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Method of Evaluating Relative Efficacy of Disguising Agents for Distasteful Drugs*

By W. Arthur Purdum†

During the long era of medical ignorance and superstition, it was common belief that medicines should be repulsive in taste or malodorous in order to drive the "evil humours" from the body. The public of today, as a whole, is not so ignorant of medical matters as were its ancestors even as little as a century ago. This has been brought about to a large extent by health education in the public schools, news accounts of the latest discoveries in pharmaceutical chemistry and pharmacodynamics, feature articles by physicians and men in allied professions appearing in newspapers and magazines, and by public lectures and radio addresses. The combined effect has been to make the public conscious of the fact that a dose of medicine need not be bitter, acrid, or nauseating, in order to be efficacious. Consequently, the physician who can prescribe effective therapeutic agents in palatable forms is more certain of success than one who has no regard for palatability. Disagreeable tasting substances are not relished by persons in good health and surely they should not be inflicted on ailing persons (for whom nausea and vomiting are not uncommon), if it is possible to avoid them.

Medicines which are administered in solid form present no serious problem with respect to taste. Provided they are not too bulky, they may easily be given in the form of cachets, capsules, coated pills or coated tablets, in which the taste of the medicament is entirely concealed. On the other hand, infants and most small children, as well as some adults, are unable to swallow such forms of medication, particularly cachets and large capsules. When such is the case, a liquid preparation must be given. Moreover, drugs in the liquid state are more quickly absorbed and thereby exhibit their therapeutic effects more promptly than solid forms of medication. Furthermore, there are a great number of drugs which are more conveniently dispensed in the liquid state. Many of these liquids are quite distasteful, solutions of iodides and bromides being notable examples.

This study was undertaken in an effort to devise a method for appraising the value of pharmaceutical vehicles as disguising agents for distasteful drugs and then to use the method for evaluating some of the more common vehicles as agents to disguise certain unsavory medicaments. A search of available literature revealed that very little has been done in this direction. Many vehicles have been recommended for distasteful drugs, but in the majority of cases there has been no obvious scientific basis for these recommendations.

Since the prime purpose of a vehicle is to lessen or completely overcome the disagreeableness of the medicament, it is rational to assume that the threshold of taste of the medicament varies directly with the disguising power of the vehicle employed,

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Presented to the Scientific Section of the A. PH. A., Detroit Meeting, 1941.

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i. e., the higher the masking power of the vehicle, the higher the threshold value of the drug in that vehicle. If then threshold values are determined for a drug in a number of vehicles, that vehicle in which the drug exhibits the highest liminal concentration is the most efficacious of the agents tested.

Various techniques have been employed by different investigators in the determination of taste limens. Komuro (1) sprinkled the tongue with from 200 to 500 cc. of a solution at a definite temperature and, as a control, repeated this procedure using tap water at the same temperature. Kionka and Strätz (2) administered to their subjects from 6 to 10 cc. of solution which was washed back and forth in the mouth. These last named experimenters started with hyperthreshold concentrations and gradually decreased the strength of the solutions until the liminal strengths were reached, the solutions being maintained at body temperature and administered by means of a graduated pipette with a dropping attachment. Salmon and Blakeslee (3) found that 0.6 cc. was an adequate quantity to administer for a single test and began their determinations with solutions of subliminal concentrations, each successive solution being twice the strength of that which preceded. Ward, Munch and their associates (4, 5, 6) have determined strychnine thresholds, employing the technique developed by Munch (7) for the biological assay of capsicum. This method consists of comparing the pungency of an alcoholic extract of capsicum with that of a standard solution of piperine. Salt thresholds have been determined by Richter and MacLean (8) using dilute solutions of sodium chloride. After experimenting with several procedures, they conclude that the method which follows is the most satisfactory. Each subject started with a solution of hypothreshold strength and tasted successively stronger solutions until the threshold of saltiness was reached. Each concentration tasted was compared with distilled water and the subjects were instructed to taste each solution as often as necessary in order to reach a decision. Some of the findings of these workers were used to advantage in the development of the procedure described in the experimental section which follows.

EXPERIMENTAL

Throughout the experiments which follow, care was taken to maintain as nearly uniform conditions as was practicable. To avoid the possibility that the small amount of salts present in city water might interfere with the threshold determinations, only freshly distilled water was used in the preparation of solutions and for rinsing purposes between tests.

The chemicals employed were of U. S. P. or N. F. quality. Some of the pharmaceutical preparations were made in the laboratory according to U. S. P. or N. F. directions and others, for reason of convenience, were purchased from one of the large pharmaceutical manufacturers.

Glass-stoppered bottles were adopted for the storage of solutions after it was found that some of the more alert tasters could detect what they described as a "mustiness" in the distilled water and in some of the very weak aqueous solutions which had been kept in bottles with cork stoppers.

The distilled water and all solutions were stored at room temperature which varied from 25° to 28° C. While Komuro (1) has shown that threshold values obtained at 10° C. are much higher than those at 20° C., he also demonstrated that the threshold values were not markedly lower at 40° C. than at 20° C. Salmon and Blakeslee (3) made threshold determinations on a number of persons at about 8° C., at room temperature and at about 55° C. and observed no variation in the results at these appreciably different temperatures. In view of the above findings, it was not deemed necessary to store the solutions in an incubator at body temperature as did Kionka and Strätz (2). Although it is true that the solutions having a temperature of about 26° C. will produce a feebly cool sensation in the mouth, this temperature sensation should not interfere with the tasting of solutions since the control solutions used were also at the same temperature.

In a further effort to maintain uniform conditions all persons participating in the tests were requested not to eat within two hours prior to a threshold determination and the tobacco smokers were asked not to smoke within one-half hour before a test.

All subjects were cautioned to wash all samples of solutions and controls back and forth in their mouths so that these samples came in contact with all regions of their tongues and oral cavities. This agitation was essential since it has been shown by Öhrwall (9) that the various parts of the tongue's surface do not respond equally to the several qualities of taste.

In the ordinary determination of taste thresholds of aqueous solutions, the subject simply has to decide whether the solution in question has taste or is tasteless. However, with vehicles other than water, the problem is not so simple. It is necessary for the taster to determine whether the medicinal solution has a taste exactly like or different from that of the plain vehicle used as the control.

Numerous preliminary trials were made before a satisfactory method for the determination of the threshold of taste of drugs in vehicles was found. While these preliminary experiments will not be discussed in detail, all findings of value are given in the paragraphs which follow.

It was found that if a small portion of solution was followed by a somewhat larger sample of control at the same temperature, the control seemed cooler to some of the subjects because it was capable of absorbing more heat from the mouth. This necessitated the administration of equal quantities of solutions and controls. Five cc. of each was arbitrarily chosen for use in subsequent experiments.

The use of full-strength syrups and elixirs as vehicles for the drugs proved unsatisfactory because, in the case of syrup of glycyrrhiza, its flavor so persisted that no reasonable number of washings with distilled water would entirely remove it from the mouth. In addition, the intensity of its taste seemed to increase, *i. e.*, the taste successively grew stronger as more samples were tasted. This cumulative effect also was reflected in the ability of the subjects to perceive the taste of the dissolved drug. As the taste of the syrup became more intense, a proportionately greater concentration of drug was required before its taste could be detected. Following this difficulty, all vehicular solutions and their corresponding controls were made to contain 10% by volume of the syrup or elixir in distilled water. The subjects reported that the flavors of the diluted vehicles did not persist and that they were rather easily removed by rinsing.

Kionka and Strätz (2) state that contradictory results have been obtained in the determination of taste limens due to advance knowledge on the part of the taster of the composition or strength of solutions to be tasted. In an effort to prevent the entrance of this psychological factor of self-deception into the results, no set order with respect to strength was followed in the administration of solutions in the early trials. This procedure was impractical because of the large number of solutions which had to be tasted with the resultant consumption of a considerable amount of time in order to make a single determination. Thereafter, the subject began with a solution of hypothreshold concentration and tasted successively stronger solutions in the series until the threshold strength had been reached. Self-deception, in all probability, is not an important factor in this work because Salmon and Blakeslee (3) have demonstrated that the threshold of a single subject varies enormously at different times and they state that extreme refinement in technique is, therefore, unnecessary.

At first, the concentration of distasteful drug in adjacent solutions in a series varied as the ratio 1 : 1.25. The subjects frequently experienced difficulty in distinguishing between solutions next to each other in a series so, in later tests, the ratio was increased to 1 : 2. This change simplified proper identification and effected a considerable saving of time in that fewer solutions had to be tasted in order to make a determination. The individuals who tasted these solutions remarked, in most instances, that the threshold concentrations were quite sharply defined. Naturally, the threshold values obtained were somewhat higher than those got formerly. From this, it was reasoned that if the ratio of strength of contiguous solutions was reduced to a point between the two already tried, greater accuracy could be attained than by use of the higher ratio without the uncertainty and confusion of opinion which resulted from use of the lower ratio. Extensive trials were made employing a series of solutions in which the concentration of drug in adjacent members varied as the ratio 1 : 1.5 and this was found to be quite satisfactory in all respects.

It became apparent that as the subjects gained experience in tasting, their acuity of perception increased for a time with a consequent lowering of threshold values. This obstacle was overcome by determining for each subject the threshold concentration of an aqueous solution of the drug immediately before each determination in a vehicular solution.

THE METHOD AND ITS APPLICATION

(A) Comparison of Efficacy of 19 Official Vehicles in Disguising the Saltiness of Ammonium Chloride.—Thirty-two adults served as subjects for these tests. It was desirable to have a minimum of 30 persons for the tests since it has been shown (10) that the accuracy of results obtained in any animal experimentation increases with the number of animals used. This is particularly true when small groups (numbering under 30) are used. When more than 30 animals are employed, the reliability of results is not increased sufficiently to warrant the time and expense of the additional determinations.

Ammonium chloride served as the distasteful drug in these experiments by reasons of its disagreeably salty taste and its wide usage as a medicinal agent. Ten concentrations of the salt ranging from 0.0044 *N* up to 0.17 *N* were used. As explained previously, a ratio of 1 : 1.5 existed between the strengths of adjacent solutions. The strength and corresponding number of each solution were as follows:

Normality	Number	Normality	Number
0.0044	1	0.033	6
0.0067	2	0.050	7
0.010	3	0.075	8
0.015	4	0.11	9
0.022	5	0.17	10

All vehicular solutions and controls contained 10% by volume of the vehicle (syrup or elixir).

Portions of 5 cc. of each strength of aqueous solution, each strength of vehicular solution, and of control, were placed in test tubes and the tubes, in turn, were placed in properly numbered racks.

On each working day, the limen for a subject was determined first in distilled water solution and then in the vehicular solution prepared for that day. The subject rinsed his mouth with distilled water and then tasted the aqueous solutions in ascending numerical order, rinsing between each solution tasted, until he reached the first solution which possessed a salty taste. Beginning one number below the number at which the threshold was reached in aqueous solution, the subject then tasted the vehicular solutions in ascending numerical order, following each with a control and rinsing before proceeding with the next solution. This was continued until the vehicular solution gave a sensation of saltiness when compared with the control. If a question arose on the part of a subject regarding the taste of one of the solutions, he was instructed to sample another portion of the same solution and if there was still doubt, to taste the solution next higher in concentration and to record this as his threshold if the taste was definite. No solutions were swallowed; all were ejected from the mouth after a decision was reached by the subject.

The difference between the aqueous and the vehicular thresholds is a measure of the disguising value of a particular vehicle. Even though the subjects develop a keener sense of taste during the progress of the experiments or if only the normal fluctuations in taste acuity occur, the mean difference should remain approximately the same; *e. g.*, if a person's threshold in aqueous solution appeared at concentration No. 4, and in a certain vehicle at No. 6, and upon repeating the test after an interval of several weeks, the numbers were 2 and 4, respectively, the difference in either case is 2. Proof of this theory is given in the next series of experiments (part *B*) in which quinine hydrochloride replaced ammonium chloride.

Since the object of this method is to establish the relative differences between the threshold values in the aqueous solutions and in the vehicular solutions, the concentrations at which the thresholds are reached simply provide the data for arriving at these differences and bear no other significance. Because of this and since the normalities represented by any two consecutive numbers in a series of solutions are proportional to those for any other pair of consecutively numbered solutions, the mean differences are expressed by numerals rather than by actual concentrations in terms of normality in Table I. These numerical differences will hereafter be referred to as "disguising potentials." The vehicles listed in Table I appear in the order of decreasing mean disguising potentials.

The standard errors for each set of determinations were computed by use of the formula $\sqrt{\frac{\Sigma d^2}{n(n-1)}}$, in which d represents the deviation of an individual determination from the mean, regardless of whether it is plus or minus, Σd^2 represents the sum of these deviations squared, and n is the number of determinations in the series.

To determine whether the mean threshold values for aqueous and vehicular solutions really differ significantly or whether these differences are due

TABLE I.—AMMONIUM CHLORIDE DISGUISING EFFICACY OF 19 DILUTED VEHICLES[a]

Vehicle	Number of Subjects Tested	Mean Threshold in Water ± Standard Error, $m_2 \pm \epsilon_2$	Mean Threshold in Vehicle ± Standard Error, $m_1 \pm \epsilon_1$	Mean Disguising Potential ± Standard Error, $D \pm \epsilon$	Significance of Difference[b]
Syrup of glycyrrhiza	32	3.56 ± 0.22	5.72 ± 0.29	2.16 ± 0.24	5.97
Syrup of raspberry	32	3.91 ± 0.21	5.72 ± 0.23	1.81 ± 0.20	5.78
Syrup of orange flowers	32	3.81 ± 0.21	5.53 ± 0.26	1.72 ± 0.14	5.20
Syrup of citric acid	31	4.10 ± 0.27	5.81 ± 0.22	1.71 ± 0.24	4.94
Syrup of tolu balsam	32	3.87 ± 0.24	5.56 ± 0.27	1.69 ± 0.17	4.76
Syrup of acacia	32	3.84 ± 0.24	5.44 ± 0.25	1.60 ± 0.13	4.60
Syrup of orange	32	3.72 ± 0.20	5.31 ± 0.24	1.59 ± 0.17	5.13
Aromatic syrup of eriodictyon	31	3.84 ± 0.19	5.39 ± 0.20	1.55 ± 0.15	5.60
Syrup of cherry	32	4.06 ± 0.23	5.59 ± 0.22	1.53 ± 0.17	4.78
Syrup of cocoa, N. F. V	32	4.00 ± 0.23	5.50 ± 0.26	1.50 ± 0.16	4.35
Syrup of prepared cacao, N. F. VI	32	3.97 ± 0.21	5.44 ± 0.27	1.47 ± 0.16	4.29
Syrup of thyme	30	3.73 ± 0.18	5.16 ± 0.25	1.43 ± 0.18	4.60
Syrup of wild cherry	32	3.78 ± 0.23	5.19 ± 0.22	1.41 ± 0.11	4.39
Syrup of cinnamon	32	4.03 ± 0.25	5.41 ± 0.25	1.38 ± 0.17	3.87
Syrup of althea	32	3.81 ± 0.23	5.09 ± 0.24	1.28 ± 0.16	3.89
Elixir of glycyrrhiza	32	3.75 ± 0.21	5.03 ± 0.26	1.28 ± 0.19	3.80
Compound syrup of sarsaparilla	32	4.03 ± 0.18	5.13 ± 0.20	1.10 ± 0.13	4.01
Aromatic elixir	32	3.78 ± 0.21	4.81 ± 0.24	1.03 ± 0.11	3.21
Syrup (simple)	32	4.15 ± 0.26	5.15 ± 0.23	1.00 ± 0.17	2.92

[a] Each vehicular solution contained 10% by volume of the respective vehicle; the remainder of the solvent was distilled water.

[b] Calculated from $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$, the significance of differences between the thresholds for distilled water and for each of the vehicles is given in this column. Since each value is greater than 1.96, there is a significant difference between the aqueous and vehicular thresholds.

TABLE II.—SIGNIFICANCE OF DIFFERENCES BETWEEN THE MEAN AMMONIUM CHLORIDE DISGUISING POTENTIALS FOR THE VEHICLES GIVEN IN TABLE I

Vehicles arranged in order of decreasing mean disguising potentials. Values of 1.96 or greater indicate significant difference. To find the value for any pair of vehicles, read down the vertical column beneath the name of the first to the junction of the horizontal column at the left of the second.

Vehicle	Syrup (Simple)	Aromatic Elixir	Compound Syrup of Sarsaparilla	Elixir of Glycyrrhiza	Syrup of Althea	Syrup of Cinnamon	Syrup of Wild Cherry	Syrup of Thyme	Syrup of Prepared Cacao, N. F. VI	Syrup of Cocoa, N. F. V	Syrup of Cherry	Aromatic Syrup of Eriodictyon	Syrup of Orange	Syrup of Acacia	Syrup of Tolu Balsam	Syrup of Citric Acid	Syrup of Orange Flowers	Syrup of Raspberry
Syrup of Glycyrrhiza	3.94	4.28	3.91	2.91	3.09	2.59	2.87	2.46	2.40	2.32	2.17	2.16	1.96	2.05	1.61	1.34	1.61	1.12
Syrup of Raspberry	3.03	3.35	2.95	1.93	2.07	1.64	1.74	1.41	1.31	1.21	1.06	1.02	0.84	0.87	0.45	0.32	0.37	
Syrup of Orange Flowers	3.26	3.88	3.30	1.91	2.12	1.58	1.78	1.30	1.18	1.07	0.88	0.83	0.60	0.63	0.14	0.04		
Syrup of Citric Acid	2.41	2.59	2.26	1.42	1.51	1.14	1.15	0.95	0.84	0.74	0.62	0.57	0.41	0.40	0.07			
Syrup of Tolu Balsam	2.84	3.22	2.76	1.63	1.77	1.30	1.39	1.06	0.94	0.82	0.67	0.61	0.42	0.41				
Syrup of Acacia	2.74	3.24	2.69	1.40	1.55	1.03	1.10	0.77	0.62	0.49	0.33	0.25	0.05					
Syrup of Orange	2.45	2.77	2.31	1.24	1.35	0.89	0.91	0.66	0.52	0.40	0.25	0.18						
Aromatic Syrup of Eriodictyon	2.38	2.72	2.25	1.12	1.23	0.75	0.75	0.51	0.36	0.23	0.09							
Syrup of Cherry	2.20	2.46	2.03	1.00	1.09	0.64	0.60	0.41	0.26	0.13								
Syrup of Cocoa, N. F. V	2.15	2.44	1.98	0.91	1.00	0.53	0.48	0.30	0.13									
Syrup of Prepared Cacao, N. F. VI	1.98	2.22	1.79	0.77	0.84	0.39	0.31	0.17										
Syrup of Thyme	1.73	1.90	1.50	0.58	0.63	0.21	0.10											
Syrup of Wild Cherry	2.00	2.42	1.83	0.61	0.68	0.15												
Syrup of Cinnamon	1.58	1.74	1.33	0.40	0.44													
Syrup of Althea	1.20	1.29	0.89	0														
Elixir of Glycyrrhiza	1.10	1.15	0.79															
Compound Syrup of Sarsaparilla	0.46	0.41																
Aromatic Elixir	0.14																	
Syrup (Simple)																		

only to inherent variations in the subjects, calculations employing the formula $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$ were made. The terms m_1 and m_2 represent the two means and ϵ_1 and ϵ_2 are their respective standard errors. Most workers agree that if the value calculated from the formula is 1.96 or greater, then the two results may be regarded as differing significantly. That the 19 vehicles employed actually possess the property of disguising the salty taste of ammonium chloride in comparison with an aqueous solution of the salt can be seen from the last column in Table I. Every value in this column is greater than 1.96, which means that the threshold for the diluted vehicle in every case is significantly greater than that for distilled water.

Next, the formula $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$ was applied to the mean disguising potentials and their standard errors to find out which vehicles are definitely better disguising agents than others. The values so derived are presented in Table II. An examination of these values leads to the following observations. Neither of two vehicles lying adjacent in the table can be claimed to be superior to the other as a disguising agent for ammonium chloride. Syrup of glycyrrhiza is not significantly better as a masking agent than the syrups of raspberry, orange flowers, citric acid and tolu balsam. Syrup of glycyrrhiza is, however, a definitely better disguising agent than any of the vehicles falling below syrup of tolu balsam. The values derived from the comparison of the results for the six vehicles appearing at the bottom of the table reveal that none of these preparations differ significantly from the others in disguising properties. The vehicles from syrup of glycyrrhiza down to syrup of tolu balsam, inclusive, are the best of the vehicles tested for disguising the taste of ammonium chloride; those from simple syrup up to and including syrup of cinnamon are the poorest; and those lying between syrup of tolu balsam and syrup of cinnamon are mediocre in disguising properties. The disguising potentialities for ammonium chloride of any pair of vehicles, the comparative value for which is not enclosed in heavy lines, are not significantly different. Any two vehicles, the value for which is enclosed by heavy lines, are different in their disguising efficacy. The practical value of this lies in the fact that the physician can choose from the vehicles possessing the greatest masking properties. In the event that one of the upper five vehicles may not be palatable to a particular patient for whom a physician is prescribing, he may select one of the other four.

(B) Comparison of Efficacy of 19 Official Vehicles in Disguising the Bitterness of Quinine.—The procedure used for the evaluation of the relative salt disguising properties of 19 official syrups and elixirs was repeated, using quinine hydrochloride in place of ammonium chloride. Naturally, bitterness rather than saltiness was the end point sought in these determinations.

This work was carried out at a time when it was known in advance that the attendance of a number of the subjects would be rather irregular. For this reason, a group of 37 persons was chosen to serve as tasters in order to have a minimum of 30 for any one determination.

TABLE III.—QUININE HYDROCHLORIDE DISGUISING EFFICACY OF 19 DILUTED VEHICLES[a]

Vehicle	Number of Subjects Tested	Mean Threshold in Water ± Standard Error, $m_2 \pm \epsilon_2$	Mean Threshold in Vehicle ± Standard Error, $m_1 \pm \epsilon_1$	Mean Disguising Potential ± Standard Error, $D \pm \epsilon$	Significance of Difference[b]
Syrup of prepared cacao, N. F. VI	30	3.50 ± 0.31	8.17 ± 0.40	4.67 ± 0.26	9.18
Syrup of glycyrrhiza	32	3.47 ± 0.27	7.88 ± 0.59	4.41 ± 0.49	6.80
Syrup of cocoa, N. F. V	30	3.87 ± 0.26	8.27 ± 0.40	4.40 ± 0.29	9.24
Aromatic syrup of eriodictyon	32	3.84 ± 0.27	7.78 ± 0.50	3.94 ± 0.38	6.94
Syrup of thyme	30	3.67 ± 0.23	7.40 ± 0.27	3.73 ± 0.25	10.60
Elixir of glycyrrhiza	30	3.73 ± 0.25	6.93 ± 0.42	3.20 ± 0.34	6.52
Syrup of tolu balsam	30	3.47 ± 0.27	6.50 ± 0.31	3.03 ± 0.21	7.37
Compound syrup of sarsaparilla	30	3.53 ± 0.28	6.53 ± 0.38	3.00 ± 0.23	6.34
Syrup of raspberry	33	3.61 ± 0.24	6.12 ± 0.32	2.51 ± 0.27	6.20
Syrup of cherry	33	3.61 ± 0.29	6.09 ± 0.40	2.48 ± 0.27	4.99
Syrup of cinnamon	31	3.74 ± 0.21	6.13 ± 0.33	2.39 ± 0.23	6.08
Syrup of citric acid	30	3.80 ± 0.25	6.13 ± 0.36	2.33 ± 0.27	5.33
Syrup of althea	31	3.55 ± 0.27	5.77 ± 0.34	2.22 ± 0.19	5.12
Syrup of wild cherry	30	3.63 ± 0.23	5.80 ± 0.41	2.17 ± 0.33	4.59
Syrup (simple)	31	3.48 ± 0.25	5.64 ± 0.31	2.16 ± 0.19	5.44
Syrup of acacia	33	3.58 ± 0.23	5.70 ± 0.30	2.12 ± 0.22	5.61
Syrup of wild cherry	36	3.44 ± 0.25	5.47 ± 0.41	2.03 ± 0.29	4.19
Syrup of orange flowers	31	3.45 ± 0.27	5.48 ± 0.31	2.03 ± 0.18	4.94
Syrup (simple)	31	3.97 ± 0.26	5.87 ± 0.40	1.90 ± 0.23	3.97
Syrup of orange	31	3.45 ± 0.27	5.19 ± 0.40	1.74 ± 0.26	3.59
Aromatic elixir	32	3.38 ± 0.25	4.97 ± 0.32	1.59 ± 0.17	3.88

[a] Each vehicular solution contained 10% by volume of the respective vehicle; the remainder of the solvent was distilled water.

[b] Calculated from $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$, the significance of differences between the thresholds for distilled water and for each of the vehicles is given in this column. Since each value is greater than 1.96, there is a significant difference between the aqueous and vehicular thresholds.

TABLE IV.—SIGNIFICANCE OF DIFFERENCES BETWEEN THE MEAN QUININE HYDROCHLORIDE DISGUISING POTENTIALS FOR THE VEHICLES GIVEN IN TABLE III

Vehicles arranged in order of decreasing mean disguising potentials. Values of 1.96 or greater indicate significant difference. To find the value for any pair of vehicles, read down the vertical column beneath the name of the first to the junction of the horizontal column at the left of the second.

	Aromatic Elixir	Syrup of Orange	Syrup (Simple)	Syrup of Orange Flowers	Syrup of Wild Cherry	Syrup of Acacia	Syrup (Simple)	Syrup of Wild Cherry	Syrup of Althea	Syrup of Citric Acid	Syrup of Cinnamon	Syrup of Cherry	Syrup of Raspberry	Compound Syrup of Sarsaparilla	Syrup of Tolu Balsam	Elixir of Glycyrrhiza	Syrup of Thyme	Aromatic Syrup of Eriodictyon	Syrup of Cocoa, N. F. V	Syrup of Glycyrrhiza
Syrup of Prepared Cacao, N. F. VI	9.87	8.01	7.94	8.41	6.80	7.54	7.87	5.92	7.63	6.27	6.57	5.82	5.82	4.81	4.96	3.40	2.59	1.58	0.70	0.47
Syrup of Glycyrrhiza	5.39	4.79	4.60	4.54	4.16	4.25	4.27	3.77	4.14	3.70	3.71	3.43	3.39	2.59	2.58	2.01	1.23	0.75	0.02	
Syrup of Cocoa, N. F. V	8.41	6.91	6.78	7.05	5.84	6.37	6.57	5.09	6.36	5.28	5.48	4.87	4.85	3.81	3.89	2.68	1.75	0.96		
Aromatic Syrup of Eriodictyon	5.60	4.76	4.54	4.53	3.98	4.14	4.18	3.49	4.02	3.44	3.47	3.11	3.07	2.10	2.09	1.44	0.46			
Syrup of Thyme	6.99	5.51	5.32	5.52	4.43	4.84	5.00	3.73	4.78	3.79	3.92	3.36	3.32	2.14	2.15	1.24				
Elixir of Glycyrrhiza	4.19	3.40	3.13	3.03	2.61	2.66	2.66	2.16	2.50	2.00	1.96	1.64	1.59	0.48	0.42					
Syrup of Tolu Balsam	5.35	3.91	3.63	3.69	2.83	3.04	3.13	2.19	2.89	2.07	2.07	1.61	1.55	0.10						
Compound Syrup of Sarsaparilla	4.91	3.65	3.35	3.35	2.63	2.79	2.84	2.05	2.62	1.90	1.88	1.46	1.40							
Syrup of Raspberry	2.91	2.08	1.73	1.51	1.22	1.14	1.08	0.80	0.89	0.48	0.34	0.08								
Syrup of Cherry	2.76	1.97	1.62	1.39	1.14	1.04	0.97	0.72	0.79	0.39	0.25									
Syrup of Cinnamon	2.78	1.88	1.49	1.24	0.98	0.85	0.78	0.55	0.57	0.17										
Syrup of Citric Acid	2.32	1.59	1.21	0.94	0.76	0.61	0.52	0.38	0.34											
Syrup of Althea	2.46	1.50	1.06	0.73	0.55	0.35	0.23	0.13												
Syrup of Wild Cherry	1.55	1.02	0.67	0.37	0.32	0.13	0.03													
Syrup (Simple)	2.24	1.32	0.87	0.51	0.38	0.14														
Syrup of Acacia	1.91	1.13	0.69	0.33	0.25															
Syrup of Wild Cherry	1.31	0.75	0.35	0																
Syrup of Orange Flowers	1.78	0.93	0.45																	
Syrup (Simple)	1.07	0.46																		
Syrup of Orange	0.48																			
Aromatic Elixir																				

The strengths of the solutions of quinine hydrochloride used ranged from 0.0000029 *N* to 0.00056 *N* and the concentrations of consecutively numbered solutions varied as the ratio 1 : 1.5. All of the strengths employed and the numbers used to designate these strengths were as follows:

Normality	Number	Normality	Number
0.0000029	1	0.000050	8
0.0000044	2	0.000075	9
0.0000067	3	0.00011	10
0.000010	4	0.00017	11
0.000015	5	0.00025	12
0.000022	6	0.00038	13
0.000033	7	0.00056	14

The results of these determinations are presented in Table III in the order of decreasing mean disguising potentials.

In order to determine the significance of the differences between the mean disguising potentials given in Table III, the formula $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$ was applied and the values appearing in Table IV were obtained.

It will be observed that simple syrup and syrup of wild cherry each appear twice in Tables III and IV. Threshold determinations employing these syrups were made on the first and second working days during this series of determinations, and then they were repeated after determinations in all of the other vehicles had been made. The amount of time which elapsed between the two determinations in either of the two syrups was 41 days. This repetition was to determine the effect, if any, of experience in tasting on disguising potentials. Prior to this work, none of the subjects had had any experience in making bitter threshold determinations. It was found that the two mean disguising potentials for simple syrup appearing in Table III differ by approximately 12% and that those for syrup of wild cherry differ by about 6%. These differences are not significant, as can be seen by inspection of the values appearing in Table IV. From this, it is concluded that satisfactory results can be obtained regardless of whether the subjects have had previous experience in the determination of taste thresholds.

A study of Table IV discloses that N. F. VI syrup of prepared cacao, syrup of glycyrrhiza, N. F. V syrup of cocoa and aromatic syrup of eriodictyon are the best of the 19 vehicles for masking the bitter taste of quinine hydrochloride. Other conclusions drawn from this table would be analogous to those in the discussion of Table II.

Now that the relative value of various pharmaceutical vehicles as masking agents for ammonium chloride and quinine hydrochloride has been determined, a question arises. Will the vehicles which are effective in disguising the tastes of these substances be effective to the same degree in disguising the salty and bitter tastes of other substances? It is very likely that the answer would be in the affirmative. However, before any definite answer can be given, it will be necessary to experiment with other salty and bitter drugs.

The procedure described herein should be equally satisfactory for similar determinations in any vehicle, using drugs possessing tastes other than salty or bitter.

CONCLUSIONS

1. A satisfactory method for the comparison of the taste-disguising properties of pharmaceutical vehicles has been devised. This method is dependent upon the threshold of taste and the application of statistical methods for the evaluation of results.

2. The relative worth of 19 vehicles of the United States Pharmacopœia and National Formulary as agents to disguise the tastes of ammonium chloride and quinine hydrochloride has been established. Of these vehicles, the syrups of glycyrrhiza, raspberry, orange flowers, citric acid and tolu balsam afford the best disguises for ammonium chloride, whereas N. F. VI syrup of prepared cacao, syrup of glycyrrhiza, N. F. V syrup of cocoa and aromatic syrup of eriodictyon are the best to disguise the taste of quinine hydrochloride.

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