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Titrimetric and spectrophotometric assay of some antihistamines through the determination of the chloride of their hydrochlorides

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Abstract

Two simple, rapid and reliable methods for the determination of four antihistamines based on the measurement of the chloride of their hydrochlorides are described. In the titrimetric method, the chloride content of each drug is determined by titrating with mercury(II) nitrate using diphenylcarbazone–bromothymol blue as indicator. In the spectrophotometric method, to a fixed concentration of mercury(II)–diphenylcarbazone complex different amounts of drug are added and the decrease in absorbance of mercury(II)–diphenylcarbazone complex, consequent to the replacement of diphenylcarbazone of the complex by the chloride of the drug, was measured at 540 nm. The stoichiometry of the reaction that forms the basis for titrimetry is assessed. Different variables affecting the color formation in spectrophotometry were studied and optimized. At the wavelength of maximum absorption, Beer's law is obeyed in the 0–100 μg ml^{-1} range. The molar absorptivity and Sandell sensitivity are calculated. The proposed methods were applied for the analysis of pharmaceutical formulations containing these drugs. Statistical treatment of the experimental results indicates that the procedures are precise and accurate. Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedures as shown by the recovery studies.

Keywords: Antihistamines; Titrimetry; Spectrophotometry; Mercury(II)nitrate; Diphenylcarbazone

1. Introduction

Cetirizine hydrochloride (CTH), diphenhydramine hydrochloride (DPH), mebrophenhydramine hydrochloride (MPH) and hydroxyzine hydrochloride (HDH) are used widely as antihistamines in therapy. CTH is a new antihistaminic drug that is used for the treatment of perennial and seasonal allergic rhinitis and chronic urticaria. It is official in EP [1]. DPH blocks histamine H-1 receptors and causes sedation and has some anticholinergic action. MPH is a H-1 antagonist used in all allergies. HDH causes depression of subcortical levels of CNS. Primarily it leads to skeletal muscle relaxation, antihistaminic and antiallergic effects. The last three drugs are not official in any of the pharmacopoeia. Not many methods are found in the literature for the assay of CTH in pharmaceutical formulations. El Walily et al. [2] have reported two methods for the determination of CTH in pharmaceutical formulations. The spectrophotometric method is based on the formation of charge-transfer complex with chloranil while the HPLC method uses salicylic acid as the internal standard with UV-detection. The drug has also been determined in tablets and capsules by HPLC technique on a reversed-phase column [3]. Its spectrophotometric determination was achieved by reaction with alizarin red S [4] and bromocresol green [5] in an acidic buffer medium followed by the extraction of an ion–associate complex in chloroform and measurement at 420 nm. Recently [6], the applicability of ion-selective electrode based potentiometry has also been investigated.

Several methods have been reported for the determination of DPH. The alkalimetric titration method [7] suffers from interferences from ephedrine. Non-aqueous titrimetric methods [8,9] require a scrupulously

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anhydrous medium. DPH has also been determined by precipitating with potassium iodobismuthate, filtering the precipitate and titrating the unreacted bismuth in the filtrate with EDTA [10], the steps being complex and time consuming. Titration with sodium tetraphenyl borate has also been reported but it requires a carefully controlled pH [11]. Most of the spectrophotometric methods reported for DPH involve the extraction of chromogen in an organic solvent before measuring the absorbance. They are based on reactions such as the ion-pair formation [12–14], charge-transfer complex formation [15,16], addition compound formation [17,18] and ternary complex formation [19–21]. These procedures involve tedious extraction steps and suffer from disadvantages such as low sensitivity, careful pH control, insufficient accuracy and precision, and/or longer extraction time. Other techniques such as fluorimetry [22], turbidimetry [23], gas chromatography [24,25], HPLC [26,27], polarography [28] and PMR spectroscopy [29] have also been employed for the determination of DPH.

Literature on the quantitation methods for MPH is scarce. There is only one visible spectrophotometric method [30] reported for MPH. Even this method involves an extraction step, which is tedious and time consuming, and the method is also less sensitive, with the range of determination being 50–500 $\mu g\,ml^{-1}$. Other procedures suggested for the assay of MPH utilize techniques such as UV-spectrophotometry [31,32], potentiometry [33] and capillary isotachophoresis [34].

Methods recommended for the assay of HDH include conductometry [35,36], gravimetry [37], liquid chromatography [38], gas chromatography [39], reversed-phase HPLC [40] and ion-exchange chromatography [41]. The visible spectrophotometric method reported by Sane et al. [42] involves the extraction of the ion-pair complex formed with acidic dyes, and is pH dependent whereas the method based on the complex formation with Cu^{2+} [43] is applicable to blood samples only. Only two titrimetric methods are found in the literature for HDH. The method by Sanrick and Janik [44] involves the precipitation of the drug with sodium tetraphenyl borate, filtration, dissolution of the precipitate in acetone and potentiometric titration with $AgNO_3$. The complexometric [45] determination of HDH also involves the precipitation of the drug with cadmium nitrate, filtration of the precipitate, and titration of residual cadmium with EDTA. The methods are laborious, time consuming and complicated.

Most of the titrimetric procedures reported for the cited drugs either use non-aqueous medium or involve precipitation, filtration and titration of the unreacted precipitant steps that are complex, tedious and time consuming. Further, most of the spectrophotometric methods involve the extraction step and suffer from disadvantages such as low sensitivity, inadequate accuracy and precision, and critical working conditions. The purpose of this investigation was to develop simple, rapid, accurate and inexpensive procedures for the quantitation of CTH, DPH, MPH and HDH, the structures of which are given in Fig. 1, in pure form and in pharmaceutical formulations. The titrimetric procedure involves the titration of the chloride content of the hydrochlorides of the drugs studied in acidic condition with mercury(II) nitrate while the spectrophotometric method uses an indirect procedure based on the measurement of the decrease in absorbance of mercury(II)–diphenylcarbazone complex caused by the replacement of diphenylcarbazone from the complex by the chloride, also in an acidic pH condition. Effectively, both methods involve the determination of the ionic chloride of the drugs investigated in aqueous solution. The present effort was prompted by the absence of suitable functional groups in the organic moiety of the molecules that can be exploited for the quantitative investigation as evident from their structures (Fig. 1).

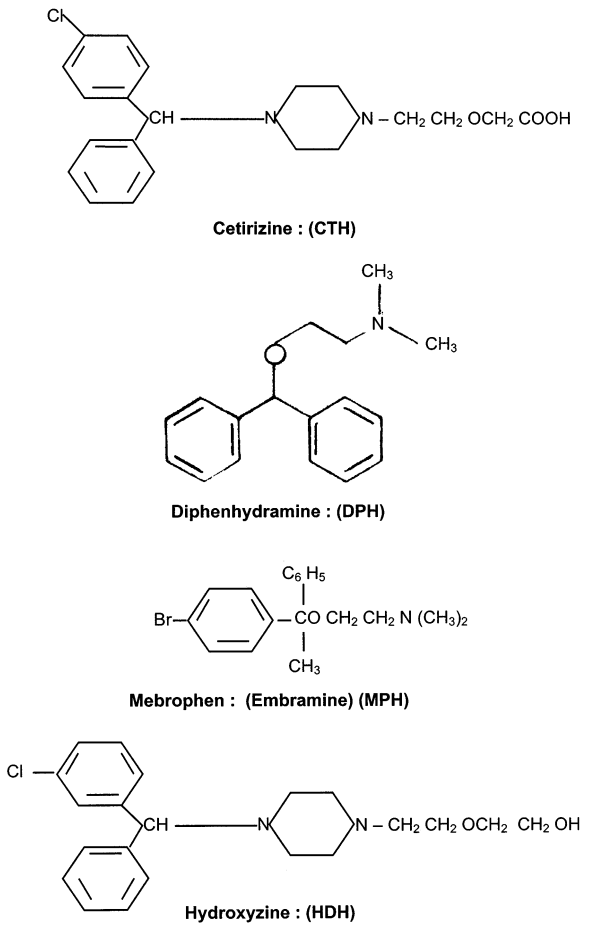

Fig. 1. Structures of the investigated antihistamines.

2. Experimental

2.1. Apparatus

A Systronics model 106 digital spectrophotometer with 1 cm matched quartz cells was used for absorbance measurements.

2.2. Reagents

All reagents, unless otherwise stated, were of the analytical grade and doubly distilled water was used always.

2.2.1. Mercury(II) nitrate

A 0.01 mol l^{-1} solution was prepared by dissolving 1.7131 g of the salt in doubly distilled water and diluting to 500 ml. The solution was standardized using pure potassium chloride [46]. The stock solution was diluted to 0.005 mol l^{-1} for the titrimetric work and diluted stepwise to obtain 200 μg ml^{-1} Hg(II) for the spectrophotometric work.

2.2.2. Diphenylcarbazone for spectrophotometry

A 0.02% solution was prepared by dissolving 20 mg of the reagent in 10 ml of 95% alcohol and diluting to 100 ml with doubly distilled water.

2.2.3. Formate buffer

Formate buffer was prepared by dissolving 0.52 g sodium formate in 70 ml of doubly distilled water and adjusting the pH to 3.4 with 0.1 mol l^{-1} nitric acid and diluting to 100 ml with doubly distilled water.

2.2.4. Diphenylcarbazone–bromothymol blue mixed indicator for titrimetry

The mixed indicator was prepared by dissolving 0.25 g of diphenylcarbazone and 0.025 g of bromothymol blue in 50 ml absolute alcohol.

Sodium hydroxide (0.05 mol l^{-1}), nitric acid (0.05 mol l^{-1}), sodium formate (0.1 mol l^{-1}), gum arabic (2%) were prepared using analytical grade reagents and doubly distilled water.

2.2.5. Antihistamines and their formulations

Pure drug samples were kindly provided by several pharmaceutical companies and used as received. Formulations containing the drugs were purchased from commercial sources. Stock standard solutions containing 1000 μg ml^{-1} drug were prepared by dissolving the weighed amount of CTH, HDH (UCB pharma Ltd), DPH (Parke Davis Ltd) and MPH (Smithkline Beecham Ltd) in doubly distilled water. Working solutions were prepared daily by an appropriate dilution of the stock solution with doubly distilled water.

2.3. Procedures

2.3.1. Titrimetry

A 10 ml aliquot of the drug solution containing 4–15 mg CTH or HDH, 5–15 mg DPH or MPH was transferred into a 100 ml conical flask and two drops of diphenylcarbazone–bromothymol blue mixed indicator was added. Sodium hydroxide (0.05 mol l^{-1}) was added dropwise till the yellow color turned blue–violet. Then, nitric acid (0.05 mol l^{-1}) was added to obtain the yellow color back. The contents were then titrated by adding mercury(II) nitrate (0.005 or 0.01 mol l^{-1}) slowly from a 10 ml burette with continuous stirring by a magnetic stirrer to a violet end-point.

The drug content was calculated from:

$$\text{mg of drug} = VMS/n$$

where V is the volume of mercury(II) nitrate added in ml; M the molecular weight of the drug; S the strength of the mercury(II) nitrate solution in mol l^{-1}; and n the number of moles of mercury(II) nitrate reacting with one mole of drug.

2.3.2. Spectrophotometry

In each of a series of 10 ml standard flasks were placed 0.0–2.0 ml of 200 μg ml^{-1} CTH, 0.0–3.0 ml of 100 μg ml^{-1} DPH, 0.0–2.5 ml of 400 μg ml^{-1} MPH or 0.0–3.0 ml of 200 μg ml^{-1} HDH solution by means of a microburette. Then, 1 ml of the formate buffer and five drops of gum arabic stabilizer (2%) were added. After the addition of 2 ml of diphenylcarbazone reagent (0.02%), the total volume was adjusted to 7 ml by the addition of requisite amount doubly distilled water. Subsequently, 2 ml of 20 μg ml^{-1} Hg(II) solution were added and the volume was diluted to the mark with doubly distilled water. The contents were mixed well and the absorbance was measured at 540 nm against doubly distilled water after 15 min. The decrease in absorbance was plotted against the drug concentration, and the concentration of the unknown was read either from the calibration graph or computed from the linear regression equation.

2.3.3. Assay procedure for formulations

Twenty to eighty tablets, depending on the active content per tablet, were weighed and ground to a fine powder. The amount of powder equivalent to about 100 mg of active component was weighed into a 100 ml beaker. The powder was extracted with three 30 ml portions of doubly distilled water and filtered into a 100 ml standard flask using a quantitative filter paper. The filtrate was washed and the washings were collected into the flask, and finally the volume was made up to the mark with doubly distilled water. A 10 ml aliquot was used for assay by the titrimetric procedure.

Table 1
Stoichiometry and range of determination by titration with mercury(II) nitrate

Antihistamine drug	Stoichiometry		
	Amount taken (mg)	Number of moles of Hg(II) nitrate consumed per mole of drug [a]	Range (mg)
CTH	4.0	2.14	4.0–15.0
	7.0	2.01	
	11.0	2.00	
	15.0	1.97	
DPH	5.0	1.04	5.0–15.0
	8.0	1.01	
	11.0	0.99	
	15.0	0.98	
MPH	5.0	1.03	5.0–15.0
	8.0	1.02	
	11.0	1.00	
	15.0	0.97	
HDH	4.0	2.04	4.0–15.0
	7.0	2.03	
	11.0	2.00	
	15.0	1.99	

[a] Average value of three determinations.

For spectrophotometry, the tablet solution was diluted appropriately to get 200 μg ml^{-1} CTH or HDH, 100 μg ml^{-1} DPH or 400 μg ml^{-1} MPH, and a suitable aliquot was treated as described under the general procedure.

In the case of capsules, the contents of 20 capsules were mixed and a quantity equivalent to 100 mg of the drug was transferred into a 100 ml standard flask. Fifty milliliters of doubly distilled water were added, shaken thoroughly for about 30 min, made up to the mark, mixed well and filtered. Then, the steps described for tablets were followed.

2.4. Recovery experiment

Known amounts of pure drug in three different levels were added to a fixed amount of the same drug present in the formulation, analyzed earlier, and the total amount of the drug was determined by using the proposed procedures. Percent recovery of the added pure drug was calculated as follows:

$$\% \text{ recovery} = [(Av - Au)/Aa] \times 100$$

where Av is the total amount of the analyte measured; Au the amount of the analyte present in the formulation; Aa the amount of the analyte added to the formulation.

3. Results and discussion

The proposed methods, in essence, are based on the determination of the chloride content of the hydrochlorides of the drugs studied by the well-known methods for chloride.

3.1. Titrimetry

Only a few titrimetric methods are found in the literature for the assay of the drugs studied that too by either non-aqueous [8,9], precipitation [44] or complexometric [10,45]. Determination of chloride by titrating with mercury(II) is one of the best-known examples of complexometric titrations involving unidentate ligands [47]. This has served as a basis for the assay of many pharmaceuticals [48–50] and plant materials [51]. This principle is used in the determination of the four antihistamines studied which ionize in aqueous solution to give the chloride ion facilitating the latter's titration. Although diphenylcarbazone is a suitable indicator for the titration of chloride with Hg(II) [52] diphenylcarbazone–bromothymol blue mixed indicator was found to give better results as reported by Clarke [53]. Best results were obtained at pH 3.2–3.3 which were adjusted by adding a requisite amount of 0.05 mol l^{-1} nitric acid. The stoichiometric study revealed that the drug–titrant ratio in the complex formed was 1:1 for monohydrochlorides, DPH and MPH, and 1:2 for dihydrochlorides, CTH and HDH (Table 1), and the quantitative calculations were based on these ratios. The results of the determination of the drugs studied are presented in Tables 3 and 4. It is clear from the tables that the proposed titrimetric method could be used for the determination of 4–15 mg of CTH (9.4×10^{-3}–3.5×10^{-3} mol l^{-1}), 5–15 mg of DPH (1.71×10^{-3}–5.1×10^{-3} mol l^{-1}), 5–15 mg of MPH

(1.3×10^{-3}–3.91×10^{-3} mol l^{-1}) and 4–15 mg of HDH (8.9×10^{-4}–3.3×10^{-3} mol l^{-1}) using 0.005 or 0.01 mol l^{-1} mercury(II) nitrate solution. Below 4 mg higher n values and above 15 mg lower n values were obtained producing deviant results.

3.2. Spectrophotometry

Among the few colorimetric methods for the determination of small amounts of chloride ion, one of the best known and most widely used is an indirect method based on the decrease in color of the mercury–diphenylcarbazone complex caused by chloride ions [54]. The method involves the following fundamental reactions:

$$Hg^{2+} + H_2DcO \rightarrow HgHDcO^+ + H^+$$

$$HgHDcO^+ + 2Cl^- \rightarrow HgCl_2 + HDcO^-$$

where H_2DcO and $HDcO^-$, represent the molecule and anion of diphenylcarbazone, respectively, and $HgHDcO^+$, the coloured complex cation with mercury.

Since the antihistamines investigated are hydrochlorides, the suitability of their assay by determining their chloride content with mercury(II) and diphenylcarbazone was examined. In aqueous solutions, these drugs exist as protonated cations and chloride ions and, the latter was determined using this method, thus allowing the indirect assay of antihistamines. The method is based on the complexation of the chloride ion of the drugs by a known excess of mercury(II) and the subsequent determination of the unreacted mercury(II) by interacting with diphenylcarbazone under acidic pH conditions. Antihistamines, when added in increasing amounts to a fixed amount of mercury(II) complex, consume the latter and consequently there will be a concomitant fall in the concentration of the mercury(II) complex. This is observed as a proportional decrease in the absorbance of the reaction mixture on increasing the concentration of drugs.

The first step in the spectrophotometric study was to evaluate the upper limit of mercury(II) which can be determined using diphenylcarbazone and this was found by treating different amounts of mercury(II) with diphenylcarbazone under the conditions described in Section 2.3. The study showed that Beer's law is obeyed up to 4 μg ml^{-1} of mercury(II) at room temperature (34 °C). Hence, different amounts of each drug were treated with 2 ml of 20 μg ml^{-1} mercury(II) solution and the unreacted mercury(II) was determined following the procedure described earlier.

Since the various parameters involved in the determination of chloride using the Hg–DPC system are well-established [54], the procedure for the determination of the drugs was optimized. Since the useful pH range for chloride determination is very narrow—the optimum lies between 3.3 and 3.5—the formate–formic acid buffer of pH 3.4, which neither complexes mercury nor contains chloride ions, was used.

A very small amount of gum arabic was necessary to stabilize the mercury–DPC complex. The maximum color intensity is developed within 15 min and is stable for at least 2 h for the four drugs studied indicating that the protonated drug moiety had no effect on the absorbance.

Two blanks were prepared for this system. The reagent blank, which contained optimum concentrations of all reagents except the drug, gave maximum absorbance. The other blank was prepared in the absence of Hg(II) nitrate and, the drug to determine the contribution of other reagents to the absorbance of the system. Since the absorbance of this second blank was negligible, the absorbance of the color developed was measured against water.

3.3. Analytical data

The linearity of the calibration graphs is apparent from the correlation coefficient, r obtained by determining the best fit line via linear least-squares treatment. The linearity is found in each instance and Beer's law is obeyed in the inverse way up to 40 μg ml^{-1} for CTH, 30 μg ml^{-1} for DPH, 100 μg $ml^{-1}$for MPH and 60 μg ml^{-1} for HDH.

The correlation coefficients, the slope, m and the intercept, Z of the equation of the regression line, $A = mC + Z$, are summarised in Table 2. The apparent molar absorptivity values and the mean Sandell sensitivities are also given in Table 2.

3.4. Accuracy and precision

In order to determine the accuracy and precision of the procedures recommended, six replicate experiments at different concentrations of drugs were carried out. The percent recoveries and relative standard deviations (Table 3) indicate that the proposed methods are highly accurate and reproducible.

3.5. Application

The methods were applied to the assay of drugs studied in tablets and capsules available in the local market. The results are tabulated in Table 4. The validity and accuracy of the methods were further ascertained through recovery studies by adding different known amounts of pure drugs to a fixed amount of preanalyzed formulations and determining the total amount by the proposed methods. The percent recovery values (Table 5) indicate that neither the end-point in

titrimetry nor the absorbance in spectrophotometry was affected by the commonly encountered excipients such as starch, lactose, talc, gelatin, sodium alginate and magnesium stearate.

In conclusion, the proposed methods are simple, accurate, precise and inexpensive, and can be used for the routine determination of the investigated antihistamines in pure form as well as in their formulations.

Table 2
Quantitative parameters for the indirect spectrophotometric determination of antihistamines

Antihistamine drug	Beer's law range (μg ml^{-1})	Molar absorptivity (10^3 l mol^{-1} cm^{-1})	Sandell sensitivity (μg cm^{-2})	Correlation coefficient, r	$A = mC + Z$ [a]	
					m	Z
CTH	0–40	5.8703	0.0072	−0.9993	-7.06×10^{-3}	0.5118
DPH	0–30	6.3366	0.0046	−0.9900	-7.57×10^{-3}	0.5126
MPH	0–100	2.6425	0.0134	−0.9710	-3.56×10^{-3}	0.5143
HDH	0–60	6.6225	0.0067	−0.9999	-5.99×10^{-3}	0.5090

[a] Regression line equation: A = absorbance; C = concentration, μg ml^{-1}; m = slope; Z = intercept.

Table 3
Evaluation of accuracy and precision of the proposed methods

	Titrimetric method				Spectrophotometric method			
Antihistamine drug	Amount taken (mg)	Amount found (mg)	Recovery (%)	RSD (%) [a]	Amount taken (μg)	Amount found (μg)	Recovery (%)	RSD (%) [a]
CTH	4.0	4.06	101.64	1.21	100	98.63	98.63	1.26
	11.0	10.95	99.58	1.32	200	198.50	99.25	0.96
	15.0	14.70	98.04	1.46	300	304.14	101.38	0.28
DPH	5.0	5.12	102.36	0.85	100	97.82	97.82	0.96
	10.0	9.87	98.72	1.39	200	195.28	97.64	1.32
	15.0	14.62	97.42	1.90	300	301.02	100.34	1.78
MPH	5.0	5.15	103.04	0.96	300	296.70	98.90	0.68
	10.0	9.91	99.12	1.12	600	585.90	97.65	1.65
	15.0	14.60	97.38	1.58	900	917.28	101.92	1.92
HDH	4.0	4.09	102.38	0.74	200	204.16	102.08	2.08
	11.0	11.04	100.34	1.38	400	411.44	102.86	2.86
	15.0	14.66	97.76	1.74	600	614.52	102.42	2.42

[a] Average of six determinations.
RSD—relative standard deviation.

Table 4
Results of assay of investigated drugs in the formulations by the proposed methods

Antihistamine	Formulations [a]	+	Label claim (mg per tablet or capsule)	Found (% recovery ± SD) [a]	
				Titrimetric method	Spectrophotometric method
CTH	Cetzine tablets	a	10	98.15 ± 0.76	97.75 ± 1.12
	Zyrtech tablets	b	10	97.89 ± 0.42	98.03 ± 0.85
	Cetrizet tablets	c	10	99.72 ± 1.42	101.14 ± 2.16
	Zyncet tablets	d	10	96.88 ± 0.86	97.12 ± 1.04
DPH	Benadryl capsules	e	25	98.15 ± 0.28	98.70 ± 0.95
MPH	Mebryl tablets	f	25	97.62 ± 1.64	98.15 ± 0.76
HDH	Atarax tablets	b	25	98.97 ± 1.26	99.31 ± 1.34

[a] Average of seven determinations.
+—marketed by: a, Glaxo lab; b, UNI-UCB; c, Sun Pharmaceuticals; d, Unichem; e, Parke–Davis; f, Smithkline Beecham.

Table 5
Results of recovery experiments

Antihistamine drug	Titrimetric method				Spectrophotometric method			
	Amount of drug present in the formulation (mg)	Amount of pure drug added (mg)	Amount of pure drug found (mg)	Recovery,%[a]	Amount of drug present in the formulation (μg)	Amount of pure drug added (μg)	Amount of pure drug found (μg)	Recovery (%) [a]
CTH, cetzine tablets (10 mg)	3.92	6.00	5.85	97.50	97.75	150	147.6	98.40
	3.92	8.00	8.21	102.62	97.75	200	198.5	99.25
	3.92	10.00	9.92	99.20	97.75	300	295.6	98.53
DPH, benadryl capsules (25 mg)	4.90	7.00	6.92	98.85	49.35	100	98.5	98.50
	4.90	8.00	7.88	98.50	49.35	150	148.2	98.80
	4.90	10.00	9.84	98.40	49.35	200	201.8	100.90
MPH, mebryl tablets (25 mg)	4.88	7.00	7.12	101.71	294.45	400	405.6	101.40
	4.88	8.00	7.94	99.25	294.45	500	497.6	99.52
	4.88	10.00	10.16	101.60	294.45	600	613.2	102.20
HDH, atarax tablets (25 mg)	3.95	6.00	6.06	101.00	198.62	200	206.2	103.10
	3.95	8.00	8.22	102.75	198.62	300	307.0	102.33
	3.95	10.00	10.21	102.10	198.62	400	408.6	102.15

[a] Average value of three determinations.

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