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"A DEVELOPMENT OF A MODIFIED USP ASSAY FOR QUINIDINE SULFATE TABLETS"

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Abstract - The non-aqueous titration method of assay of quinidine sulfate tablets outlined in the U.S.P. was examined, modified and compared with a recently published non-aquoeus titration using Barium Acetate. All methods were applied on four different commerical brands of quinidine sulfate 200 mg. uncoated tablets. The methods were comparable in specificity and reliability. However, by performing the assays on individual tablets as for content uniformity test greater variation was encountered by the U.S.P. procedure, especially on changing the time of extraction solvent or the volume of base and/or drying the siliceous earth after filtering and before adding the base. Therefore, it is recommended that the U.S.P. assay be changed to include 0.8ml of 10% NaOH, the total extraction time be reduced to 20 minutes and that the siliceous earth be dryed after filtering and before adding the base.

Quinidine was ranked 14th among the most frequently prescribed generic drugs in the United States in 1975 (1). It has been classified

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by the Academy of Pharmaceutical Sciences as one of the "commonly prescribed multiple source drugs whose solid dosage forms exhibit the most serious bioavailability and/or quality assurance problems (2).

Quinidine is known to have a narrow therapeutic index (3) and therefore requires a careful control of dosage and monitoring of blood concentration. Its usual effective blood concentration range is 2-5mcg/ml (4), however this range depends to some extent on the assay methodology (5,6). At the present time, there are more than twenty different assay procedures available for quinidine and many of them have been recently developed or modified (6-24).

The first U.S.P. quinidine sulfate tablet assay was described in the 18th revision and was modified in the 19th revision (39,55). However, preliminary studies showed to us that the procedure used in the USP method is neither accurate nor sensitive enough. It does not specify the number and time of extractions, the volume of NaOH used is in excess which results in an increase in the alkalinity of the medium, the quantity (1 Gram) or siliceous earth used is not enough etc.

Therefore, it was decided to evaluate the USP XIX assay method for quinidine sulfate tablets and to determine if any modifications are needed to improve its accuracy, sensitivity and reproducibility. In addition, the USP method was compared with another non-aqueous titration assay method that has recently been published (17). Finally, the interference by a common tablet lubricant, magnesium stearate will be evaluated.

EXPERIMENTAL

Materials - The following chemicals and solutions were used: Magnesium stearate[1], chloroform[1], 0.1N solution of perchloric acid in glacial acetic acid[1], 0.2% (w/v) solution of gentian violet indicator[1] in

[1] Fisher Scientific Co., Fair Lawn, N.J.

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glacial acetic acid[2], 10% (w/v) aqueous solution of sodium hydroxide[2], purified siliceous earth (Kieselguhr G)[3], 0.3N barium acetate solution (29.604 g of barium carbonate[4] in approximately 500 ml of glacial acetate acid which is boiled for three minutes, cooled and diluted to 1000 ml with glacial acetic acid) (17), 0.25% (w/v) solution of p-naphtholbenzein[5] in glacial acetic acid, four commerical samples of quinidine sulfate tablets (uncoated), each with a label claim of 200 mg quinidine sulfate per tablet[6-9] and quinidine sulfate reference powder[6,8]

Twenty quinidine sulfate tablets from each of the four chosen brands were weighed and finely pulverized. A portion equivalent to 100 mg or 200 mg of quinidine sulfate was used for the analysis by the USP method (18) and the barium acetate method (17), respectively. USP Method - four 100 mg aliquots of quinidine sulfate were tested separately. Each aliquot was mixed with one gram siliceous earth in a 25 ml coarse-porosity, sintered-glass filtering funnel. The funnel was connected to a 250 ml conical flask containing 40.0 ml of glacial acetic acid. Each mixture is then wetted with one milliliter of sodium hydroxide solution and extracted eight times with warm chloroform. Each chloroform portion is removed by gentle suction into the acetic acid containing flask. The solution is titrated against 0.1N perchloric acid with p-naphtholbenzein as indicator. Blank determinations were conducted simultaneously in a similar manner but without quinidine sulfate. The

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2 J.T. Baker Chemical Co., Phillipsburg, N.J.

3 E. Merck AG., Darmstadt, West Germany

4 Merck & Co., Rahway, N.J.

5 Eastman Kodak Co., Rochester, N.Y.

6 # WB 252, Parke, Davis & Co., Detroit, Michigan
7 # 9UB98E, Eli Lilly & Co., Indianapolis
8 # RY 14553, Danbury Pharmacal, Danbury, Conn.
9 # 2201-122, Zenith Laboratories, Northvale, N.J.

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perchloric acid solution temperature at the time of the experiment was recorded to correct its mormality. The recovery of quinidine sulfate from each sample was calculated from the following equation:

$$\text{Milligrams quinidine sulfate per tablet} = \frac{(E - B) \times N \times 195.7 \times W_1}{W \times 20} \quad \text{(Eq. 11)}$$

where:

E = ml of perchloric acid consumed in the experimental itiration

B = ml of perchloric acid consumed in the blank

N = normality of the perchloric acid standard solution

W_1 = weight of 20 tablets in milligrams

W = weight of the tablet aliquot in milligrams and

195.7 = equivalent weight of quinidine sulfate

Barium Acetate Method - This method involves gently heating a powdered aliquot equivalent to 200 mg quinidine sulfate for a few minutes in a 100 ml beaker containing 30.0 ml of glacial acetic acid. To this 4.0 ml of 0.3N barium acetate solution are added slowly with constant stirring. The mixture is then titrated with 0.1N perchloric acid, using gentian violet as indicator until a pure blue endpoint is reached. Blank determinations were performed in the same manner but without quinidine sulfate. The milliliters of 0.1N perchloric acid equivalent to quinidine sulfate in the sample were calculated by multiplying the difference between the milliliters of 0.1N perchloric acid consumed in the experimental titration and those consumed by the barium acetate in the blank, by two. The mean content of quinidine sulfate per tablet was further calculated using Equation 1.

Content Uniformity - Both the USP and the barium acetate methods were utilized in this test. They were carried out on 10 randomly chosen

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tablets from each of the four brands. Each tablet was weighed, pulverized and assayed.

Determination of the Reliability of the Blanks - In order to evaluate the blank determinations of the USP and the barium acetate methods, four blank experiments were conducted for each method by titrating the reagents alone (reagent blank). Additional four simultaneous experimentally treated blank determinations were performed following the two assay procedures but without quinidine sulfate samples. The blank values were converted to milligrams of quinidine sulfate by multiplying the milliliters of 0.1N perchloric acid consumed by the equivalent weight of 195.7.

Determination of Sodium Hydroxide Effects on the USP Method - The USP assay procedure was conducted with two modifications. First, after adding the specified 1.0 ml sodium hydroxide solution, allow time for the excess fluid to evaporate. Chloroform extractions were started after waiting periods of 15, 30, 45, 70, 80 and 110 minutes. Second, by changing the amount of sodium hydroxide used to liberate the quinidine base. The amounts used were 0.5, 0.7, 0.8, 1.0, 1.5 and 2.0 ml on three samples. These samples contained quinidine sulfate reference substance, quinidine sulfate powder with 2% magnesium stearate and the Eli Lilly tablets. The blanks were treated in the same manner.

Interference by Magnesium Stearate in Assay Methodologies - Quinidine sulfate samples containing different percentages of magnesium stearate were prepared. An aliquot equivalent to 100 mg quinidine sulfate was used for the USP assay method. Another aliquot equivalent to 200 mg was used for the barium acetate method. The percent recoveries were calculated as quinidine sulfate. Blank determinations were performed simultaneously in a similar manner.

Efficiency of Chloroform Extraction for Quinidine - These experiments were conducted on the Eli Lilly tablets. Aliquots equivalent to 100 mg

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quinidine sulfate were used in a modified USP procedure. Each of the eight chloroform extractions was drawn off into separate flasks, contained 20.0 ml glacial acetic acid. The quinidine content in each chloroform-acetic acid mixture was titrated and calculated as quinidine sulfate. The total extraction time followed a descending order of 40, 25, 20 and 15 minutes. Furthermore, the USP does not specify a time period for the extraction of quinidine with chloroform. Therefore, the individual extraction time as well as the total time required for complete extraction of quinidine was determined. Experiments were conducted on the Eli Lilly tablets to determine the shortest extraction time necessary for 100% quinidine sulfate recovery.

RESULTS AND DISCUSSION

In ananlytical procedures used in the assay of commerical tablets, a number of factors must be taken into consideration. The most important and critical factors are the accuracy and reliability of the assay method when applied to various commercial tablets, possible interference caused by the reagents and/or inert ingredients present in the tablet formation, and finally, simplicity and rapidity of the assay procedure. The barium acetate method, previously mentioned (17), was chosen as the method for comparison with the USP XIX method (18), since it has been reported to be both an accurate and a rapid assay.

The precision of these two methods was evaluated initially by performing tablet assays and content uniformity tests on four commercially-available quinidine sulfate uncoated tablets and on reference quinidine sulfate powder. Furthermore, blank determinations were evaluated and also found to present some difficulty.

Although all quinidine sulfate recoveries obtained by both methods were within the USP limits for the tablet assay and content

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uniformity test, the results from the barium acetate method were more reliable. The mean percent deviation using he barium acetate method was very small for the four tablet brands included in the study. Also, there was a greater variability in the intra-test percent recoveries with the USP method than with the barium acetate method. The data of the content uniformity test, also indicated that the variations between individual assays were more pronounced with the USP method. The percent of quinidine sulfate recovered per tablet varied considerably. The values approached the upper and lower limits described in the USP but the results of the barium acetate method were closer to the claimed amount of 200 mg quinidine sulfate per tablet.

Furthermore, the two methods were evaluated by using standard quinidine sulfate powder. A number of standard quinidine sulfate percent recoveries were outside the specified range when the USP method was used. However, the means were within the designated limits. Percent recoveries with the barium acetate method were well within the expected range. It was observed that a wide variability between the four determined blanks using the USP method existed although the experiments were conducted simultaneously under the same conditions. Table I shows that the volume of the titrant, perchloric acid consumed in the USP blanks ranged between 0.4 to 0.7 ml. These values were equivalent to 7.83 and 13.70% quinidine sulfate, respectively. Since the blank determinations are usually done to minimize systematic errors resulting from differences in experimenta conditions, intrinsic variations in the blank values will mask the actual precent recoveries of quinidine sulfate in the sample.

In attempt to determine the source of error in the blank determinations using the USP method, the volume of the titrant consumed by the reagents in the titration medium (reagent blank) was determined by titrating a mixture of 40.0 ml glacial acetic acid and 80.0 ml chloroform. The

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TABLE I - Blank Determinations[a] Using the USP XIX and the Modified USP Methods

Sample #	Reagent Blank[b]		Blank[c]					
			USP XIX Method		Modified USP Methods[d]			
					I[e]		II[f]	
	ml	#	ml	%	ml	%	ml	%
1	0.05	0.98	0.50	9.79	0.05	0.98	0.10	1.96
2	0.05	0.98	0.70	13.70	0.05	0.98	0.10	1.98
3	0.10	1.96	0.60	11.74	0.05	0.98	0.05	0.98
4	0.05	0.98	0.40	7.83	0.10	1.99	0.05	0.98
$\bar{X}$	0.06	1.23	0.55	10.76	0.06	1.23	0.07	1.47

[a] Milliliters 0.1N perchloric acid were converted to precent recovery of quindine sulfate.

[b] 80.0 ml chloroform + 40.0 ml glacial acetic acid, titrated against 0.1N perchloric acid.

[c] 80.0 ml chloroform + 40.0 ml glacial acetic acid; the blank was treated with dosium hydroxide as the sample.

[d] Total extraction time is 20 minutes.

[e] Drying time is 70 minutes

[f] Using 0.8 ml of 10% sodium hydroxide solution

average volume consumed corresponded to 1.23% quinidine sulfate, compared to an average value of 10.76% for the USP experimentally treated blanks (Table I). Such a sharp increase in the titrant consumption indicates that the alkalinity of the titration medium has been increased during the experimental procedure.

Since stechiometric calculations indicated that the volume of sodium hydroxide solution listed in the USP method (1.0 ml) was ten times the amount needed to liberate the quinidine base from its sulfate salt and since sodium hydroxide was believed to be the cause of the blank's variability, its volume was reduced in the modified USP methods. At this point, it may be worthwhile to mention that the siliceous earth on the filter in the blank and the standard experiments appeared to be too moist when mixed with one milliliter of sodium hydroxide solution as recommended in the USP. Similar observations were made when assaying light tablets such as the Eli Lilly brand. Their aliquots for 100 mg quinidine sulfate occupied smaller volumes. However, this effect was less noticable with heavier tablets in which larger aliquots were used for the assay. If the powder volume was not large enough to adsorb all the added alkali solution, there was an increase in quinidine sulfate recovered and an increase in variations between the individual assays for the sample. This can be explained by the hypothesis that the unadsorbed sodium hydroxide solution is carried by suction through the filter pores with the warm chloroform, during the extraction procedure. Any trace of a strong alkali in the non-aqueous medium where a weak base like quinidine is titrated, introduces the potential for serious error in the assay results. The amount of sodium hydroxide that is introduced in the above manner, depends upon additional factors, including the condition of the filtering funnel and its pores, the method of mixing the powder with the alkali solution, the loss of alkali through the funnel pores during mixing and the strength of

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the vacuum. All these factors can vary between simultaneous determinations. Therefore, two tests were initiated to prevent sodium hydroxide from reaching the titration medium. In the first, the volume of alkali specified in the USP was used but the mixture was allowed to dry before extraction. The second involved the use of different amounts of alkali to determine the minimum volume necessary to liberate the quinidine from its sulfate salt.

As can be seen in Table II the longer the time of drying, the more reliable are the data for both the blank and the standard determinations, and that a minimum drying time of 70 minutes was required to obtain accurate results. Furthermore, it can be seen from Table III the optimum

Table II - Recovery Of Quinidine Sulfate Standard Substance at Different Drying Times Using the Modified USP Method

Time[a]	Blank		Quinidine Sulfate	
			Percent	
Min.	0.1N Perchloric Acid consumed, ml	Percent[b]	Recovery[c] (Corrected)	Deviation
0	0.45	8.81	103.39	+3.39
15	0.40	7.83	102.91	+2.91
30	0.30	5.87	102.98	+2.98
45	0.10	1.96	101.06	+1.06
70	0.05	0.98	100.01	+1.01
90	0.05	0.98	100.27	+0.27
110	0.05	0.98	99.86	-0.14

[a] Time relapsed between the addition of sodium hydroxide solution and the onset of extraction with chloroform

[b] Percent of quinidine sulfate equivalent to the volume of titrant consumed, average of two determinations

[c] Difference between the percentage of quinidine sulfate recovered and the blank[b].

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TABLE III - Variations in Recovery of Quinidine Sulfate by Altering the Volume of Sodium Hydroxide, Using a Modified USP Method

10% Sodium Hydroxide Added ml	Blank[a]		Experiment No. I[b]		II[c]		III[d]	
			Quinidine Sulfate, %[e]					
	ml	%	Recovery	Deviation	Recovery	Deviation	Recovery	Deviation
0.50	0.05	0.98	96.94	-0.06	95.96	-2.04	95.79	-4.21
0.70	0.05	0.98	99.33	-0.67	96.45	-1.55	98.29	-1.71
0.80	0.07	1.37	100.28	+0.28	98.65	+0.65	100.21	+0.21
1.00	0.44	8.61	103.46	+3.46	101.85	+3.85	104.97	+4.97
1.50	0.88	17.22	115.37	+15.37	113.85	+15.85	111.44	+11.44
2.00	1.30	25.44	152.07	+52.07	139.71	+41.71	129.49	+29.49

[a] Avergae volume of perchloric acid consumed in the blank of Experiments I, II and III; percentages were calculated as quinidine sulfate dihydrate

[b] Assay of quinidine sulfate standard substance.

[c] Quinidine sulfate containing 2% of magnesium stearate

[d] Eli Lilly tablets

[e] Average of three determinations

volume of sodium hydroxide solution which insured full recovery of quinidine sulfate without interfering with the accuracy of the assay was 0.8 milliliter. The deviations were +0.28% in the case of the standard treatment, +0.65% for the 2% magnesium stearate-containing quinidine sulfate powder and +0.21% for the Eli Lilly tablets. A comparison of the blank determinations of the modified U.S.P. method with a 70 minute drying period or the modified U.S.P. method using 0.8 ml alakli with no drying time, versus the U.S.P. method confirms the reliability of the modified methods (Table I).

The effect of magnesium stearate, a common lubricant in many tablet formulations on the three procedures are shown in Table IV. It is apparent that by using the USP method, when the percentage of magnesium stearate was increased, there was a slight decrease in the percent deviation of quinidine sulfate recovered. The decrease may be caused by the lubricating effect of magnesium stearate which physically decreased the mixing of sodium hydroxide with chloroform. Subsequently, less interfering alkali would be present in the titration medium. In the modified USP method, no significant interference was observed, while the effect of magnesium stearate on the precision of the barium acetate method was insignificant up to a concentration of three percent. At higher concentrations, there was a sharp increase in the percent deviations of quinidine sulfate recovered. However, incorporation of more than 2.8% of magnesium stearate is not common in commerical tablets.

The assay procedure outlined in the USP XIX for quinidine sulfate tablets does not include a specific time for extraction of the quinidine base with chloroform. Therefore, the minimum time required to insure adequate and complete extraction of the base was determined. Furthermore, the optimum time for each of the eight extractions was evaluated by performing several extractions of the alkaloid at different time periods.

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TABLE IV - Interference of Magnesium Stearate in Assay Methodologies

Sample #	Weight, mg		Quinidine Sulfate, %[a]					
			USP XIX Method		Modified USP Method		Barium Acetate Method	
	Magnesium Stearate Added	Quinidine Sulfate Added	Recovery	Deviation	Recovery	Deviation	Recovery	Deviation
1	0.0	100.00	103.85	+3.85	100.60	+0.60	100.09	+0.09
2	0.5	99.50	103.06	+3.56	100.25	+0.75	99.43	-0.07
3	1.0	99.00	102.05	+3.05	98.49	-0.51	98.64	-0.36
4	1.5	98.50	100.96	+2.46	97.65	-0.85	98.91	+0.41
5	2.0	98.00	100.85	+2.85	98.62	+0.62	97.30	-0.70
6	3.0	97.00	94.62	-2.38	97.80	+0.80	98.27	+1.27
7	4.0	96.00	98.45	+2.45	95.08	+0.92	100.30	+4.30
8	5.0	95.00	97.03	+2.03	93.75	-1.25	89.93	-5.07
9	8.0	92.00	89.80	-2.20	92.67	+0.67	97.41	+5.41
10	9.0	91.00	89.01	-1.99	92.09	+1.09	96.20	+5.20

[a] Average of three determinations

[b] Drying time is 70 minutes, total extraction time is 20 minutes

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TABLE V - Extraction Recovery of Quinidine Sulfate by Modifying the USP Assay

Extrac-time No.	Volume, ml		Extraction Time, Min. Protocol No.					Quinidine Sulfate Recovered, % Protocol No.				
	Chloroform	Acetic Acid	1[a]	2[b]	3[a]	4[a]	5[a]	1[a]	2[b]	3[a]	4[a]	5[a]
1	10.0	20.0	5	20	6	5	4	63.32	63.98	61.19	63.95	62.86
2	10.0	20.0	5	5	5	4	3	13.66	12.01	17.96	14.02	13.89
3	10.0	20.0	5	5	4	3	2	6.62	8.54	5.72	6.85	4.90
4	10.0	20.0	5	3	3	3	2	5.20	6.85	7.31	5.01	4.86
5	10.0	20.0	5	2	2	2	1	3.31	4.11	2.80	3.92	5.82
6	10.0	20.0	5	2	2	1	1	2.84	3.73	1.96	2.88	0.99
7	10.0	20.0	5	2	2	1	1	1.89	1.37	2.99	1.86	2.90
8	10.0	20.0	5	1	1	1	1	0.95	0.70	0.52	0.89	0.96
Σ =	80.0	160.0	40	40	25	20	15	99.79	101.29	100.45	99.38	98.18
						Deviation:		-0.21	+1.29	+0.45	-0.62	-1.82

[a] Drying time is 70 minutes

[b] 0.8 ml sodium hydroxide, no drying time

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TABLE VI - Variations in Recovery of Quinidine Sulfate from Eli Lilly Tablets by Altering the total Extraction Time in the Modified USP Method[a]

Sample #	Extraction No.									Percent	
	1	2	3	4	5	6	7	8	Total Minutes	Recovery	Deviation
	Extraction Time, Min										
1	15	10	5	3	2	2	2	1	40	101.26	+1.26
2	10	10	15	3	2	2	2	1	35	100.98	+0.98
3	8	5	5	4	2	2	2	2	30	100.37	+0.37
4	6	4	3	3	3	2	2	2	25	99.98	-0.02
5	5	4	3	3	2	1	1	1	20	100.02	+0.02
6	4	3	2	2	1	1	1	1	15	98.65	-1.35
7	2	2	1	1	1	1	1	1	10	97.93	-2.07

[a] Drying time is 70 minutes

Two 40 minutes extraction trials were conducted using modified USP methods; in one a 70 minute drying period was used, and in the other, 0.8 ml sodium hydroxide was used with no drying time. Table V shows that there was no significant change in the relative percentages of the alkaloid extracted using either extraction trial. Since there was no difference in the amount extracted using the two modified USP methods, the four succeeding protocols utilizing shorter extraction time periods were performed using only the 70 minute drying time procedure. Similar results were seen in these four protocols. The initial extraction by chloroform removes approximately 65% of quinidine. Evaluation of the minimum total extraction time required for the quantitative recovery of quinidine sulfate was carried out using the modified U.S.P. method with 70 minutes drying time. Table VI summarizes the recoveries of quinidine sulfate after seven different total extraction times. It is apparent that the 20 minute extraction trial showed negligible losses, while the 15 minute trial did not allow adequate extraction of the alkaloid.

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