriminating instrument to investigate differences in disintegrating properties between tablets.

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