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Performance of USP calibrator tablets in flow-through cell apparatus

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Abstract

USP dissolution calibrator tablets were analysed by the flow-through cell method with the intention of examining its applicability for the flow-through cell apparatus suitability test. Test was performed with Dissotest CE-6 apparatus, (Sotax, Switzerland) in flow-through cells for tablets and capsules: smaller cells of 12 mm diameter and larger ones of 22.6 mm diameter. Analyses were performed with laminar and turbulent flow of dissolution medium. The flow rates were 16 and 8 ml/min for laminar flow and only 16 ml/min for turbulent flow. From the results it can be concluded that both salicylic acid tablets and prednisone tablets could be used for apparatus suitability test also for the flow-through cell under the conditions of laminar flows of 16 and 8 ml/min in cells ϕ 12 and 22.6 mm. As regards the turbulent flow of 16 ml/min, without a holder, cells ϕ 12 mm could be used for salicylic acid tablets and both cells (ϕ 12 and 22.6 mm) for prednisone tablets.

Keywords: USP calibrator tablets; Flow-through cell; Laminar flow; Turbulent flow; Dissolution profiles

1. Introduction

The dissolution test for active substances from tablets and capsules by the flow-through cell method was introduced in the USP with 4th Supplement to USP XXII in 1991.

The apparatus suitability test with the calibrator tablets for apparatus 1 (basket) and apparatus 2 (paddle), which are most frequently used, was introduced in USP XX. The performance of the dissolution test with calibrator tablets is important for the comparison of results obtained with apparatuses of various manufacturers but according to the same description. A review of these results contributes to setting the dissolution values for calibrator tablets for the apparatus with a flow-through cell.

2. Materials and methods

2.1. Materials

USP dissolution calibrator disintegrating type: prednisone tablets, 50 mg Lot L;

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USP dissolution calibrator non-disintegrating type: salicylic acid tablets, 300 mg Lot N;
USP reference standard prednisone Lot K-1;
USP reference standard salicylic acid Lot J;
Glass microfibre filter, Whatman GF/F.

2.2. Apparatus

Dissolution tester Dissotest CE-6, Sotax AG, Basel;
Dissolution flow-through cell for tablets and capsules with a diameter of 22.6 and 12 mm, Sotax AG, Basel;
Piston pump CY 7, Sotax AG, Basel;
Software IDIS (Icalic Data Systems), Sotax AG, Basel;
UV/VIS spectrometer Lambda 2S, Perkin–Elmer;
Flow cell for spectrometer with path length $d = 10$, 2 and 1 mm, Hellma.

2.3. Method

The apparatus and the flow-through cell, and the method, respectively, are basically in accordance with the USP XXIV and Eur. Ph., respectively: one glass bead of 5 mm diameter is positioned in the apex of the flow-through cell.

With the laminar flow, the lower conical part of the cell was filled with glass beads of about 1 mm diameter, i.e. 7.40 g for cell 22.6 mm diameter and 0.733 g for cell 12 mm diameter. A tablet was put on the top of a layer of beads.

With the turbulent flow, without a layer of beads, the analyses were performed in two ways: with a tablet put on a tablet holder and without a tablet holder. The procedure for dissolution was in accordance with the USP procedure for the respective calibrator tablets.

The analyses were preformed at flow rates of 16 ml and 8 ml/min. At a flow rate of 16 ml/min, the analyses of both kinds of calibrator tablets in cells of both diameters were performed at the laminar flow without a tablet holder and at the turbulent flow on a tablet holder and without a tablet holder. At a flow rate of 8 ml/min, the analyses of both kinds of calibrator tablets in cells of both diameters were performed only at the laminar flow, without a tablet holder. The differences among the performances under different conditions are most expressed in the first part of the curve, although the scattering of the results is also higher there. That is why the curves are presented for all conditions, and both kinds of tablets, in the time range from 0 to 120 min. At least six tablets were tested in each run, somewhere also more for the purpose of greater accuracy. There was an exception in one test of salicylic acid tablets (turbulent flow, no holder, 240 min), because, the tablets were practically dissolved already at 180 min. All the analyses were performed with the automated method. The dissolution results are presented as the mean value of minimum six tablets in %, sample standard deviation (S.D.), and relative standard deviation (R.S.D.), in %.

3. Results and discussion

The flow rate for all analyses was from 98 to 102% of the nominal flow rate. The results were obtained with automatic calculation considering the actual flow rate for each tablet. All the absorbance measurements were within the range of linearity.

3.1. USP dissolution calibrator, disintegrating type: prednisone tablets, 50 mg Lot L

The linearity of prednisone was established in a range of 1 to 60 μg/ml (to 2.650 absorbance), with the USP reference standard prednisone Lot K-1 and the correlation coefficient, R^2, was 0.9999, slope of the regression line, k, was 0.0440 ± 0.0004 and the intercept of the regression line, b, was -0.00 ± 0.01.

The influence of different flow rates: 16 and 8 ml/min at the laminar flow, and the influence of different ways of flow (laminar and turbulent) at 16 ml/min on the dissolution results for prednisone tablets for cells of the same diameter are presented for cell ϕ 12 mm in Table 1 and in Fig. 1. In the same way, the dissolution results are presented for cell ϕ 22.6 mm in Table 2 and in Fig. 2.

Table 1
Dissolution of prednisone for cell ϕ 12 mm at 16 ml/min: laminar ($n = 6$), turbulent on a tablet holder ($n = 6$) and turbulent without a tablet holder ($n = 7$) and at 8 ml/min: laminar ($n = 6$)

Time (min)	16 ml/min laminar		16 ml/min turbulent on holder		16 ml/min turbulent no holder		8 ml/min laminar	
	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)
15	28.5 ± 1.3	4.4	33.9 ± 2.7	7.9	32.6 ± 2.1	6.4	19.7 ± 1.7	8.5
30	40.6 ± 1.6	4.0	45.9 ± 3.3	7.3	44.3 ± 2.8	6.4	31.6 ± 1.8	5.7
60	55.6 ± 2.0	3.6	60.6 ± 3.9	6.5	59.1 ± 3.6	6.1	46.8 ± 2.1	4.4
120	73.9 ± 2.5	3.3	74.8 ± 4.5	6.0	73.9 ± 4.2	5.7	67.2 ± 2.4	3.6
180							80.3 ± 2.6	3.3
240							88.4 ± 2.5	2.8
300							93.5 ± 2.3	2.5

From Table 1 and Fig. 1, it is evident that the results in the turbulent way with and without a tablet holder are practically the same. For the laminar flow, it can be seen that the results at 16 ml/min are higher than those at 8 ml/min.

Table 2 and Fig. 2 show that for cell ϕ 22.6 mm, as well as for the above-mentioned cell ϕ 12 mm, there are no significant differences between the results for turbulent flow on a holder and without a holder. The results for laminar flow at 16 ml/min are higher than those at 8 ml/min and the differences for cell ϕ 22.6 mm are higher compared to cell ϕ 12 mm in Table 1 above.

To link the results obtained with the flow-through cell to the values applied to prednisone tablets, 50 mg Lot L for apparatus 1 (basket), i.e. 38 to 55% at 100 rpm and 30 min, a function that would be the nearest approach to the measured values was looked for. The functions were calculated from the time range up to 120 min, except for cell ϕ 22.6 mm with the laminar flow at 8 ml/min (from the range up to 360 min). The functions were predominantly potential and R^2 was from 0.9904 (cell ϕ 22.6 mm, turbulent flow, on a holder) to 0.9977 (cell ϕ 12 mm, laminar flow 16 ml/min). From the obtained functions, the dissolution times to get 46.5% of dissolved prednisone were calculated. This value was chosen as a mean of the values 38 to 55% quoted above. The dissolution times calculated in this way and the relating experimental data at this time point are presented in Table 3.

3.2. USP dissolution calibrator, non-disintegrating type: salicylic acid tablets, 300 mg Lot N

The plan of conducting tests was the same as for prednisone tablets. First the linearity of salicylic acid was established in a range of 1–78 μg/ml (to 1.997 absorbance), with the USP reference standard salicylic acid Lot-J. The correlation coefficient, R^2, was 0.9999, slope of the regression line, k, was 0.0256 ± 0.0002 and the intercept of the regression line, b, was 0.008 ± 0.010.

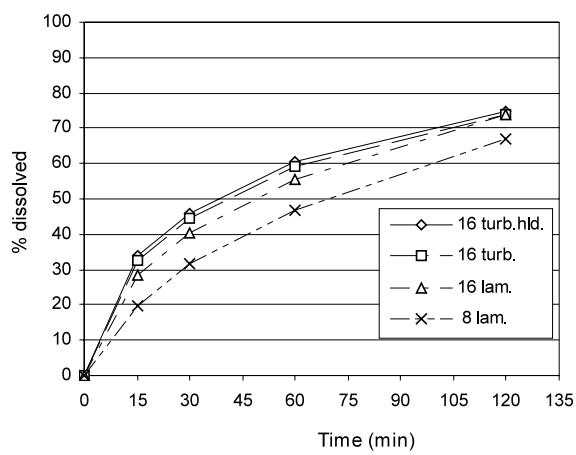

Fig. 1. Dissolution profiles for prednisone tablets 50 mg USP Lot L in cells ϕ 12 mm at a flow of 16 ml/min: laminar ($n = 6$), turbulent on a tablet holder ($n = 6$) and turbulent without a tablet holder ($n = 7$); and at 8 ml/min: laminar ($n = 6$).

Table 2
Dissolution of prednisone for cell ϕ 22.6 mm at 16 ml/min: laminar ($n = 6$), turbulent on a tablet holder ($n = 7$) and turbulent without a tablet holder ($n = 6$) and at 8 ml/min: laminar ($n = 6$)

Time (min)	16 ml/min laminar		16 ml/min turbulent on holder		16 ml/min turbulent no holder		8 ml/min laminar	
	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)
15	15.3 ± 0.6	4.0	32.8 ± 2.0	6.0	32.0 ± 2.6	8.1	6.7 ± 1.0	14.5
30	25.8 ± 1.5	5.7	44.4 ± 2.3	5.3	43.4 ± 3.3	7.6	13.2 ± 1.5	11.3
60	39.7 ± 2.5	6.4	59.1 ± 2.6	4.4	57.2 ± 3.7	6.4	24.2 ± 2.1	8.8
120	59.1 ± 2.2	3.7	71.6 ± 2.9	4.1	69.0 ± 3.4	4.9	40.9 ± 2.9	7.2
180							53.9 ± 3.2	5.9
240							64.3 ± 3.1	4.8
300							72.6 ± 2.9	3.9
360							79.2 ± 2.6	3.2

The same different conditions of dissolution tests as those for prednisone tablets were also examined. So the influence of different flow rates: 16 and 8 ml/min at the laminar flow, and the influence of different ways of flow (laminar and turbulent) at 16 ml/min on the dissolution results for salicylic acid tablets for cell ϕ 12 mm are presented in Table 4 and Fig. 3. The dissolution results for cell ϕ 22.6 mm are presented in the same way in Table 5 and Fig. 4.

From Table 4 and Fig. 3, it is clear that the results in the turbulent way with a tablet holder are different from those without a holder and that the latter are at the same time the highest of all presented conditions. For the laminar flow, it can be seen that the results at 16 ml/min are higher than those at 8 ml/min.

Table 5 and Fig. 4 show that for cell ϕ 22.6 mm, the results for the turbulent flow on a holder and without a holder, differ from each other, as for cell ϕ 12 mm above. The results with the turbulent flow without a holder are the highest of all the presented conditions. The results for laminar flow at 16 ml/min are higher than those at 8 ml/min and the differences for cell ϕ 22.6 mm are lower compared to cell ϕ 12 mm in Table 4 above.

The evidence that the tests were well performed was based on weighing the respective tablet before the analysis and on the dissolution expressed by weight at the final time of dissolution. The obtained ratio confirms that as much salicylic acid was obtained with this analysis as was present in tablets. This 'analysis yield' was 99.6% ($n = 7$, S.D. = 0.5, cell ϕ 12 mm, laminar flow 8 ml/min, 300 min), 99.6% ($n = 3$, S.D. = 0.5, cell ϕ12 mm, turbulent flow, no tablet holder, 16 ml/min, 180 min) and 99.8% ($n = 3$, S.D. = 0.7, cell ϕ 22.6 mm, turbulent flow, no tablet holder, 16 ml/min, 180 min).

The dissolution values applied to salicylic acid calibrator tablets Lot N for apparatus 1 (basket) at 100 rpm and 30 min are 23–29% according to USP 24. The mean of these values is 26%.

The dissolution times corresponding to this value with a flow-through cell (apparatus 4 ac-

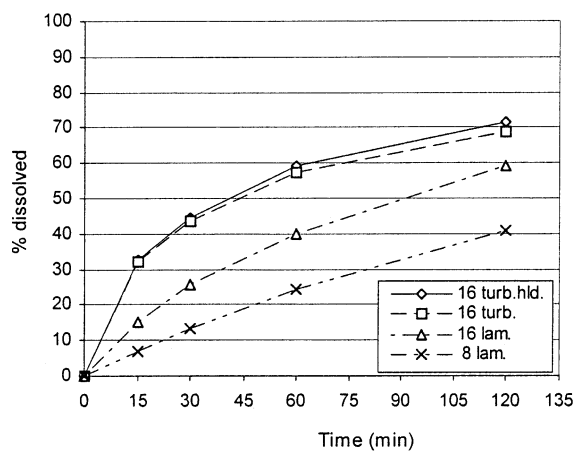

Fig. 2. Dissolution profiles for prednisone tablets 50 mg USP Lot L in cells ϕ 22.6 mm at a flow of 16 ml/min: laminar ($n = 6$), turbulent on a tablet holder ($n = 7$) and turbulent without a tablet holder ($n = 6$); and at 8 ml/min: laminar ($n = 6$).

Table 3
Dissolution times to reach 46.5% of dissolved prednisone and results at this time point

Flow	Cell ϕ 12 mm			Cell ϕ 22.6 mm		
	Time (min)	Mean ± S.D. (%)	R.S.D. (%)	Time (min)	Mean ± S.D. (%)	R.S.D. (%)
Laminar 16 ml/min	42.1	47.5 ± 1.8	3.8	79.3	46.8 ± 2.6	5.5
Laminar 8 ml/min	61.5	47.9 ± 2.1	4.4	145.6	46.8 ± 3.2	6.7
Turbulent, on holder 16 ml/min	32.4	47.4 ± 3.4	7.2	35.4	47.7 ± 2.4	5.1
Turbulent, no holder 16 ml/min	35.1	47.4 ± 3.0	6.4	38.2	48.0 ± 3.5	7.2

Table 4
Dissolution of salicylic acid for cell ϕ 12 mm at 16 ml/min: laminar ($n = 6$), turbulent on a tablet holder ($n_{\text{to 60 min}} = 8$, $n_{\text{to 180 min}} = 7$, $n_{\text{to 240 min}} = 6$) and turbulent without a tablet holder ($n_{\text{to 180 min}} = 6$, $n_{\text{to 240 min}} = 3$) and at 8 ml/min: laminar ($n = 6$)

Time (min)	16 ml/min laminar		16 ml/min turbulent on holder		16 ml/min turbulent no holder		8 ml/min laminar	
	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)
15	12.5 ± 0.2	1.5	5.5 ± 0.9	15.3	14.8 ± 0.4	2.5	7.5 ± 0.3	4.4
30	24.4 ± 0.4	1.5	12.3 ± 1.8	14.3	30.9 ± 0.3	1.0	15.7 ± 0.4	2.6
60	46.0 ± 0.6	1.3	22.5 ± 3.3	14.7	59.3 ± 0.5	0.8	31.3 ± 0.8	2.7
120	79.4 ± 1.1	1.3	39.1 ± 5.0	12.7	94.2 ± 0.3	0.3	58.2 ± 1.6	2.7
180	98.5 ± 2.0	2.0	53.2 ± 5.8	10.9	99.9 ± 1.3	1.3	81.0 ± 1.6	2.0
240	99.2 ± 2.2	2.2	65.2 ± 7.1	10.9	99.9 ± 1.9	1.9	97.8 ± 1.9	1.9
300							99.9 ± 2.3	2.3

cording to USP 24) were calculated from the function which is the nearest approach to the measured values. The functions were calculated from the time range up to 120 min, except for cell ϕ 22.6 mm with the turbulent flow, on a holder, at 16 ml/min from the range to 240 min. The functions were predominantly square and R^2 was from 0.9980 (cell ϕ 22.6 mm, laminar flow at 16 ml/min) to 1.0000 (cell ϕ 12 mm, laminar flow at 16 ml/min). So calculated dissolution times and the relating experimental data at this time point are presented in Table 6.

From Table 6, it is evident that the quoted dissolution value of 26% is reached in a shorter time at a higher flow rate and a smaller cell diameter. A turbulent flow of 16 ml/min with a tablet holder is unsuitable for these tablets, because, apart from scattering of the results, tablets

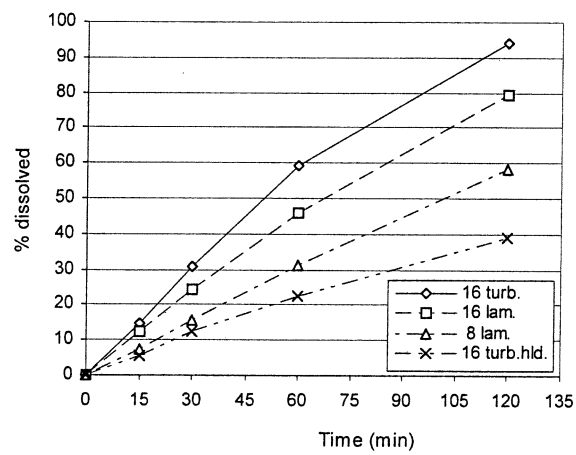

Fig. 3. Dissolution profiles for salicylic acid tablets 300 mg USP Lot N in cells ϕ 12 mm at a flow of 16 ml/min: laminar ($n = 6$), turbulent on a tablet holder ($n_{\text{to 60 min}} = 8$, $n_{\text{to 120 min}} = 7$) and turbulent without a tablet holder ($n = 6$); and at 8 ml/min: laminar ($n = 7$).

Table 5
Dissolution of salicylic acid for cell ϕ 22.6 mm at 16 ml/min: laminar ($n = 7$), turbulent on a tablet holder ($n_{to\ 120\ min} = 9$, $n_{to\ 180\ min} = 8$, $n_{to\ 240\ min} = 6$) and turbulent without a tablet holder ($n_{to\ 180\ min} = 6$, $n_{to\ 240\ min} = 3$) and at 8 ml/min: laminar ($n = 7$)

Time (min)	16 ml/min laminar		16 ml/min turbulent on holder		16 ml/min turbulent no holder		8 ml/min laminar	
	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)	Mean ± S.D. (%)	R.S.D. (%)
15	4.0 ± 0.3	7.9	3.0 ± 0.6	21.2	12.6 ± 2.0	15.8	3.1 ± 0.2	6.9
30	9.4 ± 0.5	5.0	6.1 ± 1.3	21.8	26.6 ± 4.2	15.8	7.1 ± 0.4	5.2
60	20.1 ± 0.7	3.3	12.3 ± 2.7	22.2	53.1 ± 6.7	12.6	15.6 ± 0.8	5.2
120	40.6 ± 1.1	2.6	23.9 ± 5.3	22.4	91.8 ± 3.3	3.6	32.1 ± 1.1	3.5
180	59.0 ± 0.9	1.6	35.2 ± 8.0	22.7	99.4 ± 1.6	1.6	47.4 ± 1.2	2.6
240	75.8 ± 1.1	1.5	44.9 ± 9.2	20.5	99.7 ± 1.8	1.8	61.6 ± 1.3	2.2
300							72.6 ± 1.8	2.4
360							83.9 ± 1.8	2.2

sometimes fall from the tablet holder and begin to dissolve under other conditions and this result cannot be taken into account.

3.3. Comparison of the results for prednisone USP calibrator tablets, 50 mg Lot L and salicylic acid USP calibrator tablets, 300 mg Lot N

Laminar flows of 16 and 8 ml/min are acceptable for both cells (ϕ 12 mm and ϕ 22.6 mm) and for both kinds of tablets. With both kinds of tablets, the scattering of results, expressed as %R.S.D., is lower with cell ϕ 12 mm compared to cell ϕ 22.6 mm. It is lower for salicylic acid tablets compared with prednisone tablets.

A turbulent flow of 16 ml/min with a tablet holder is not recommendable for salicylic acid tablets, which are of non-disintegrating type, without a tablet holder, %R.S.D. within the first hour of dissolution is too high for cell ϕ 22.6 mm, while the results for cell ϕ 12 mm are homogeneous.

A turbulent flow of 16 ml/min, with a tablet holder is senseless for prednisone tablets, which are of disintegrating type, because, the results do not differ significantly from those without a tablet holder. It is also understandable, because, a tablet disintegrates immediately and is no longer on the tablet holder.

In two previous papers on dissolution using the flow-through method for USP dissolution calibrator salicylic acid tablets 300 mg Lot H (Nicklasson et al., 1987) and for USP dissolution calibrator prednisone tablets 50 mg Lot H (Wennergren et al., 1989), a flow-through cell of 12 mm diameter filled with 2.5 g of 1 mm glass beads was used. In the second mentioned article (by Wennergren et al., 1989), the description of the flow-through cell of 12 mm diameter is not the same as the one described in USP 24 for the cell for tablets and capsules of 12 mm diameter. Due to these differences and the different lots of tablets, the

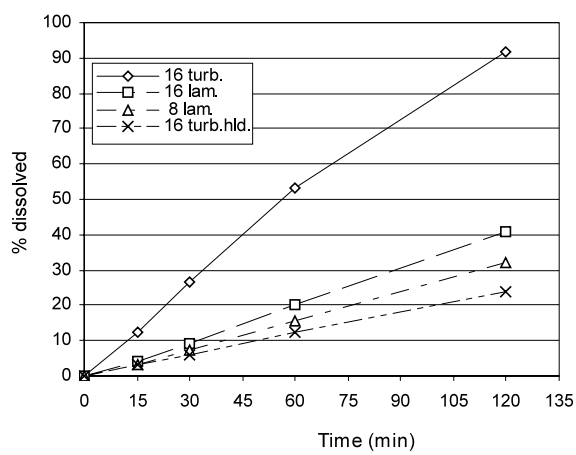

Fig. 4. Dissolution profiles for salicylic acid tablets 300 mg USP Lot N in cells ϕ 22.6 mm at a flow of 16 ml/min: laminar ($n = 7$), turbulent on a tablet holder ($n = 9$) and turbulent without a tablet holder ($n = 6$); and at a 8 ml/min: laminar ($n = 7$).

Table 6
Dissolution times to reach 26% of dissolved salicylic acid and results at this time point

Flow	Cell ϕ 12 mm			Cell ϕ 22.6 mm		
	Time (min)	Mean ± S.D. (%)	R.S.D. (%)	Time (min)	Mean ± S.D. (%)	R.S.D. (%)
Laminar 16 ml/min	32.0	26.0 ± 0.4	1.5	77.5	26.2 ± 0.7	2.7
Laminar 8 ml/min	50.0	26.2 ± 0.7	2.6	97.6	25.9 ± 1.0	3.8
Turbulent, on holder 16 ml/min	71.3	26.2 ± 3.9	15.0	131.0	26.2 ± 6.1	23.2
Turbulent, no holder 16 ml/min	24.2	24.8 ± 0.4	1.5	28.4	25.1 ± 4.0	15.9

results presented in this paper cannot be compared to those in the above articles; although for USP dissolution calibrator prednisone tablets 50 mg Lot L, disintegrating type, the results at a laminar flow of 16 ml/min, with a cell of 12 mm diameter, at 30 min are almost the same.

4. Conclusion

Based on the performed analyses, it can be concluded that the USP calibrator tablets: salicylic acid and prednisone could be used for apparatus suitability test for the flow—through cell dissolution method—apparatus 4 according to USP. As the dissolution values are set for each new current lot of calibrator tablets, the use of salicylic acid tablets, 300 mg Lot N would be recommended at this time. For a new lot of prednisone tablets, the dissolution times should be established.

The recommended values for cell ϕ 12 mm with the laminar flow at 16 and 8 ml/min are 23–29% of dissolved salicylic acid at the dissolution times presented in Table 6 rounded to a whole number, i.e. 32 and 50 min, respectively. Similarly, the recommended values for cell ϕ 22.6 mm with the laminar flow at 16 and 8 ml/min are 23–29% at 78 and 98 min, respectively. According to the directions for USP calibrator tablets, each of six individual calculated values for each cell at both indicated rates should be within the specified range. If equipment is dedicated for use with only one cell (ϕ 12 or 22.6 mm), then the calibration is not required for both cells. The chosen flow rate for calibration should be that which is closer to further used experimental conditions.

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