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Softening and Liquefaction Temperature of Suppositories

By IVO SETNIKAR and SERGIO FANTELLI

A method is described for testing the softening and liquefaction temperature of suppositories. The data obtained yield the maximum environmental temperature at which suppositories retain sufficient firmness for handling and for ordinary storage. The physical properties of 44 bases were investigated by this new method. The melting point was determined by the open capillary method. Of 27 fatty bases, only 8 present properties which are as satisfactory as or better than those of theobroma oil. Most of the 17 water-soluble bases investigated have very satisfactory firmness, but their melting point is above body temperature so that, for liquefaction, they must dissolve in water drawn from the rectal mucosa.

RECTAL suppositories, if well formulated, should melt, soften, or dissolve when introduced into the rectum and yet retain their firmness and shape in ordinary storage conditions.

Melting, softening, or dissolving may be tested in an apparatus which reproduces the physical conditions of the rectum (1). This apparatus, however, does not give indications as to the firmness of the suppositories. The following characteristics may be examined in order to test firmness.

Melting temperature.—Melting temperature may be determined (*a*) by the open capillary method for fatty substances (*cf.* U.S.P. XVI, p. 926, class II) or by the sealed capillary method (2). Only suppository bases can be tested and the results are influenced by the technique used in the preparation of the capillary (2). (*b*) The suppository may be put in an aqueous environment whose temperature is raised until the suppository melts (3–6). In these conditions only strictly water-insoluble suppositories can be tested. Suppositories containing water-soluble substances soften or dissolve in the aqueous environment irrespective of temperature. (*c*) The temperature of the air surrounding the suppository may be gradually raised until melting. This method was followed by Erbe (7) who used an apparatus described by Bogs (8).

Hardness—Malangeau (3) molded a cylinder with a diameter of 9 mm. of the same composition of the suppository and determined the temperature at which the cylinder collapsed under a weight of 500 Gm. (8 Gm./-mm.^{2}). Münzel (9) and other authors (2, 10, 11) used the penetrometric method described in U.S.P. XIV, p. 693. Büchi and Oesch (12) stated that a suppository, at a temperature of 22°, should not be deformed by a weight of 500 Gm.

The first two methods cannot be used directly on suppositories while the method of Büchi and Oesch can, though it gives only limited information on the maximal temperature at which a suppository still shows sufficient mechanical stability. We describe here a method for determining the softening and melting temperatures directly on suppositories.

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METHODS

The apparatus (Fig. 1) consists of a 200-mm. long glass tube with an internal diameter 1–3 mm. larger than the maximal diameter of the suppository to be tested. The tube, in the middle part, has a constriction with an internal diameter of 3 mm. This constriction supports the suppository. The tube is surrounded by a glass mantle fitted with two connections through which water circulates. The temperature of the circulating water can be read on a thermometer.

The suppository is introduced into the upper part of the tube as shown in Fig. 1. Then a 120-mm. long glass rod, which has a diameter 2 mm. smaller than the internal diameter of the tube, is placed on the suppository. A short thick-walled rubber tube is slipped over the glass rod in such a way that, when the rod rests on the suppository, there is a distance of 14 mm. between the lower end of the rubber and the upper end of the glass tube. The rubber supports a lead cylinder which moves freely on the glass rod. The lead cylinder and glass rod with rubber have a weight of 500 Gm. when the test is performed on suppositories of a diameter of 9–10 mm. For thinner suppositories, the weight should be about 7 Gm./mm.^{2}. When the suppository collapses, the lead cyclinder sinks 5 mm., then it is stopped by a support which prevents any further sinking of the lead. We define the temperature at which this happens as the softening temperature (*ST*).

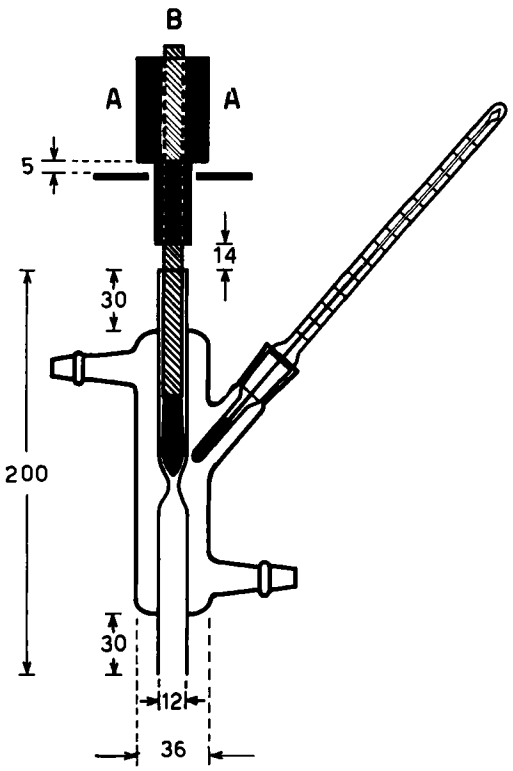

Fig. 1.—Apparatus described in the text for the determination of the softening and liquefaction temperatures. *A*, lead cylinder weighing 460 Gm.; *B*, glass rod, over which a rubber tube is fitted, supporting the lead cylinder. The glass rod and rubber tube have a weight of 40 Gm. The glass rod rests on the suppository. When the suppository collapses the glass rod sinks. After sinking 5 mm. the lead cylinder is supported by a rest and on the suppository there remains only the weight of the glass rod. All measures are in mm. The internal diameter of the glass tube may differ according to the diameter of the suppository. For suppositories of 9.5-mm. diameter, as those used in our experiments, an internal diameter of the tube of 12 mm. is satisfactory.

An alternative method consists in putting on the glass rod, and therefore on the suppository, increasing weights, *e.g.*, lead disks of 100 Gm. In this way the collapsing weight (CW_t) of a suppository may be determined at a given temperature.

When the suppository has collapsed so that it no longer supports the lead cylinder or disks, it bears the weight of the glass rod (30–40 Gm.) only. As the temperature of the water jacket rises, the suppository liquefies, and the glass rod can then sink for another 9 mm. until the rubber rests on the glass tube. We define the temperature at which this happens as the liquefaction temperature (*LT*).

The glass rod is very useful because, as pointed out by Reznek (6) and by Krowczynski (4), an objective measurement of the "melting" or rather of the liquefaction, can be performed only when the suppository is subjected to a light mechanical stress. In our opinion the term "liquefaction temperature" is more proper than that of "melting temperature," since very often suppositories contain drugs which do not melt together with the base and the base, too, may be a mixture of substances with different melting points.

When the suppository has liquefied it flows through the 3-mm. constriction of the glass tube of the apparatus. This usually happens at the liquefaction temperature as defined above. Only for very viscous mixtures is the flow temperature (*FT*) 0.5–1.0° higher than the *LT*.

As described in the result section, we found it convenient to raise the temperature in the apparatus at the rate of 0.1°/min. A simple method of doing this automatically is to drive the thermoregulation knob of a Tecam-Tempunit thermostat water pump with a synchronous motor at the rate of 0.1 angular degrees per minute. Furthermore the sinking of the lead weight or of the glass rod can switch off the current to the motor by means of a microswitch and thus the temperature remains constant when the *ST* or the *LT* is reached.

In order to verify the results obtained, the melting temperature of the bases was determined also by the capillary method for class II substances described in U.S.P. XVI, p. 926 (capillary melting temperature—*CMT*). For water-soluble bases, instead of a water bath, a liquid petrolatum bath was used. In both cases the temperature was raised at the rate of 0.5°/-min.

The melting temperature was controlled by putting the suppositories in a small metallic basket with 5-mm. meshes and keeping these suppositories in an incubator in which the temperature was raised 0.5° every 4 hours. We defined the incubator liquefaction temperature (*ILT*) as the temperature at which at least $^2/_3$ of the suppository had passed through the meshes of the basket.

RESULTS

A very important factor for correct use of the apparatus is the rate at which the temperature is raised in the water jacket. If this rate is too high, the temperature of the suppository remains below that of the water jacket and the temperature read on the thermometer at the moment of softening or of liquefying of the suppository does not correspond to the temperature within the suppository. It is therefore important to define the time necessary to reach thermal equilibrium between the suppository and the water jacket of the apparatus. For this determination we adopted the procedure previously described (1), *i.e.*, we inserted a thermocouple in the middle of a suppository of the shape represented in Fig. 2. The suppository so prepared was then kept for several hours at a temperature of 18 ± 0.2° and then put in the apparatus with the circulating water at 2–3° below the liquefaction temperature of the suppository.

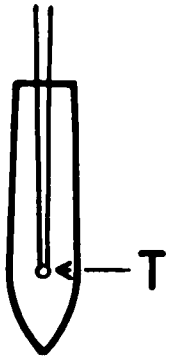

Fig. 2.—Shape and actual size of the suppositories used in our experiments. The position of the thermocouple (T) in the suppository is also shown.

The temperatures measured in the suppository were subjected to a quantitative treatment as previously described. The thermal equilibrium curves obtained on suppositories made with different bases (Fig. 3) show that a 90% thermal equilibrium is reached in 8.5 min. by Carbowax 6000 suppositories, in 12.0 min. by Imhausen H suppositories, in 15.5 min. by theobroma oil suppositories, in 21.5 min. by Neosuppostal suppositories, and in 33.5 min. by Imhausen E suppositories.

On the basis of these data, several procedures of raising the temperature in the apparatus were tried and the following was found convenient. The suppository was put in the apparatus kept at 28.0 ± 0.1° and left at this temperature for 1 hour. Then the temperature was raised at the rate of 0.1°/min. until the ST and the LT were reached. Table I shows the temperature read on the thermometer and the differences between this temperature and the one measured in the middle of the suppository. This difference is not more than 2.0° and, at liquefaction temperature, it becomes very small, probably because heat transmission is improved by the melted part of the suppository which fills the space between the glass tube and the suppository.

Table II gives the capillary melting temperature (CMT), the incubator liquefaction temperature (ILT), the liquefaction temperature (LT), the softening temperature (ST), and the collapsing weight at 25° (CW_{25}) observed in 44 bases or suppositories made with these bases and tested 1–6 months after their preparation.

Table III gives the CMT, the LT, and the ST determined during a 4-month observation on some suppository bases. The same data determined on Carbowax 4000 and on Tween 61 did not show significant changes.

DISCUSSION

Table II shows that there is usually a good agreement between the ILT and the LT, whereas the CMT may be up to 6° lower than the ILT. Since the actual storage conditions of the suppositories are certainly better reproduced by the incubator than by the capillary, the CMT must be considered critically, especially when it is determined on fatty bases and found close to 37°. Indeed, fatty base suppositories liquefy in the rectum only when their liquefaction temperature is below 37° (1). An error of 2–6° in the estimation of the melting temperature means that in some cases a suppository base, which really liquefies above 37° and therefore does not liquefy in the rectum may be accepted as

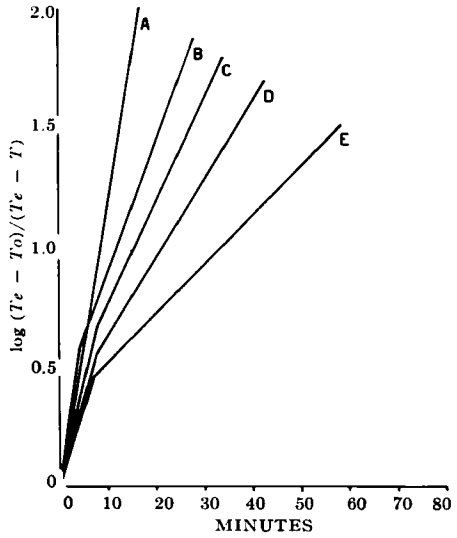

Fig. 3.—Thermal equilibrium curves determined on suppositories obtained with different bases. *Ordinate:* log $(Te - To)/(Te - T)$ (Te is the temperature measured in the suppository at equilibrium, To is the temperature measured at time zero, *i.e.*, at the beginning of the experiment, T is the temperature of the suppository measured at the time corresponding to the abscissa). *Abscissa:* time in minutes. The inclination of the curves expresses the thermal equilibrium rate constant k of the equation: $dT/dt = k(Te - T)$ where t is the time in minutes. A 90% thermal equilibrium is reached in correspondence with $\log (Te - To)/(Te - T) = 1$. A is the curve obtained with a Carbowax 6000 suppository ($k = 0.118$); B, an Imhausen H suppository, ($k = 0.055$); C, a theobroma oil suppository ($k = 0.044$); D, a Neosuppostal suppository ($k = 0.033$); E, an Imhausen E suppository ($k = 0.021$),

TABLE I.—TEMPERATURE IN THE APPARATUS AND DIFFERENCES FROM THE TEMPERATURE IN THE MIDDLE OF THE SUPPOSITORY. TEMPERATURE IN THE APPARATUS WAS INCREASED AT THE RATE OF 0.1°/MIN.

Apparatus	Carbowax 6000	Imhausen H	Theobroma Oil	Imhausen E
28	0	0	0	0
29	−0.1	−0.3	−0.5	−0.1
30	−0.1	−0.7	−0.7	−0.2
31	−0.1	−1.0	−1.0	−0.5
32	−0.1	−1.3	−1.4	−0.9
33	−0.1	−1.5	−2.0	−0.9
34	−0.1	−1.5	−1.0	−1.1
35	−0.1	−0.8	−0.3 (*LT*)	−1.2
36	−0.1	−0.4 (*LT*)		−1.5
37	−0.1			−1.2
38	−0.2			−1.0
39	−0.2			−0.5 (*LT*)
40	−0.2			
45	−0.4			
50	−0.4			
55	−0.5			
60	−0.4			
61	−0.3			
62	−0.2			
63	−0.1 (*LT*)			

satisfactory on the basis of a *CMT* found below 37°. The capillary method has the further disadvantage that some formulations for suppositories, like those containing a large amount of insoluble drugs (*e.g.*, 0.5 Gm. aminophylline in theobroma oil suppositories), are difficult to test since the mixture can not be homogeneously introduced into the capillary. Finally, by this method, it is not possible to determine the melting temperature directly on suppositories, as is necessary, for example, after stability tests, *etc.* For the liquefaction temperature determination, the incubator method and the apparatus described in this paper seems therefore more suitable.

Before choosing the 500-Gm. weight for the determination of the softening temperature, suppositories made with mixtures of theobroma and almond oils were submitted for examination to pharmacists and physicians. The suppositories considered sufficiently firm for handling, storage, and for introduction into the rectum supported a weight between 500 and 700 Gm. (7–10 Gm./mm.^{2}). Since Büchi and Oesch (12) and Malangeau (3) proposed that suppositories of about the same diameter should not be deformed by a weight of 500 Gm., we finally adopted this weight for the determination of the *ST* on our suppositories.

The determination of the *ST* is particularly important for suppositories which must be handled and stored in warm or hot climates. An estimation of the *ST* through the collapsing weight at a given temperature (CW_t), as proposed by Büchi and Oesch (12), is possible only if the two values are very well correlated. The regression calculated on the data obtained on 27 fatty suppository bases is $ST = (24.1 \pm 0.5) + (2.4 \pm 0.33)\, CW_{25}$, from which *ST* can be estimated from the CW_{25} value with an error which may be as much as ±6.7° ($P = 0.05$).

The regression calculated on the data obtained on the 17 water-soluble bases is $ST = (25.88 \pm 1.51) + (5.53 \pm 0.90)\, CW_{25}$, from which *ST* can be estimated with an error which may be as much as ±13.3° ($P = 0.05$). In both cases the correlation of *ST* to CW_{25} is evidently so poor that the determination of the *ST* cannot be replaced by that of the CW_t.

Some comment on the physical qualities of the bases investigated is also relevant. Of the fatty bases, theobroma oil may still be considered as a standard, although it was criticized for its rather low melting temperature and for the comparatively low consistency. On the basis of the *LT* and the *ST* reported in Table II, however, it must be concluded that, of the fatty bases, only Estarinum A, BB, and Pi, Imhausen H, OG, and W, Suppocire A, and Vi-Tin 136, present properties which are as satisfactory as, or better than, those of theobroma oil. However, of the bases with an *LT* higher than 37°, many can be considered for correcting the *LT* of some particular formulations with an *LT* below 35°.

The water-soluble bases, with their high *ST* and *LT*, seem ideally suited for hot climates. But it must be emphasized that these bases liquefy only by a process of dehydrating the rectal mucosa, which is antiphysiological, sometimes irritant and painful, and very often so slow that the drugs vehicled are liberated after only some considerable time (1).

A disadvantage of theobroma oil is its unstable forms, with low melting temperature, which is particularly evident after a heating above 37–40° (13, 14). A consequence of this is that the suppositories remain liquid after pouring in the molds unless these are kept at fairly low temperature. Another consequence is that for the experimenter, it is impossible to know the final physical characteristics of the suppositories for some time after preparation.

In order to investigate the importance of the unstable forms from the analytical point of view, we performed the experiments summarized in Table III. The results show that not only theobroma oil, but also other fatty bases as Dehydag III, Estarinum A and BB, Imhausen H and W, and Suppocire A, reach a stable form not after a few days, as usually stated in the literature, but after 10–30 days. Theobroma oil heated beyond the transition temperature, however, does not reach a stable form even after 4 months. The changes in physical properties are particularly evident in the light of the *CMT* and

TABLE II.—PHYSICAL CHARACTERISTICS OF SOME SUPPOSITORY BASES

Base	CMT,[a] °C.	ILT,[a] °C.	LT,[a] °C.	ST,[a] °C.	CW_{25},[a] Kg.	Supplier
Fatty Bases						
Theobroma Oil	31.6	35	34	29	3.4	.....
Caol TR	39.4	..	39[b]	30	1.6	Sarn, Novara, Italy
Caol TR 38/40	41.7	..	44[b]	34	3.1	" " "
CBSA "N"	36.6	..	37	<18[b]	0.15	Calvè, Delft, Holland
Dehydag III	33.7	40	39[b]	37	>5.0	Deutsche Hydrier-Werke
Dehydag IV	33.7	39	38[b]	36	5.0	" " "
Estarinum A	34.7	37	37	32	4.5	Edelfettwerke, Hamburg
Estarinum B	36.6	39	38[b]	34	5.0	" "
Estarinum BB	34.7	37	36	31	4.2	" "
Estarinum C	38.6	..	40[b]	36	>5.0	" "
Estarinum D	43.3	..	45[b]	41	>5.0	" "
Estarinum Pi	35.0	37	37	34	5.0	" "
Imhausen E	38.2	..	39[b]	33	4.7	Chemische Werke Witten
Imhausen ET	34.7	38	39[b]	33	4.5	" " "
Imhausen H	34.4	36	36	32	4.7	" " "
Imhausen OG	33.5	36	37	29	2.3	" " "
Imhausen W	34.6	37	37	31	4.0	" " "
Imhausen W/N	38.6	..	39[b]	33	3.4	" " "
Lipomassa C.F.M.	38.7	..	39[b]	25[b]	0.5	C.F.M., Milano, Italy
Neo Suppostal	36.5	41	41[b]	28[b]	0.9	Mediframa, Milano, Italy
Suppostal ES	42.2	..	45[b]	32	1.1	" " "
Suppocire A	34.8	36	37	30	2.5	Gattefossè, Lyon
Suppocire B	36.4	38	38[b]	30	3.4	" "
Suppocire C	38.0	..	39[b]	33	4.0	" "
Suppolanol	33.5	..	35	25[b]	0.5	Esperis, Milano, Italy
Vi-Tin 136	34.7	37	37	35	3.9	Treves, Torino, Italy
Vi-Tin 138	36.6	41	39[b]	36	4.3	" " "
Water-soluble Bases						
Carbowax 1540	45.7	..	46	37	2.0	Union Carbide, New York
Carbowax 4000	57.1	..	59	55	>5.0	" " " "
Carbowax 6000	61.6	..	63	56	>5.0	" " " "
Carbowax 6000 + 20% H_2O	58.0	..	61	51	2.0	" " " "
Glycerinated gelatin U.S.P.	48.3	..	50	25[b]	0.5	.....
Idromassa C.F.M.	58.0	..	60	56	4.3	C.F.M., Milano, Italy
Idropostal	58.2	..	60	56	>5.0	Medifarma, Milano, Italy
Idropostal 90% + liquid Idropostal 10%	57.2	..	58	52	>5.0	" " "
Idropostal G 60% + Glicerol 40%	47.0	..	52	37	1.5	" " "
Idropostal M 90% + H_2O 10%	56.2	..	57	49	3.0	" " "
Idrorectonal H	49.6	..	54	41	2.5	Frat. Giacomini, Milano, Italy
Idrorectonal HL	42.0	..	41	30	1.9	" " " "
Idrorectonal W	51.8	..	55	42	4.3	" " " "
Massa Neutralis C.F.M.	39.0	..	39	29	1.3	C.F.M., Milano, Italy
Myrj 52	46.3	..	47	42	>5.0	Atlas Powder
Neutril	57.9	..	59	54	4.9	I.C.V., Como, Italy
Tween 61	40.1	..	39	25	0.5	Atlas Powder

[a] *CMT* = capillary melting temperature; *ILT* = incubator liquefaction temperature; *LT* = liquefaction temperature; ST = softening temperature; CW_{25} = collapsing weight at 25°. [b] Unsatisfactory characteristic.

the *ST* values, though the *LT* temperature reaches a stable value earlier.

The water-soluble bases investigated (Carbowax 4000 and Tween 61) do not show unstable forms.

CONCLUSIONS

As already pointed out by Caldwell (13) the definitions of the suppositories reported in the pharmacopeias, in which it is stated that they should soften, melt, or dissolve at body temperature, are of little assistance unless the method of determining these characteristics is given. In point of fact, different methods give quite different results and sometimes suppositories may be accepted as satisfactory on the basis of the capillary melting temperature for example, even when they do not melt, soften, or dissolve in the rectal environment. Besides this, there should be an accepted method for finding out whether a suppository is sufficiently firm to be introduced in the rectum, handled and stored at ordinary room temperatures or in warm climates.

The method proposed in this paper supplies this information and, for suppositories with fatty bases, shows also whether the liquefaction temperature is sufficiently low to permit liberation of the contained drugs after introduction in the rectum. As a matter of fact all the fatty

TABLE III.—PHYSICAL PROPERTIES OF SOME SUPPOSITORY BASES DURING 120-DAY OBSERVATION

Days		0.1	1	10	20	30	60	120
Theobroma Oil,	CMT	32.2	31.6	33.6	34.3	34.9	35.0	34.6
(heated at 35°C.)	LT		34	34	34	34	35	35
	ST		30	30	30	30	32	32
Theobroma Oil,	CMT	25.1	27.5	27.7	28.0	32.8	32.4	32.0
(heated at 55°C.)	LT		29	29	29	30	34	34
	ST		24	24	24	24	24	30
Dehydag III	CMT	33.3	33.7	35.0	35.0	35.5	36.6	36.9
	LT		36	37	37	38	39	39
	ST		35	35	35	36	37	37
Estarinum A	CMT	32.7	34.7	36.7	36.8	37.5	37.0	36.6
	LT		37	38	38	38	38	37
	ST		31	32	32	31	30	31
Estarinum BB	CMT	32.8	34.7	35.2	35.9	36.7	37.1	37.0
	LT		36	36	36	37	37	37
	ST		32	32	31	30	31	32
Imhausen H	CMT	34.4	34.4	34.6	34.7	34.4	36.7	37.0
	LT		35	36	37	37	37	37
	ST		32	32	32	31	29	29
Imhausen W	CMT	34.2	34.8	35.9	36.0	36.4	36.8	36.5
	LT		36	36	36	37	37	37
	ST		31	31	29	28	28	28
Suppocire A	CMT	34.4	34.8	35.9	36.0	36.5	36.8	36.5
	LT		36	36	36	37	37	37
	ST		31	31	29	28	28	28

bases of Table II with a liquefaction temperature below 37° liquefy in rectal conditions as shown by the results reported by Setnikar and Fantelli (1). But this is not necessarily true for fatty bases with a capillary melting temperature below 37°.

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Proposed Method of Assay for Diaphene

By SOBHI A. SOLIMAN and LOYD E. HARRIS

A rapid and convenient differential spectrophotometric assay is proposed for the assay of Diaphene in liquid soaps and hand creams.

DIAPHENE[1] is a mixture of 5,4′-dibromosalicylanilide and 3,5,4′-tribromosalicylanilide, and is used in toilet detergent formulations. It is reported to possess an unusually long-lasting germicidal effect.

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[1] Trademark of Norton Co., Worcester, Mass. Contributed and marketed by Stecker Chemicals, Inc., Ridgewood, N. J.

Methods described in the literature for the determination of phenolic antiseptics in soaps employ colorimetric or spectrophotometric techniques. The method of Gottlieb and Marsh (1), depending on color formation by the reaction of a phenol with 4-aminoantipyrine in the presence of potassium ferricyanide as an oxidizing agent, was reported to give unreliable results since the color fades rapidly. Ettinger, *et al.* (2), in an attempt to stabilize the color, concentrated the reaction products by extraction with chloroform. This modification, however, does not stabilize the color produced to any degree of accuracy.

The colorimetric method of Johnson and Savidge (3) depends upon the measurement of the