Ultrasonic Method for Direct and Simultaneous Determination of Alcohol and Soluble Solids Content of Mouthwash

W. C. WINDER *, F. H. LOHMAN ‡x, R. F. TORDE *, and R. J. WAGNER *

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Abstract □ A technique for the determination of certain soluble species in solution by the changes they produce in the speed of propagation of ultrasonic waves in the solution was applied to measure the alcohol and soluble solids levels of mouthwashes. The simultaneous determination of these two quantities is made possible by measuring the wave velocity at two different temperatures. The method gives accurate, precise results for the general range of mouthwash compositions in use with appropriate calibration. The advantages of this method over other current methods are precision, speed, and convenience. It is not a suitable regulatory method, however, because calibration must be done with known variations of the particular mouthwash composition to be analyzed.

Keyphrases □ Alcohol—ultrasonic analysis in pharmaceutical formulations □ Solids, soluble—ultrasonic analysis in pharmaceutical formulations □ Ultrasonic analyses—alcohol and soluble solids in pharmaceutical formulations □ Mouthwashes—ultrasonic analysis of alcohol and soluble solids

Rapid, yet accurate, methods of analysis for the alcohol and soluble solids content of mouthwashes are essential in the toilet goods industry. Whether they are classified as "old drugs," "new drugs," or cosmetic products, mouthwashes, like wines, are subject to strict composition control for quality under some code of good manufacturing practice. The alcohol content is of primary interest for its germicidal activity and because of the legal requirements for strict accounting of its use. Determination of the soluble solids content may serve as an indicator of proper formulation for individual batches of mouthwash.

Currently, there are no officially validated methods for the determination of the alcohol and soluble solids content in mouthwashes. There are two methods in the USP (1) for determining alcohol in extracts and tinctures: a distillation method like the AOAC method and a GLC method. The individual manufacturers have, rather successfully, adapted or modified these methods used in the pharmaceutical industry and by the AOAC for determination of alcohol in wine and alcoholic beverages (2, 3). However, certain constituents of mouthwash such as glycerin and flavoring and foaming agents may interfere with the standard wine methods, and correction factors may have to be applied.

The GLC method and the AOAC distillation/specific gravity method have been adapted for the determination of alcohol. Both methods necessitate the attention of relatively skilled technicians; the GLC technique requires expensive equipment and does not consistently give the precision required, while the AOAC method is slow and tedious and requires a correction for glycerin when it is present.

Winder *et al.* (4) demonstrated that an instrument[1] that precisely measures the velocity of ultrasonic waves in a homogeneous liquid (solution) could be utilized to determine simultaneously the alcohol and extract content of finished wines rapidly and accurately. The ultrasonic wave velocity method depends on a correlation of the acoustic properties of a solution with its gross composition. In preliminary studies, it was demonstrated that if the soluble solids content of a mouthwash were held constant, an ultrasonic solution analyzer operating at 20° could be used to determine the alcoholic content. The standard deviation of differences between formulation values and the ultrasonic solution analyzer results was ±0.07% alcohol for six samples of specially prepared mouthwash. These initial values were well within the accuracy limits desired.

Since the soluble solids content as well as the alcohol content affects the acoustic properties of liquids, studies were made to determine whether the ultrasonic analyzer technique could be utilized for quality control analyses of mouthwash.

EXPERIMENTAL

Instrumentation for Acoustic Measurements—Figure 1 shows a diagram of the test cell and associated circuitry in the ultrasonic solution analyzer.

Built into the sample cell is a stainless steel reflector facing two ultrasonic ceramic transducers enclosed in stainless steel. The transducers are positioned at an approximately 20° angle from the reflector. Coaxial cables connect the transducers to the oscillator circuit of the electronic system. The electronic blocking oscillator produces a pulse of alternating voltage of short duration, which travels through the cable to the transmitting transducer.

By piezoelectric action, the electrical pulse alternately deforms and relaxes the ceramic element, causing it to vibrate at a high frequency. As a result, a short pulse of compressional energy is produced; it travels through the liquid, is reflected, and is received by the second transducer. The pressure variations of the sound pulse being received are changed to voltage variations, which indicate the useful output of the pulse. This output is sent through an automatic gain control device, which amplifies and shapes the signal. The signal is then returned to the oscillator, which triggers a second (or new) electrical pulse to be propagated through the circuit again.

The process keeps repeating itself as one pulse triggers the next. The

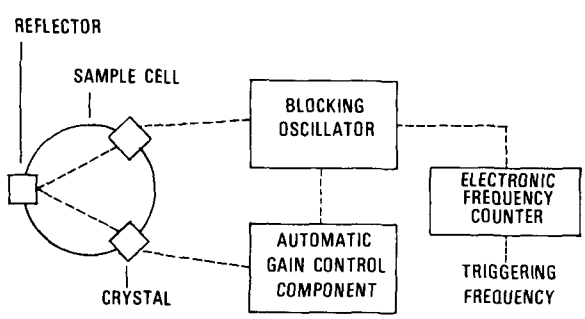

Figure 1—*Functional diagram of the ultrasonic solution analyzer.*

[1] Solution analyzer, Gould, Inc., Chesapeake Instrument Division, Shadyside, Md.

Table I—Effect of Soluble Solids Level on Solution Analyzer Triggering Frequency at Various Temperatures with Three Prepared Samples of Mouthwash

Soluble Solids, %	Δf_{10}		Δf_{20}		Δf_{30}		Δf_{41}		Δf_{65}	
11.0	2624	2	2074	14	1651	24	1220	32	500	51
10.0	2622	83	2060	63	1627	46	1188	31	449	1
9.0	2539		1997		1581		1157		448	

triggering rate is measured with a digital frequency counter, which displays the count on the face of the instrument. The rate of pulse initiation or triggering is a function of several constant factors: the temperature of the liquid medium, the path length in the sample cell, and the time delay of the electronic circuit. As a result, the only variable in the triggering rate or triggering frequency is the effect of the composition of the liquid sample. Thus, the triggering frequency is related directly to the sound velocity through the test medium.

For the study reported in this paper, knowledge of actual sound velocity through the sample was academic. Instead, all data were reported in terms of triggering frequency, an indirect measure of sound velocity. Since water is the continuous medium (primary solvent) in mouthwash, the triggering frequency value in distilled water at each test temperature was determined first. This value was subtracted from the triggering frequency observed with each sample to obtain the change caused by the constituents, other than water, in that sample. A change in triggering frequency from that in water was reported as Δf. All correlations of data were made in terms of Δf.

General Procedure—To operate the instrument, it is turned on and the water baths are allowed to equilibrate to precisely controlled temperatures (±0.01°). When the triggering frequency in water in the 35-ml test cell does not change during a 1-min interval, the sample and the water bath are at temperature equilibrium. The triggering frequency from the distilled water is programmed into the instrument as the reference point for direct readout of Δf values.

The water is then drained from the cell in about 5 sec by opening a solenoid valve connected to a vacuum system. The valve is closed, and about 20 ml of the new sample is introduced to flush the cell. After flushing, the test sample is then poured into the cell. A vacuum-operated outlet at the top of the test cell drains away any excess, thus eliminating the need for accurate measurement of the quantity of sample.

When the sample is in the test cell, the space above the cell is closed with a 5.1-cm (2-in.) cartridge of solid insulation to ensure precise temperature stability. The test sample is then allowed to temperature equilibrate, after which its triggering frequency is measured. The triggering frequency of the water is automatically subtracted from the triggering frequency of the test sample, and a Δf value is obtained for that temperature.

Choice of Test Temperatures—To determine both solids and alcohol in mouthwash systems with the ultrasonic solution analyzer, their respective effects on sound velocity must be dissimilar at two test temperatures. A graphical presentation of the data of Nozdrev (5) presented previously (4) illustrates the profound temperature effect on sound velocity in alcohol–water solutions. In the present study, each sample of several series of standard mouthwash samples was tested in ultrasonic solution analyzers operated at several temperatures until the best two temperatures for simultaneous determination of alcohol and soluble solids were chosen. Each standard mouthwash sample was prepared to a specific composition.

Table II—Summary of Solution Analyzer Δf Values for Five Levels of Alcohol and Soluble Solids at Three Different Temperatures

Sample	Normal Soluble Solids, %	Alcohol, % (w/v) 16.5	17.5	18.5	19.5	20.5
		Test Temperature = 20°				
E	90	2026	2074	2118	2154	2185
D	95	2046	2095	2136	2169	2195
A	100 (normal)	2082	2117	2159	2186	2210
B	105	2091	2138	2177	2208	2230
C	110	2120	2164	2201	2228	2246
		Test Temperature = 41°				
E	90	1162	1168	1170	1164	1149
D	95	1174	1178	1179	1172	1158
A	100 (normal)	1189	1193	1190	1186	1173
B	105	1206	1208	1203	1194	1178
C	110	1225	1225	1220	1207	1193
		Test Temperature = 65°				
E	90	443	417	377	338	284
D	95	450	418	380	342	291
A	100 (normal)	457	429	387	355	313
B	105	469	436	396	352	303
C	110	479	442	401	335	314

Table III—Standard Deviations of Differences, Ranges, and Mean Differences between As-Made Values and Solution Analyzer Values Obtained from Paired Data Taken at 20, 41, and 65° with 25 Samples of Moderate Soluble Solids Mouthwash

Temperature Combinations	Standard Deviations: Alcohol, % (w/v)	Standard Deviations: Soluble Solids[a]	Ranges: Alcohol, % (w/v)	Ranges: Soluble Solids[a]	Mean Differences: Alcohol, % (w/v)	Mean Differences: Soluble Solids[a]
20 and 65°	±0.09	±1.15	−0.14–+0.23	−2.53–+1.94	0	−0.010
20 and 41°	±0.10	±1.86	−0.32–+0.16	−3.54–+1.71	−0.012	−0.014
41 and 65°	±0.09	±1.38	−0.15–+0.26	−3.25–+1.76	0	−0.011

[a] Values are expressed as a percentage of normal soluble solids content.

RESULTS

Relationships among Parameters—To determine the effect of variations in the soluble solids content on sound velocity as a function of temperature, three specially prepared samples of mouthwash with a moderate (10%) soluble solids content were analyzed. The alcohol content of each sample was 18.5% (v/v), while the soluble solids content was 9, 10, and 11%. Each sample was tested in ultrasonic solution analyzers operating at 10, 20, 30, 41, and 65°. This temperature range covered the practical operating limits of the instruments. Below 20°, temperature control to within 0.01° was difficult to maintain; above 65°, vaporization of the alcohol and water occurred.

From the Δf values obtained and the incremental changes with temperature (Table I), it is apparent that the effect of the soluble solids content on Δf values is markedly different at different temperatures. These results indicate that a two-temperature method for the simultaneous determination of the alcohol and soluble solids content might be feasible.

To determine the soluble solids *versus* Δf relationships at different alcohol levels and the alcohol *versus* Δf relationships at different levels of soluble solids, 25 samples of a moderate soluble solids type of mouthwash were specially prepared in a 5 × 5 matrix. The alcohol content ranged from 18.9 to 23.7% (v/v) (17.0–20.0% w/v), and the soluble solids level ranged from 9.0 to 11.0%, representing 90–110% of the normal 10% level. All samples were tested in ultrasonic solution analyzers operating at 20, 41, and 65° (Table II).

These data were subjected to multiple regression analyses, and correlations were calculated to determine the best relationships among Δf values, alcohol content, and percentage of normal soluble solids.

The equations derived, expressing the appropriate relationships for data from determinations at 20, 41, and 65°, were of the following general type:

$$\Delta f_t = b_1 a + b_2 a^2 + b_3 s + c \qquad \text{(Eq. 1)}$$

where:

Δf_t = change in triggering frequency from that of water at 20, 41, or 65°
b_1 = regression coefficient for the alcohol content at 20, 41, or 65°
a = percentage of alcohol

Table IV—Standard Deviations of Differences, Ranges, and Mean Differences between the Actual Values and Solution Analyzer Values Obtained with Data Taken at 20 and 65° with 37 Samples of a Mouthwash of Moderate Soluble Solids Level

	Alcohol, % (v/v)	Soluble Solids, % of Normal
Standard deviation	±0.11	±1.08
Range of differences	−0.20–+0.30	−2.85–+1.46
Mean difference	+0.002	+0.002

Table V—Summary of Δf Values Obtained with Solution Analyzers Operated at 20 and 65° and Comparison of Formulated and Determined Values for Alcohol and Soluble Solids for 27 "Unknown" Standard Samples of Mouthwash of the Moderate Soluble Solids Class

Sample	Δf (20°)	Δf (65°)	Alcohol, % (v/v) Added	Found	Difference (Added − Found)	Percentage of Normal Soluble Solids Added	Found	Difference (Added − Found)
A'5	2034	482	18.25	18.10	+0.15	100	100.90	−0.90
A1	2071	457	18.99	19.01	−0.02	100	99.18	+0.82
A'6	2101	435	19.73	19.78	−0.05	100	98.52	+1.48
A2	2119	427	20.1	20.12	−0.02	100	99.76	+0.24
B'1	2037	492	17.89	17.89	0.00	105	104.38	+0.62
B'2	2069	477	18.48	18.53	−0.05	105	104.35	+0.65
B1	2095	467	18.9	19.00	−0.10	105	105.46	−0.46
B2	2140	434	20.1	20.14	−0.04	105	104.86	+0.14
B3	2178	395	21.3	21.34	−0.04	105	104.33	+0.67
C1	2123	478	18.9	18.99	−0.09	110	112.62	−2.62
C2	2166	443	20.1	20.17	−0.07	110	111.24	−1.24
C3	2199	405	21.3	21.30	0.00	110	109.98	+0.02
C4	2223	366	22.43	22.32	+0.11	110	109.31	+0.69
D'1	2032	457	18.59	18.66	−0.07	95	93.36	+1.64
D1	2046	449	18.9	18.97	−0.07	95	93.27	+1.73
D'2	2072	433	19.52	19.57	−0.05	95	93.31	+1.69
D2	2095	418	20.1	20.11	−0.01	95	93.72	+1.28
D3	2137	380	21.3	21.32	−0.02	95	94.04	+0.96
E'1	1858	495	16.05	16.18	−0.13	86	84.35	+1.65
E'2	1919	479	16.92	17.13	−0.21	86	85.20	+0.80
E'3	1972	458	18.0	18.09	−0.09	86	85.16	+0.84
E1	2026	443	18.9	18.93	−0.03	90	88.65	+1.35
E'4	2023	434	19.01	19.10	−0.09	86	85.83	+0.17
E2	2028	440	19.04	19.01	+0.03	90	88.16	+1.84
E3	2118	375	21.3	21.27	+0.03	90	89.60	+0.40
E4	2168	307	22.75	23.18	−0.43	90	90.93	−0.93
E5	2182	289	23.7	23.68	+0.02	90	92.53	−2.53
				Mean difference = −0.049			Mean difference = +0.41	
				Standard deviation of differences = ±0.13			Standard deviation of differences = ±1.25	

b_2 = regression coefficient for the percentage of alcohol squared at 20, 41, or 65°
a^2 = percentage of alcohol squared
b_3 = regression coefficient for the percentage of normal soluble solids at 20, 41, or 65°
s = percentage of normal soluble solids (normal = 100%)
c = ordinate at 20, 41, or 65°

The equations derived with data obtained at 20, 41, and 65° with the 25 samples were paired to produce three pairs of simultaneous equations (20 and 41, 20 and 65, and 41 and 65°). From these pairs, the alcohol and percentage variation from normal soluble solids contents of each sample were calculated by inserting the observed Δf values and solving the paired equations simultaneously. Comparisons of known values with ultrasonic solution analyzer values were made from standard deviations, means, and ranges of differences (Table III).

The best pair of test temperature equations was obtained with data taken at 20 and 65°. These superior results were attributed to the fact that a plot of Δf values against alcohol concentration exhibited a moderately steep positive slope for data at 20° whereas the slope was negative to about the same degree at 65°. Thus, the equations expressing the relationships for those temperatures were markedly different, lending accuracy to the results. At 41°, the plot was relatively horizontal; therefore, changes in Δf values with changes in alcohol concentration were relatively small and could not be expected to yield sensitive results. The slopes (changes in Δf/change in percent of alcohol) at constant soluble solids can be compared for the three test temperatures by reading across the horizontal lines of Δf values in Table II. Conversely, the slope (change in Δf/change in percent of normal soluble solids) at a constant percent of alcohol can be compared for the three test temperatures by reading down the vertical lines of Δf values.

The standard deviations of differences between the solution analyzer method and the theoretical values were ±0.09% alcohol and ±1.15 percentage of normal soluble solids. These results were considered to be excellent. Correlation coefficients for the 20 and 65° equations were 0.993 and 0.994, respectively.

Having established optimum temperatures for the simultaneous determination of alcohol and soluble solids, 12 additional samples in a 4 × 3 matrix were prepared to extend the alcohol range of samples studied. The alcohol content was varied in four steps from 16.0 to 19.0% (v/v) (from 14.1 to 16.6% w/v), and the soluble solids portion was prepared as 9.0, 10.0 (normal), and 11.0%. All samples were analyzed in ultrasonic solution analyzers operating at 20 and 65°. Data obtained with these 12 samples were combined with the data from the 5 × 5 matrix series to extend the alcohol range to 16.0–23.7% (v/v). New coefficients for the equations were derived from regression analysis, since the combined data were compatible.

With these equations, the alcohol and soluble solids content of each sample in the combined series was recalculated, and the results were compared with the nominal values of the standard formulations. A summary of the statistical analysis of these comparisons is presented in Table IV. Agreement between actual and determined values was excellent and not significantly different from that obtained with the previous 5 × 5 matrix series alone, indicating that accurate results could be obtained for both alcohol and soluble solids throughout the concentration ranges by these equations.

Validation of Method for Mouthwash with Moderate Soluble Solids Content—To confirm the accuracy and reproducibility of the procedures developed for mouthwash with moderate levels of soluble solids, 27 additional samples of known composition were prepared in which both alcohol and soluble solids contents were varied. In addition,

Table VI—Summary of Δf Values, Percentage of Normal Soluble Solids, and Percent Alcohol for Four Production Samples of a Moderate Soluble Solids Mouthwash

Sample	Δf_{20}	Δf_{65}	Alcohol, % (v/v) AOAC Method	Solution Analyzer (SA)	Difference (AOAC − SA)	Percentage of Normal Soluble Solids Standard Formulation	Solution Analyzer (SA)	Difference (Formulated − SA)
748	2072	453	19.20	19.11	+0.09	100.0	98.63	+1.37
749	2074	450	19.12	19.20	−0.08	100.0	98.23	+1.77
750	2084	448	19.29	19.33	−0.04	100.0	99.16	+0.84
751	2072	454	19.09	19.09	0.00	100.0	98.86	+1.14
					Average = −0.008			Average = +1.28

Table VII—Comparison of Formulated Values and Solution Analyzer Values Obtained from Analysis of 19 High Soluble Solids Type Mouthwashes

Sample Code	Alcohol, % (v/v)			Percentage of Normal Soluble Solids		
	Added	Solution Analyzer (SA)	Difference (Added − SA)	Added	Solution Analyzer (SA)	Difference (Added − SA)
31F082 A	15.78	15.83	−0.05	95	92.80	+2.20
31F082 B	15.86	16.01	−0.15	105	106.13	−1.13
31F082 C	15.92	15.94	−0.02	110	112.55	−2.55
31F082 D	18.10	18.39	−0.29	90	87.64	+2.36
31F082 E	18.24	18.38	−0.14	105	105.34	−0.34
31F082 F	18.29	18.43	−0.14	110	110.46	−0.46
31F082 G	20.51	20.76	−0.25	95	95.49	−0.49
31F082 H	20.45	20.63	−0.18	90	90.61	−0.61
31F082 I	20.62	20.80	−0.18	105	105.11	−0.11
31F082 J	22.83	22.98	−0.15	95	96.24	−1.24
31F082 K	22.79	22.82	−0.03	90	91.91	−1.91
31F082 L	23.01	23.32	−0.31	110	106.64	+3.36
30F129 B[a]	19.78	19.28	+0.50	100	100.09	−0.09
30F146 B	15.83	15.61	+0.22	100	99.63	+0.37
30F146 C	17.04	16.82	+0.22	100	100.00	0.00
30F146 D	18.22	18.09	+0.13	100	99.44	+0.56
30F146 E	20.56	20.44	+0.12	100	99.91	+0.09
30F146 F[a]	21.74	21.39	+0.35	100	99.91	+0.09
30F146 G[a]	22.92	22.56	+0.36	100	100.33	−0.33
		Mean difference = +0.0005			Mean difference = −0.012	
		Range of differences = +0.50–−0.31			Range of differences = +3.36–−2.55	
		Standard deviation of differences = ±0.239			Standard deviation of differences = ±1.42	

[a] Sample bottles with loose or cracked caps as received for ultrasonic solution analysis (likely alcohol loss).

four production samples of this type of mouthwash of "unknown" composition were selected. Each sample was analyzed, without prior knowledge of its composition, in ultrasonic solution analyzers operating at 20 and 65°.

The simultaneous equations using measured Δf values were solved with a digital computer. All calculations and references to soluble solids were expressed as a percentage of normal. Normal soluble solids was considered to be 100%. Thus, ±5% of normal was expressed as 105 and 95%, respectively. A detailed summary of Δf values and the percentage of alcohol and percentage of soluble solids calculated from the previously derived equations is presented in Table V.

Although results were slightly less accurate than those obtained on the 37 standard samples actually used for the derivation of the regression equations, they were still very good. An error in preparation probably accounts for the larger deviation in alcohol content of Sample E4.

Results of the four "unknown" production samples are presented in Table VI. The composition of these four samples was determined only after analysis by the solution analyzer was completed. The average differences were 0.05% alcohol and 1.28 percentage of normal soluble solids. These results represented good confirmation of the equations and the procedure.

Applicability of Method to Other Types of Mouthwash—To determine whether the methods and principles developed for mouthwash of a moderate soluble solids level could be applied more generally, samples simulating high and low soluble solids types were prepared and analyzed in the latest model of the ultrasonic solution analyzer[2]. Nineteen samples of high soluble solids types covering the ranges of 15.78–23.01% (v/v) (13.0–19.0% w/v) alcohol and 19.37, 21.52, and 23.67% soluble solids and seven samples of low soluble solids type covering the ranges of 27.27–33.87% (v/v) (24–30% w/v) alcohol and 2.62% soluble solids were analyzed at 20 and 65°. The newer model ultrasonic solution analyzer contains a computer module that is programmed to give a direct readout of the percentage of alcohol and soluble solids on the display panel.

Regression equations were developed for the percent of alcohol and percentage of normal soluble solids from the data at 20 and 65° for the high soluble solids type and for the percent of alcohol only with the low soluble solids type since the soluble solids content of this type had not been varied. Results are presented in Tables VII and VIII.

The standard deviation of differences for alcohol content between formulated values and ultrasonic solution analyzer values was slightly larger than that found with the larger population of moderate soluble solids mouthwash samples but was well within acceptable limits. Larger deviations might be expected, because the composition of samples in these series may have varied more widely from theoretical formulation values since much smaller samples were prepared. Also, some sample bottles exhibited cracked or loose caps after shipment for ultrasonic solution analysis. Again, specific gravity determinations to convert alcohol content from weight per volume to volume per volume were made several months later. Ultrasonic solution analysis offered an opportunity for alcohol evaporation in some samples.

[2] Model 2200, Gould, Inc., Chesapeake Instrument Division, Shadyside, Md.

DISCUSSION

Across the entire group from low to high soluble solids types of mouthwash, there was an overall range of 18% (v/v) alcohol and about 21% soluble solids absolute. Despite these wide ranges in composition and the very different constituents comprising the soluble solids portion in each type, it was possible to determine gross composition of any sample with acceptable accuracy.

When the soluble solids content was expressed as a percentage of normal, of course, each of the three types of mouthwash had to be treated separately since each had a different normal content. Within each type, accuracy was good; greater confidence with the general method could be achieved through an enlarged testing program in the high and low soluble solids types. Apparently, all three types can be tested utilizing a separate pair of simultaneous equations for each type. The possibility exists that other types of mouthwash may not conform to the acoustic properties

Table VIII—Comparison of Formulated Values and Solution Analyzer Values for Alcohol Content Obtained from Analysis of Seven Low Soluble Solids Mouthwash Samples at 20 and 65°

Sample Code	Alcohol, % (v/v)		
	Added	Solution Analyzer (SA)	Difference (Added − SA)
		20°	
31F144 A	30.70	30.62	+0.08
31F144 B	27.37	27.51	−0.14
31F144 C	28.53	28.13	+0.40
31F144 D	29.63	30.11	−0.48
31F144 E	31.73	31.40	+0.33
31F144 F	32.77	32.90	−0.13
31F144 G	33.87	33.88	−0.01
		Mean difference = +0.0071	
		Range of differences, = +0.40–−0.48	
		Standard deviation of differences = s = ±0.30%	
		65°	
31F144 A	30.70	30.65	+0.05
31F144 B	27.37	27.59	−0.22
31F144 C	28.53	28.08	+0.45
31F144 D	29.63	29.87	−0.24
31F144 E	31.73	31.71	+0.02
31F144 F	32.77	32.86	−0.09
31F144 G	33.87	33.82	+0.05
		Mean difference = +0.0029	
		Range of differences = +0.45–−0.24	
		Standard deviation of differences = s = ±0.23%	

found here. Nonetheless, the ultrasonic solution analyzer method offers great promise as a single, rapid, and accurate control procedure for determining the alcohol and soluble solids content of mouthwashes.

A distinct advantage over conventional methods of analysis is the test's simplicity. No alcohol distillation is necessary; in a one-step procedure, with the latest models of the instrument, values for two parameters are available within 5 min on a direct readout display.

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In Vitro Evaluation of Three Commercial Sustained-Release Papaverine Hydrochloride Products

ROBERT J. TIMKO and NICHOLAS G. LORDI ×

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Abstract □ Three commercial sustained-release papaverine hydrochloride products in the form of microencapsulated pellets were evaluated. Three different dissolution apparatuses were used: a continuous flow apparatus, the USP rotating basket apparatus, and a modified reciprocating basket apparatus. The frequency rate of the reciprocating basket apparatus could be varied from 0 to 32 strokes/min. Salicylic acid compacts were used as a standard to characterize each apparatus. A linear log–log correlation between dissolution rate and apparatus speed or flow rate was obtained. Release of papaverine hydrochloride from the commercial preparations was affected significantly by the pH of the dissolution media but not by the agitation intensity.

Keyphrases □ Papaverine hydrochloride—dissolution, three commercial sustained-release products, three different apparatuses compared □ Dissolution—papaverine hydrochloride, three commercial sustained-release products, three different apparatuses compared □ Apparatus, dissolution—three types compared, papaverine hydrochloride, three commercial sustained-release products □ Relaxants, smooth muscle—papaverine hydrochloride, dissolution, three commercial sustained-release products, three different apparatuses compared

In recent years, the study of dissolution of drugs from solid dosage forms has become increasingly important. The rate and extent of dissolution from tablets, capsules, and pellets affect both the absorption and therapeutic effect of a drug. Different formulations of the same drug may exhibit different absorption characteristics and, subsequently, different therapeutic activity (1).

Although it is agreed that dissolution testing is important, there is disagreement as to the apparatus and method that should be used as a standard. A simple inexpensive apparatus and method that could be used for most products would be ideal. Such a development is a difficult task, however, because of the numerous factors influencing dissolution testing. Some of these factors are related to the product, such as the physical–chemical properties of the drug and variations in formulation; others, such as the amount and type of solvent and the geometry of the container, are unrelated to the product.

The objective of this study was to evaluate the *in vitro* release characteristics of sustained-release papaverine hydrochloride pellets, produced by various manufacturers, under a variety of conditions. This evaluation was made in three different dissolution apparatuses using a nondisintegrating compact as a standard.

EXPERIMENTAL

Materials—Standard nondisintegrating disks have been used (2, 3) as a means of comparing different dissolution apparatuses. In this study, salicylic acid compacts were chosen as the standard and were used to characterize each apparatus under varying experimental conditions.

About 350 mg of salicylic acid powder[1] was compressed at 1860 kg, using a hydraulic press[2] with a motorized attachment operated at 1.0 cm/sec. Standard 0.95-cm concave punches were employed, and the die was held in place with an acrylic[3] mold. The compacts had an initial average weight of 345 mg with an average thickness and diameter of 0.465 and 0.961 cm, respectively.

The sustained-release papaverine products, A–C[4], were encapsulated pellets containing 150 mg of papaverine hydrochloride/capsule.

Test Fluids—Gastric fluid was prepared according to the method described in USP XIX without the addition of enzyme.

The other test fluids, pH 4.50, 6.00, and 7.00, contained 6.8 g of monobasic potassium phosphate/liter. The monobasic potassium phosphate was dissolved in about 950 ml of water, the pH was adjusted to the desired value with 36.5% (w/w) HCl or 5% (w/v) NaOH, and the volume was brought to 1 liter.

Assay Method—Beer's law curves were constructed for papaverine hydrochloride and salicylic acid. The maximum wavelengths for the two test materials are: salicylic acid in gastric fluid, λ = 302 nm; papaverine hydrochloride in gastric fluid, λ = 309 nm; papaverine hydrochloride in pH 4.50 fluid, λ = 309 nm; papaverine hydrochloride in pH 6.00 fluid, λ = 310 nm; and papaverine hydrochloride in pH 7.00 fluid, λ = 325 nm.

In most cases, these wavelengths allowed direct absorbance readings under experimental conditions. Linearity was followed in the concentration ranges used.

Dissolution Methods—Each of the three dissolution methods affected

[1] Reagent grade, J. T. Baker Chemical Co., Clifton, N.J.

[2] Model C, Fred S. Carver, Menomonee Falls, Wis.

[3] Lucite.

[4] Product A was lot 3H518, Vitarine Co.; Product B was Pavabid lot 12023, Marion Laboratories; and Product C was Cerespan lot 55282, USV Pharmaceutical Corp.