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Development and validation of a dissolution test for a once-a-day combination tablet of immediate-release cetirizine dihydrochloride and extended-release pseudoephedrine hydrochloride

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Abstract

A dissolution test for a once daily combination tablet containing 10 mg of cetirizine dihydrochloride (cetirizine HCl) for immediate release and 240 mg of pseudoephedrine hydrochloride (pseudoephedrine HCl) for extended release was developed and validated according to current ICH and FDA guidelines. The cetirizine HCl is contained within an outer layer of the tablet while a semipermeable membrane of cellulose acetate and polyethylene glycol controls the rate at which pseudoephedrine HCl is released from the tablet core. The dissolution method, which uses USP apparatus 2 with paddles rotating at 50 rpm, 1000 ml of deaerated water as the dissolution medium, and reversed-phased HPLC for quantitation, was demonstrated to be robust, discriminating, and transferable. These test conditions were selected after it was demonstrated that the cetirizine HCl portion of the tablet rapidly dissolved in aqueous media over the physiologically relevant pH range of 1.1–7.5, and that the extended-release profile of pseudoephedrine HCl was independent of dissolution conditions (i.e., apparatus, pH, and agitation).

Keywords: Asymmetric membrane film-coated tablets; Cetirizine; Dissolution; Method development and validation; Osmotic drug delivery; Pseudoephedrine; Reversed-phase high-performance liquid chromatography

1. Introduction

Cetirizine dihydrochloride (cetirizine HCl) is a selective histamine (H_1)-receptor antagonist that is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis [1]. Pseudoephedrine hydrochloride (pseudoephedrine HCl) is an α-adrenoreceptor agonist that is used for the symptomatic relief of nasal congestion in patients with allergic rhinitis [2]. The chemical structures of these active pharmaceutical ingredients (APIs) are shown in Figs. 1 and 2. Both of these drugs are well absorbed after oral administration [3,4], and they may be co-administered. For example, ZYRTEC-D 12 HOUR® Extended Release Tablets are available that contain 5 mg of cetirizine HCl and 120 mg of pseudoephedrine HCl [5].

This paper describes the development and validation of a dissolution test for a once-a-day combination tablet that contains 10 mg of cetirizine HCl for immediate release and 240 mg of pseudoephedrine HCl for extended release. The combination tablet, which is shown schematically in Fig. 3, uses an osmotically controlled drug delivery system based on asymmetric membrane (AM) technology to deliver the pseudoephedrine HCl [6]. The dissolution method was developed and validated according to current ICH [7,8] and FDA [9] guidelines.

2. Experimental

2.1. Materials

The AM-coated tablets of pseudoephedrine HCl were manufactured as previously described [10]. The target AM

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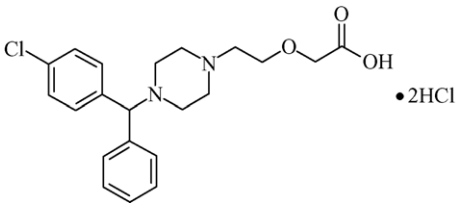

Fig. 1. The chemical structure of cetirizine dihydrochloride (CAS No. 83881-52-1).

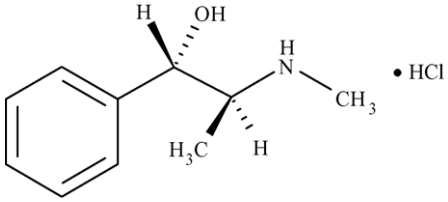

Fig. 2. The chemical structure of pseudoephedrine hydrochloride (CAS No. 345-78-8).

coating weight was 88.0 mg. The immediate-release layer of cetirizine HCl, followed by a taste-masking layer, was sprayed onto the AM-coated tablets [11]. The total weight of the tablet was approximately 673.0 mg. The AM-coated tablets described in Section 3.3.2, however, were not coated with the cetirizine HCl or taste mask layers.

ACS reagent grade chemicals were used unless otherwise indicated. Hydrochloric acid was obtained from EM Science (Gibbstown, NJ). Potassium biphthalate, monobasic potassium phosphate, and sodium dihydrogen phosphate monohydrate were obtained from J.T. Baker (Phillipsburg, NJ). HPLC grade methanol and sodium 1-octanesulfonate (OSA) were obtained from Burdick & Jackson (Muskegon, MI) and J.T. Baker, respectively. The 0.1 M hydrochloric acid solution (pH 1.1), potassium biphthalate USP buffer (pH 4.5; 5 mM), monobasic potassium phosphate USP buffer (pH 6.8; 50 mM), and simulated intestinal fluid (SIF; pH 7.5) were prepared according to the directions in USP 23 [12], except that the potassium biphthalate buffer concentration was decreased

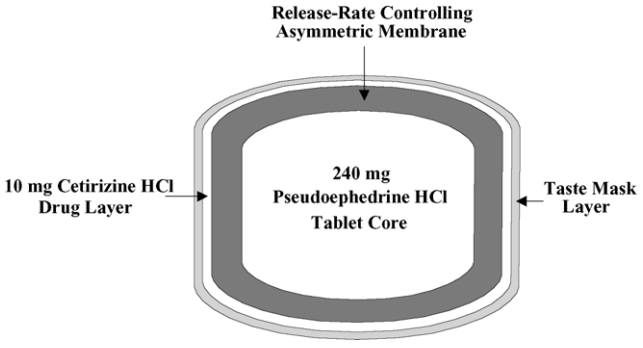

Fig. 3. Cross-section of the cetirizine HCl/pseudoephedrine HCl 10 mg/240 mg tablet.

to minimize chromatographic interferences and the SIF was prepared without pancreatin. These media were deaerated prior to use by sparging with helium for 15 min. The cetirizine HCl and pseudoephedrine HCl reference standards, which were characterized by tests including appearance, IR spectroscopy, acid–base titration, chromatographic purity by HPLC, loss on drying, and residue on ignition, were assigned purity values of 99.6 and 100.0%, respectively, when dried prior to use.

2.2. Dissolution test conditions

Dissolution testing was performed in compliance with USP ⟨7 1 1⟩ using apparatus 2 (e.g., Hanson SR8—Plus™ Dissolution Test Station) with paddles rotating at 50 rpm. The dissolution medium was 1000 ml of deionized water having a resistivity of about 18 MΩ cm. The medium, which was deaerated using a "Dissofill" Media Preparation System from Copley Scientific (Nottingham, UK), was maintained at 37 ± 0.5 °C. The 1-liter glass dissolution vessels were covered to minimize evaporation. The tablets were inserted into capsule weights to keep them from sticking to the walls of the dissolution vessel. Twelve tablets were tested unless otherwise indicated. Sample aliquots were withdrawn at 15, 30, 45, and 60 min, and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h. When manual sampling was used, aliquots of 5 ml were withdrawn from the dissolution vessel using a glass hypodermic syringe equipped with a stainless steel needle. These solutions were immediately filtered using a 0.45-μm Millex®-HV PVDF filter from Millipore (Billerica, MA). The first 3–4 ml of filtrate was discarded prior to collecting the sample for analysis. For automated sampling, a Dissoette II autosampler from Hanson Research (Chatsworth, CA) was used to withdraw 5 ml aliquots through a 10-μm HDPE filter from SEAL Analytical (Mequon, WI).

2.3. HPLC method

An HPLC method with UV detection was selected because of its ability to separate cetirizine and pseudoephedrine from each other and from the tablet excipients. The reversed-phase HPLC procedure utilized a Zorbax® StableBond SB-CN column (5 μm; 15 cm × 4.6 mm i.d.) from Agilent Technologies (Palo Alto, CA) and UV detection at 214 nm. The column temperature was maintained at 30 °C. The mobile phase of sodium phosphate (pH 6.5; 0.1 M)–methanol (1:1, v/v) also contained OSA (5 mM) as an ion-pairing agent. The flow rate was 1.0 ml/min, the injection volume was 10 μl, and the run time was 10 min. A combined standard solution containing cetirizine HCl and pseudoephedrine HCl at concentrations of 10 μg/ml and 0.12 mg/ml, respectively, was prepared in deionized water and used for quantitation. This solution contains 100% of the final, or "nominal," assay concentration of cetirizine HCl (i.e., 10 mg into 1000 ml of the dissolution medium) and 50% of the nomi-

nal assay concentration of 0.24 mg/ml for pseudoephedrine HCl.

2.4. Statistical analysis

Statistical analyses were performed using JMP™ v. 5.1.1 software from SAS Institute Inc. (Cary, NC). The SAS procedure PROC MIXED v. 6.12 was used to analyze the robustness data and Design-Expert® v. 5.0 from Stat-Ease, Inc. (Minneapolis, MN) was used to generate contour plots for each response.

3. Results and discussion

The dissolution test was developed based on the physicochemical properties of the APIs, the gastrointestinal conditions that the tablet is likely to encounter, and the drug-delivery characteristics of the dosage form.

3.1. Physicochemical properties of the APIs

The chemical name of cetirizine HCl is (±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid dihydrochloride. It is a racemic compound with a molecular formula of $C_{21}H_{25}ClN_2O_3{\cdot}2HCl$ and a molecular weight of 461.81. Cetirizine has three macroscopic pK_a values of 2.19, 2.93, and 8.00, and it exists primarily as a zwitterion between pH 3.5 and 7.5 [13]. Since this API is "freely soluble" in water (i.e., its solubility is ≥100 mg/ml) [14], the dissolution test was conducted under USP sink conditions [15]. The particle size distribution and crystal form of the ingoing cetirizine HCl lot cannot affect the performance of the product because this API is dissolved in an aqueous coating solution before it is sprayed onto the tablet.

The chemical name for pseudoephedrine HCl is (1*S*,2*S*)-(+)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride. This compound has a molecular formula and weight of $C_{10}H_{15}NO{\cdot}HCl$ and 201.69, respectively. Pseudoephedrine is a weak base having a single pK_a of approximately 9.59 [16]. The dissolution test was conducted under sink conditions for this API as well, since its solubility is approximately 2 g/ml in water [17]. Only one polymorph of pseudoephedrine HCl has been observed, and, as expected for a highly soluble compound, there was no evidence that the particle size distribution of the ingoing API lot influenced the performance of the product.

3.2. Validation of the HPLC method

The HPLC method used to analyze the dissolution samples was validated according to current ICH and FDA guidelines. The validation included specificity, linearity, accuracy, precision, range, robustness, filter suitability, and solution stability studies.

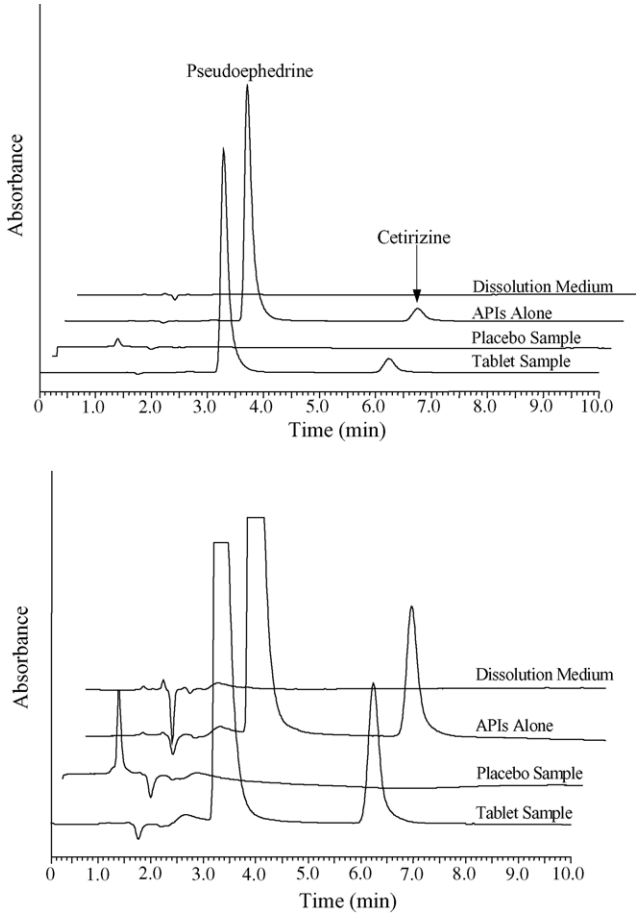

Fig. 4. Representative full- (top) and expanded-scale (bottom) chromatograms.

3.2.1. Specificity

The specificity of the method was evaluated by injecting an aliquot of the dissolution medium (i.e., deionized water) and the following: (1) a solution containing the APIs at nominal concentration, (2) a placebo solution prepared from a synthetic blend of the tablet excipients, and (3) a sample solution prepared from a synthetic blend of the APIs and tablet excipients. These solutions were prepared in deionized water and stirred at 37 °C for 24 h prior to being centrifuged and injected into the chromatographic system. As shown in Fig. 4, there were no system-, filter-, or excipient-related peaks that interfered with the quantitation of either active ingredient. This method also separates the APIs from their primary degradation products (data not shown). These results demonstrate the specificity of the method.

3.2.2. Linearity

The linearity of the method was evaluated from 20–125% and 5–125% of the nominal assay concentration for cetirizine HCl and pseudoephedrine HCl, respectively. Solutions of known concentration were prepared from a stock solution and injected into the chromatographic system. Calibration plots were constructed by plotting the area of the main peak

Table 1
Calculated linear regression parameters with 95% confidence limits[a]

	Cetirizine HCl	Pseudoephedrine HCl
R^2	0.9998	0.9978
Slope	$1.63\ (\pm 0.03) \times 10^4$	$1.16\ (\pm 0.06) \times 10^7$
y-Intercept	$-1.2\ (\pm 2.4) \times 10^3$	$-1.2\ (\pm 12.1) \times 10^4$
%Bias[b]	−0.8	−0.4

[a] Standard concentrations were 2.0, 4.0, 5.0, 7.5, 10.0, 11.0, and 12.5 μg/ml for cetirizine HCl and 0.012, 0.060, 0.12, 0.18, 0.24, 0.26, and 0.30 mg/ml for pseudoephedrine HCl.
[b] y-Intercept bias Calculated vs. the predicted peak area response at nominal assay concentration.

versus the concentration of the API, and calibration lines were calculated using the method of ordinary least squares. As shown in Table 1, these regression lines had coefficients of determination (R^2) that were ≥0.9978 and y-intercepts that were not significantly different from zero at the 95% confidence level. These data indicate that the method is linear for both cetirizine HCl and pseudoephedrine HCl.

3.2.3. Accuracy

The accuracy of the method was evaluated at 50, 100, and 125% of the nominal assay concentration for cetirizine HCl, and at 5, 50, 100, and 110% of nominal for pseudoephedrine HCl. As indicated in Tables 2 and 3, the average recoveries ranged from 99.6 to 101.3% for cetirizine HCl and from 97.0 to 100.5% for pseudoephedrine HCl. The accuracy of the method was considered acceptable based on its intended use.

Table 2
Accuracy results for cetirizine HCl (%recovery)

Sample	%Nominal concentration		
	50	100	125
1	99.4	100.4	101.3
2	99.7	100.8	100.5
3	99.1	100.0	101.4
4	100.0	100.4	102.1
5	–	102.0	–
6	–	100.5	–
Average	99.6	100.7	101.3
%R.S.D.	0.4	0.7	0.6

Table 3
Accuracy results for pseudoephedrine HCl (%recovery)

Sample	%Nominal concentration			
	5	50	100	110
1	101.5	99.9	97.7	96.9
2	101.1	99.8	97.8	96.9
3	100.8	99.7	97.5	97.2
4	98.7	99.9	97.7	96.9
5	–	–	97.6	–
6	–	–	97.3	–
Average	100.5	99.8	97.6	97.0
%R.S.D.	1.2	0.1	0.2	0.2

3.2.4. Precision

System precision: The injection precision of the method was evaluated by performing five replicate injections of the combined standard solution on five separate occasions. The peak area R.S.Ds. were ≤1.0% for cetirizine HCl and ≤0.8% for pseudoephedrine HCl. This reproducibility was considered acceptable.

Repeatability: The recovery data at the 100% level in Tables 2 and 3 were used to assess the precision of the method. The R.S.D. values of 0.7% for cetirizine HCl and 0.2% for pseudoephedrine HCl demonstrate that the method is precise.

Intermediate precision: As stated in the ICH [7] and FDA [9] guidelines, intermediate precision is not required when the reproducibility of the method has been demonstrated (see Section 3.3.3).

3.2.5. Range

Based on the linearity, accuracy, and precision data, the validated range of the method is from 50 to 125% of the nominal concentration for cetirizine HCl, and from 5 to 110% of the nominal concentration for pseudoephedrine HCl.

3.2.6. Robustness

The robustness of the method was evaluated during development by making small, but deliberate, changes to the method parameters. An experimental design was used to determine how changes in column temperature and mobile phase composition affect the chromatography of cetirizine and pseudoephedrine. As shown in Table 4, four factors were evaluated at two levels each. For practical reasons, a split-plot design was used where the temperature of the column was held constant for short periods of time [18]. A solution containing the APIs at 60% of their nominal concentrations was assayed according to the experimental conditions listed in Table 5. Predictive mathematical models were developed for all of the responses other than peak tailing, which exhibited limited variability. All of the experimental conditions yielded acceptable results. As shown in Fig. 5, however, it was noted that the retention time of cetirizine increases as the column temperature and/or methanol content of the mobile phase decreases. These results demonstrate that the method is robust to small deviations from the nominal conditions.

Table 4
Conditions for the robustness study

Factor	Level		
	Low (−)	Nominal	High (+)
Column temperature (°C)	25[a]	30	35
pH[b]	6.3	6.5	6.7
OSA[c] (mM)	4.5	5.0	5.5
MeOH[d] (%)	47.5	50.0	52.5

[a] The actual temperature inside the column heater was approximately 26 °C.
[b] pH of the sodium phosphate buffer used to prepare the mobile phase.
[c] Concentration of sodium 1-octanesulfonate in the mobile phase.
[d] Percent methanol in the mobile phase.

Table 5
Results from the robustness study

Expt no.	ABCD[a]	Pseudoephedrine				Cetirizine			
		t[b]	*A* (%R.S.D.)[c]	*T*[d]	*N*[e]	*t*	*A* (%R.S.D.)	*T*	*N*
1	Nominal	2.6	0.07	1.6	4054	6.8	0.58	1.1	5181
2	−++−	2.8	0.30	1.6	3400	8.0	0.58	1.1	4807
3	−+−+	2.7	0.44	1.6	3586	6.5	1.04	1.2	4585
4	−−++	2.6	0.27	1.6	3837	6.9	0.70	1.2	4754
5	−−−−	2.7	0.71	1.6	3259	8.4	0.89	1.1	4755
6	Nominal	2.7	0.60	1.6	3959	6.8	0.83	1.1	5135
7	+−−+	2.6	0.43	1.6	4368	5.8	0.73	1.2	5213
8	+−+−	2.6	0.47	1.5	4446	6.8	0.85	1.1	5563
9	++−−	2.8	0.57	1.6	4213	6.8	0.83	1.1	5710
10	++++	2.7	0.35	1.6	3790	5.5	0.34	1.2	5346
11	+++−	2.9	0.27	1.6	4431	6.7	0.87	1.1	5399
12	+−++	2.7	1.06	1.6	3837	6.1	1.13	1.2	5715
13	+−−−	2.7	0.41	1.5	4585	7.0	1.28	1.2	5825
14	++−+	2.7	0.29	1.6	4098	5.5	0.69	1.2	5427
15	−−−+	2.7	0.46	1.6	3352	7.0	0.84	1.2	4397
16	−−+−	2.8	0.53	1.6	3618	8.3	1.25	1.2	4520
17	−+++	2.9	0.38	1.7	3515	6.7	1.44	1.2	4419
18	−+−−	3.1	0.26	1.7	3460	8.8	1.60	1.2	4623
19	Nominal	2.8	0.48	1.6	4275	6.8	1.26	1.1	5209
Minimum		2.6	0.07	1.5	3259	5.5	0.34	1.1	4397
Maximum		3.1	1.06	1.7	4585	8.8	1.60	1.2	5825

[a] A, column temperature (°C); B, pH; C, OSA (mM); and D, MeOH (%).
[b] Retention time (min) of the API peak.
[c] %R.S.D. of the API peak areas from 5 injections.
[d] Tailing factor of the API peak.
[e] Number of theoretical plates associated with the API peak.

3.2.7. Filter suitability

Two types of filters, one for manual sampling (Millex-HV) and one for automated sampling (HDPE), were evaluated using the dissolution medium and the following solutions prepared in deionized water: (1) a solution containing both APIs at nominal concentration, (2) a solution containing the tablet excipients at nominal concentrations, (3) a solution containing pseudoephedrine HCl, cetirizine HCl, and the excipients at 5, 50, and 100% of their nominal concentrations, respectively, and (4) a solution containing the APIs and excipients at 125 and 100% of their nominal concentrations, respectively. These solutions were stirred at 37 °C for 24 h prior to being filtered. In the case of the Millex-HV filter, sample aliquots were collected for analysis after discarding the first 1, 3, 5, or 7 ml of filtrate. To evaluate the HDPE filter, 5 ml of each solution was withdrawn through a fresh filter and analyzed without discarding any of the filtrate. These studies were repeated with five additional filters of each type. There were no chromatographic peaks observed due to extractable materials from either filter. Both APIs were quantitatively recovered (average recoveries were within 98–102% of theory) after discarding the first 3 ml of filtrate through the Millex-HV filter, or after withdrawing 5 ml of solution through the HDPE filter. These data demonstrate that the filters are suitable when used as directed.

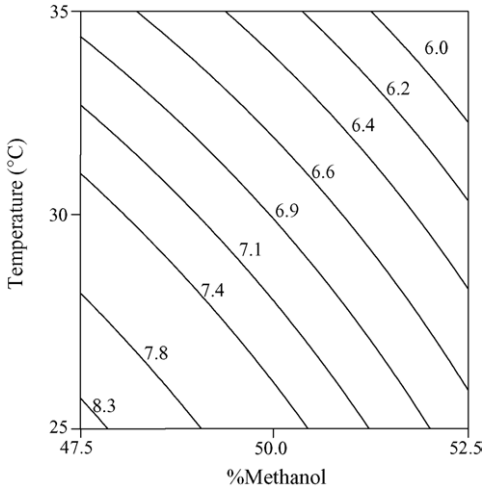

Fig. 5. Contours of predicted retention time (min) for cetirizine vs. column temperature and percent methanol in the mobile phase (OSA = 5.0 mM; pH = 6.5).

3.2.8. Solution stability

The combined standard solution of cetirizine HCl and pseudoephedrine HCl was stored, unprotected from light, at ambient conditions and assayed after 1, 2, 3, 4, and 7 days against a freshly prepared standard solution. All of the assay results during this time period were within 98–102% of the initial value and no degradation products were observed in any of the chromatograms. The standard solution is therefore

considered stable for at least 7 days under normal laboratory conditions.

The last two solutions described in Section 3.2.7 were used to assess the stability of the sample solutions during the course of the experiment. The solutions were placed into covered dissolution vessels, stirred at 50 rpm, and assayed after 0.5, 1.0, 1.5, 24, and 36 h at 37 °C. Over this time period, the assay values for cetirizine and pseudoephedrine were within 97–103% and 98–102% of initial, respectively, and no degradation products were observed. These experiments demonstrate that the APIs are stable under the conditions of the test for at least 36 h.

In addition, another aliquot was withdrawn from each vessel at the 24 h time point to determine how long the filtered sample solutions could be stored at ambient conditions before assay. These solutions were stored, unprotected from light, and assayed after 24, 48, and 72 h. During this time period, all of the assay results were within 98–102% of initial and no degradation products were observed in any of the chromatograms. The filtered solutions are therefore considered stable at ambient conditions for at least 72 h.

3.3. Development of the dissolution test

3.3.1. Selection of the test conditions

The dissolution test conditions were selected based on a screening study with USP apparatus 1 (100 rpm baskets) and USP apparatus 2 (50, 75, and 100 rpm paddles). The tablets were tested in 1000 ml of 0.1 M HCl, USP pH 4.5 buffer, USP pH 6.8 buffer, deionized water, and SIF. The data for cetirizine HCl are given in Table 6. As expected for a highly soluble compound contained within a thin coating layer, the dissolution of cetirizine HCl was rapid and essentially complete within 30 min under all of these test conditions.

The drug release data for pseudoephedrine HCl are given in Table 7. These data show that premature drug release (i.e., "dose dumping") does not occur, and that 92% or more of the dose is released over 24 h.

The data in Table 7 also suggest, in that the average results differ by ≤10% at each time point, that the release of pseudoephedrine HCl is independent of dissolution conditions. To evaluate this further, the mean profiles were compared in a pairwise fashion using the similarity factor (f_2) approach proposed by Moore and Flanner [19]. This factor is calculated as follows:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(\bar{X}_i - \bar{Y}_i)^2\right]^{-0.5} \times 100\right\},$$

where $\bar{X}_i$ and $\bar{Y}_i$ are the average values of the two data sets at the ith time point and n is the total number of time points. The value of this factor equals 100 when the profiles are identical and approaches zero as the profiles become increasingly dissimilar. According to the SUPAC-MR guidance document [20], two curves are considered similar if the f_2 value is between 50 and 100. This document also recommends that only one point past the plateau of the profiles be used to calculate this factor. As a conservative measure, therefore, only the data from the first eight time points (i.e., from 1 to 14 h) were used to calculate the similarity factor. All of the mean profiles were found to be similar since the f_2 value for each pair was ≥56.

Based on these data, USP apparatus 2 with paddles rotating at 50 rpm was selected as the dissolution apparatus and 1000 ml of deionized water was chosen as the dissolution medium. The apparatus and paddle speed were selected based on regulatory guidelines for immediate-release [21] and extended-release [22] products. Since this screening study demonstrated that the choice of the dissolution medium was not critical, water was chosen because it is used as the medium for other products that contain pseudoephedrine. In fact, this method uses the same apparatus, paddle speed, and dissolution medium as that used for pseudoephedrine hydrochloride tablets, extended-release capsules, and extended-release tablets [23].

3.3.2. Discriminating power of the test

The ability of the dissolution method to discriminate between similar formulations was tested by analyzing tablets coated with different amounts of the asymmetric membrane. The mean profiles ($N = 6$ tablets) are shown in Fig. 6. As expected, the release of pseudoephedrine HCl was faster from the more lightly coated tablets.

Table 6
Screening study results for cetirizine HCl (%dissolved at 30 min)[a]

Medium	USP apparatus 1	USP apparatus 2		
	100 rpm	50 rpm	75 rpm	100 rpm
0.1 M HCl (pH 1.1)	97 (88–107)	95 (89–101)	95 (85–101)	97 (94–101)
USP pH 4.5 buffer	90 (81–99)	100 (91–107)	98 (91–105)	91 (83–101)
Water (pH 6.1)[b]	98 (94–110)	95 (91–103)	95 (90–100)	97 (92–104)
USP pH 6.8 buffer	95 (90–100)	95 (91–100)	101 (94–109)	95 (87–100)
SIF (pH 7.5)	–[c]	93 (84–100)	–	–

[a] The average result is reported followed by the range in parentheses.
[b] This was the average pH of the medium in a separate test using USP apparatus 2. The individual values for six tablets ranged from 5.8 to 6.3.
[c] Data not collected.

Table 7
Screening study results for pseudoephedrine HCl (cumulative %released)[a,b]

	Time (h)											
	2	4	6	8	10	12	14	16	18	20	22	24
0.1 M HCl (pH 1.1)												
50 rpm Paddles	8 (3.2)	29 (4.9)	47 (5.1)	59 (5.3)	70 (4.3)	77 (3.9)	82 (3.4)	86 (3.1)	89 (2.8)	90 (2.5)	92 (2.3)	93 (2.4)
75 rpm Paddles	8 (4.0)	28 (6.4)	45 (6.1)	59 (6.6)	69 (6.4)	78 (5.5)	83 (4.8)	88 (4.2)	91 (3.6)	93 (3.2)	95 (3.1)	97 (2.5)
100 rpm Paddles	5 (1.8)	24 (3.1)	42 (3.3)	56 (3.3)	67 (3.1)	75 (2.9)	81 (2.7)	85 (2.4)	89 (2.3)	91 (2.2)	93 (2.2)	95 (2.5)
100 rpm Baskets	6 (2.7)	26 (4.4)	44 (4.6)	57 (4.3)	68 (3.7)	76 (3.1)	82 (3.0)	87 (2.3)	90 (2.8)	93 (1.7)	95 (1.7)	95 (1.6)
USP pH 4.5 buffer												
50 rpm Paddles	6 (3.7)	26 (6.2)	43 (6.6)	56 (6.4)	66 (6.0)	73 (5.4)	79 (4.7)	83 (3.7)	86 (3.7)	89 (3.0)	91 (3.4)	92 (2.7)
75 rpm Paddles	6 (2.3)	26 (4.2)	43 (4.9)	57 (5.0)	67 (4.9)	75 (4.6)	81 (4.2)	86 (3.8)	89 (3.7)	92 (3.1)	94 (2.7)	96 (2.6)
100 rpm Paddles	6 (2.7)	26 (4.7)	43 (4.6)	56 (4.7)	66 (4.3)	73 (4.6)	79 (3.5)	83 (3.0)	86 (2.6)	89 (2.2)	91 (2.1)	92 (2.0)
100 rpm Baskets	6 (4.0)	24 (7.7)	40 (8.8)	53 (8.9)	64 (8.6)	72 (7.7)	78 (7.1)	83 (6.2)	86 (5.4)	89 (4.6)	90 (4.0)	92 (3.6)
Water (pH 6.1)												
50 rpm Paddles	9 (2.9)	32 (4.3)	50 (4.0)	61 (3.6)	70 (3.1)	78 (2.6)	85 (2.2)	89 (1.8)	91 (1.7)	93 (1.5)	92 (1.4)	92 (1.3)
75 rpm Paddles	6 (3.6)	26 (6.0)	44 (7.4)	58 (6.9)	68 (6.8)	76 (6.1)	82 (5.4)	86 (4.5)	90 (4.1)	92 (3.2)	94 (3.5)	94 (2.6)
100 rpm Paddles	8 (4.0)	29 (6.8)	48 (7.3)	61 (6.9)	71 (6.6)	78 (5.9)	84 (5.0)	89 (4.2)	91 (3.8)	93 (3.0)	94 (3.2)	95 (2.8)
100 rpm Baskets	8 (3.2)	29 (5.4)	48 (5.8)	62 (5.7)	72 (5.3)	79 (4.7)	84 (4.1)	88 (3.6)	91 (3.1)	92 (2.7)	94 (1.4)	95 (2.1)
USP pH 6.8 buffer												
50 rpm Paddles	9 (3.6)	31 (5.4)	48 (5.5)	62 (4.9)	72 (4.6)	78 (3.9)	83 (3.2)	87 (2.8)	90 (2.7)	92 (2.3)	93 (2.1)	94 (2.0)
75 rpm Paddles	8 (4.2)	28 (5.8)	46 (5.6)	60 (5.3)	70 (4.8)	78 (4.2)	83 (3.7)	87 (3.4)	90 (3.4)	91 (3.1)	93 (3.2)	94 (2.8)
100 rpm Paddles	7 (1.5)	28 (2.8)	46 (3.1)	60 (3.0)	70 (2.8)	78 (3.2)	82 (2.1)	86 (1.7)	89 (1.9)	91 (1.8)	93 (1.5)	94 (1.6)
100 rpm Baskets	7 (3.3)	28 (5.2)	46 (5.4)	60 (5.1)	70 (4.6)	77 (4.0)	83 (3.6)	86 (3.1)	89 (2.8)	92 (2.6)	93 (2.3)	94 (2.1)
SIF (pH 7.5)												
50 rpm Paddles	9 (2.2)	31 (3.2)	49 (3.2)	63 (3.0)	73 (2.5)	80 (2.3)	85 (2.2)	89 (2.0)	92 (1.4)	94 (1.1)	95 (1.2)	96 (1.5)

[a] The average result is reported followed by the standard deviation in parentheses.
[b] Nearly all (97%) of the individual tablet results at 1 h were ≤2%, and all of the results were 8% or less.

In addition, the Tukey-Kramer HSD (Honestly Significant Difference) method [24] was used to test the average results at 4 h for significant differences at the 5% level. As shown in Table 8, the results at the 50, 60, 77, and 122% coating weight levels were significantly different than those at the 97% level. The dissolution method is therefore able to discriminate between product batches coated with the targeted amount of the asymmetric membrane, and those that are coated with ≤77% or ≥122% of this nominal weight.

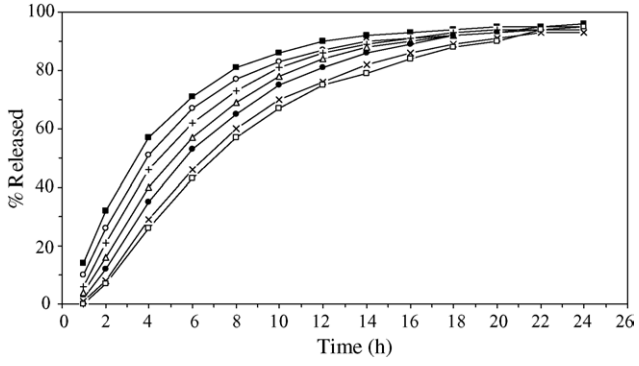

Fig. 6. Mean cumulative %release profiles for pseudoephedrine HCl from tablets coated with 50 (■), 60 (◯), 77 (+), 86 (△), 97 (●), 110 (×), and 122% (□) of the target AM coating weight.

3.3.3. Reproducibility

The reproducibility of the method was assessed by means of an inter-laboratory study, where two laboratories used the dissolution test to assay tablets from three different lots. As shown in Table 9, both laboratories found that the dissolution of cetirizine HCl was rapid and essentially complete within 30 min.

The data for pseudoephedrine HCl are tabulated in Table 10. The results from the two laboratories were considered equivalent since the average values differed by 6% or less at each time point. In addition, the profiles were found to be similar to one another in that the f_2 values were ≥71 for each lot. These data support the conclusion that the method is rugged and transferable.

Table 8
Cumulative% pseudoephedrine HCl released at 4 h vs. AM coating weight[a]

Coating weight (%target)	Mean ± 95% confidence limits						
50	57 ± 2.7	A					
60	51 ± 3.7	A	B				
77	46 ± 4.1		B	C			
86	40 ± 5.2			C	D		
97	35 ± 4.8				D	E	
110	29 ± 2.8					E	F
122	26 ± 6.0						F

[a] Coating weight levels not connected by the same letter are significantly different at $\alpha = 0.05$.

Table 9
Reproducibility results for cetirizine HCl (%dissolved)[a,b]

Time (min)	Lot 1		Lot 2		Lot 3	
	Lab A	Lab B	Lab A	Lab B	Lab A	Lab B
15	95 (90–99)	92 (83–98)	91 (89–94)	94 (88–100)	96 (92–97)	97 (90–100)
30	96 (90–101)	93 (84–99)	94 (90–99)	94 (88–98)	95 (93–97)	98 (90–101)
45	96 (91–100)	94 (86–99)	94 (92–99)	95 (90–98)	96 (94–97)	100 (92–106)
60	97 (91–101)	95 (87–102)	95 (91–99)	96 (90–100)	98 (96–99)	100 (92–103)

[a] Laboratory A tested six tablets.
[b] The average result is reported followed by the range in parentheses.

Table 10
Reproducibility results for pseudoephedrine HCl (cumulative %released)[a,b,c]

Time (h)	Lot 1		Lot 2		Lot 3	
	Lab A	Lab B	Lab A	Lab B	Lab A	Lab B
2	10 (2.4)	10 (3.4)	7 (4.3)	9 (3.3)	4 (3.2)	7 (2.7)
4	32 (3.2)	32 (5.3)	29 (6.8)	31 (4.6)	22 (6.9)	27 (5.3)
6	52 (3.0)	51 (5.4)	47 (7.0)	48 (5.2)	39 (7.6)	45 (6.1)
8	66 (3.0)	64 (5.1)	61 (6.4)	60 (5.4)	54 (7.9)	58 (6.1)
10	76 (2.3)	74 (4.5)	72 (5.9)	70 (4.0)	65 (7.8)	69 (5.8)
12	83 (1.8)	80 (3.6)	80 (5.2)	78 (4.0)	73 (6.9)	76 (5.4)
14	89 (1.6)	86 (3.1)	85 (4.3)	84 (2.9)	80 (6.1)	81 (4.8)
16	92 (0.6)	90 (2.9)	89 (3.8)	88 (3.2)	85 (6.5)	85 (4.3)
18	95 (0.8)	92 (2.2)	93 (3.5)	91 (3.0)	88 (4.9)	87 (3.7)
20	96 (0.9)	93 (2.1)	95 (3.4)	91 (3.6)	91 (4.8)	90 (3.3)
22	97 (1.0)	94 (1.8)	96 (2.7)	90 (3.5)	92 (4.4)	91 (3.6)
24	100 (1.1)	95 (1.6)	98 (2.5)	93 (1.9)	93 (4.5)	93 (3.2)

[a] Laboratory A tested six tablets.
[b] The average result is reported followed by the standard deviation in parentheses.
[c] All of the individual results at 1 h were ≤3%.

4. Conclusions

A robust, discriminating dissolution method was developed for a combination tablet of cetirizine HCl and pseudoephedrine HCl. A screening study was conducted to select the dissolution apparatus, rotation speed, and dissolution medium for the test. The method was successfully validated according to current ICH and FDA guidelines, and the transferability of the method was demonstrated during an interlaboratory trial. This method will be used to optimize the formulation and manufacturing process, to assess the quality and performance of each tablet lot, and to minimize the risk of releasing bioinequivalent product batches.

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