

Source	Nature of Solution	pH
A	Simple aqueous, 2.5%	6.6
B	Simple aqueous, 2.5%	7.1
C	Simple aqueous, 2.5%	6.9
D	Aqueous buffered sodium phosphate, 2.5%	7.4

In their paper, Cotter and MacNeal state that each of four ampul solutions of sodium citrate which they observed had a pH value of 8.0 or over. As the identity of the manufacturers of the ampuls used by Cotter and MacNeal in their observations is unknown, it is impossible to decide on a definite reason for such divergent results. So far as the ampul solutions examined in the Hospital Pharmacy are concerned, the variations in pH values (from 6.6 to 7.4) can, on the basis of the available information, be explained only by assuming that varying grades of glass were used in the manufacture of the empty ampuls.

CONCLUSIONS

1. The pH of a 3.5% solution of Sodium

Citrate U. S. P. in freshly distilled water is 7.3.

2. This value does not change during the process of sterilization when such solutions are contained in properly prepared pyrex bottles.¹

3. A simple, aqueous 3.5% solution of Sodium Citrate U. S. P., in freshly distilled water, is satisfactory for use as an anticoagulant, since it is of the proper pH and can be prepared, bottled and sterilized without a change of pH.²

REFERENCES

- (1) Cotter, J., and MacNeal, W. J., *Proc. Soc. Exptl. Biol. Med.*, 38 (1938) 757-758.

¹ Such bottles in the proper size are now readily available.

² pH values determined experimentally by the author are electrometric readings.

Some Notes on Chalk Mixture*

By Louis W. Schleuse† and J. Richard Stockton‡

A chalk mixture was included in the first "Pharmacopœia of the United States," and each revision has retained a mixture of prepared chalk (Table I). Although several changes have been made, the present official product is little different from the original, and both possess two objectionable features: They are fermentable, and the acacia is not a satisfactory suspending agent.

The unstable character of the preparation and the "positively injurious" effect (1) of the sucrose prompted Reynolds (2) in 1870, Kennedy (3) in 1872 and Hommel (1) in 1911 to recommend replacement of the sucrose with glycerin. The Fifth Revision of the "Pharmacopœia" (Convention of 1870) made such a change (Table I), and much later the Tenth Revision (1920) replaced both sucrose and acacia with glycerin (Table I), but neither modification survived the revision in which it appeared.

Jones (4) in 1870 and Rother (5) in 1873

proposed the use of compound chalk powders from which chalk mixture could be prepared when wanted. The Sixth Revision of the "Pharmacopœia" (1880) adopted a method of preparing chalk mixture from compound chalk powder, a practice retained in each subsequent revision except the Tenth (Table I).

Fantus and Snow (6) in 1922 also objected that fermentable carbohydrates (sugar and acacia) were "illogical . . . as ingredients of a medicine employed in fermentative diarrhea." They considered a carbohydrate-free formula containing prepared chalk, saccharin, cinnamon water and water, but found that "when kept exposed to sunlight for quite some time, it developed an offensive odor reminding one somewhat of hydrogen sulfide or of illuminating gas, with progressive diminution and final loss of cinnamon flavor." They observed no decomposition when fennel, anise or peppermint flavors were substituted for cinnamon.

In addition to the ease with which it is fermented, acacia is also objectionable as a suspending agent for prepared chalk. When the official chalk mixture is allowed to stand for a few days, all of the chalk

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TABLE I.—PHARMACOPŒIAL CHALK MIXTURES

Pharmaco- pœia	Prepared Chalk	Compound Chalk Powder	Acacia	Sucrose	Glycerin	Diluent and Flavor	
1820	℥ iss	...	℥ ss	℥ i	...	Oil cinnamon	℥ x
						Water	℥ xx
1830 (New York)	℥ ij	...	℥ i	℥ i	...	Peppermint water	℥ viij
1830 (Philadelphia)	℥ ss	...	℥ ij	℥ ij	...	Cinnamon water	
						Water, <i>āā</i>	℥ iv
1840	℥ ss	...	℥ ij	℥ ij	...	Cinnamon water	
						Water, <i>āā</i>	℥ iv
1850	℥ ss	...	℥ ij	℥ ij	...	Cinnamon water	
						Water, <i>āā</i>	℥ iv
1860	℥ ss	...	℥ ij	℥ ij	...	Cinnamon water	
						Water, <i>āā</i>	℥ iv
1870	℥ ss	...	℥ ij	...	℥ ss	Cinnamon water	
						Water, <i>āā</i>	℥ iv
1880	...	20 parts	Cinnamon water	40 parts
						Water	40 parts
1890	...	200 Gm.	Cinnamon water	400 cc.
						Water, <i>q. s.</i>	1000 cc.
1900	...	20 Gm.	Cinnamon water	40 cc.
						Water, <i>q. s.</i>	100 cc.
1910	...	20 Gm.	Cinnamon water	40 cc.
						Water, <i>q. s.</i>	100 cc.
1920	6 Gm.	10 cc.	Cinnamon water	40 cc.
						Dist. water, <i>q. s.</i>	100 cc.
1930	...	20 Gm.	Cinnamon water	40 cc.
						Dist. water, <i>q. s.</i>	100 cc.

settles as a hard, compact layer very difficult to resuspend.

The excellent suspending qualities and the freedom from toxicity¹ of bentonite led us in the summer of 1940 to investigate the applications of this mineral as a suspending agent for insoluble materials in diarrhea mixtures. It was found to be especially suitable for preparations containing bismuth subcarbonate or prepared chalk, which suggested that bentonite might be preferable to acacia in the official chalk mixture.

Furthermore, bentonite is a domestic product and is much less expensive than imported acacia.

EXPERIMENTAL

Materials Used.—Two commercial bentonites (subsequently designated 1 and 2), prepared chalk, soluble saccharin (in stock solution, 10 mg./cc.), cinnamon water, peppermint water, distilled water and compound chalk powder.

Replacement of Acacia and Sucrose by Bentonite and Soluble Saccharin in Chalk Mixture.—A 6% magma of each bentonite was prepared with the aid of a mechanical agitator and allowed to stand over night. A series of ten chalk mixtures was made

¹“Bentonite meets the requirements of the test for arsenic, U. S. P. XI, p. 436, and the test for heavy metals, U. S. P. XI, p. 447.” Private communication from American Colloid Company, Chicago, Ill., September 3, 1940.

from each bentonite magma according to the following formula:

Prepared chalk	3.0 Gm.
Bentonite magma	Variable
Soluble saccharin	0.01 Gm.
Cinnamon water, enough to make	50.0 cc.

The individual preparations differed only in bentonite content, from 0.3% in the lowest to 3% in the highest. These chalk mixtures were compounded by triturating 3 Gm. of chalk with the bentonite magma, followed by the addition of 1 cc. of soluble saccharin solution and enough cinnamon water to make the volume 50 cc. A sample of chalk mixture U. S. P. XI and a suspension of 3 Gm. of prepared chalk in 50 cc. of cinnamon water were used for comparison.

All were shaken at the same time and allowed to settle, examinations and photographs being made at suitable intervals. The photographs made at 1 hr. and at 20 hrs. are shown in Fig. 1 and Fig. 2, respectively. These satisfactorily show that the rate of settling is dependent upon the amount of bentonite present. But the photographs fail to show the extent of settling in the U. S. P. XI chalk mixture, in which after 20 hrs. the chalk had most completely settled to the bottom leaving, however, a small amount of fine chalk in suspension, thereby forming a hazy supernatant layer, opaque in the photographs.

Comparison of the two series of mixtures shows little difference in suspending powers of the two bentonites. Although the preparations containing less than 0.9% of bentonite (*i. e.*, less than 7.5 cc. of 6% magma per 50 cc.) settled appreciably within an

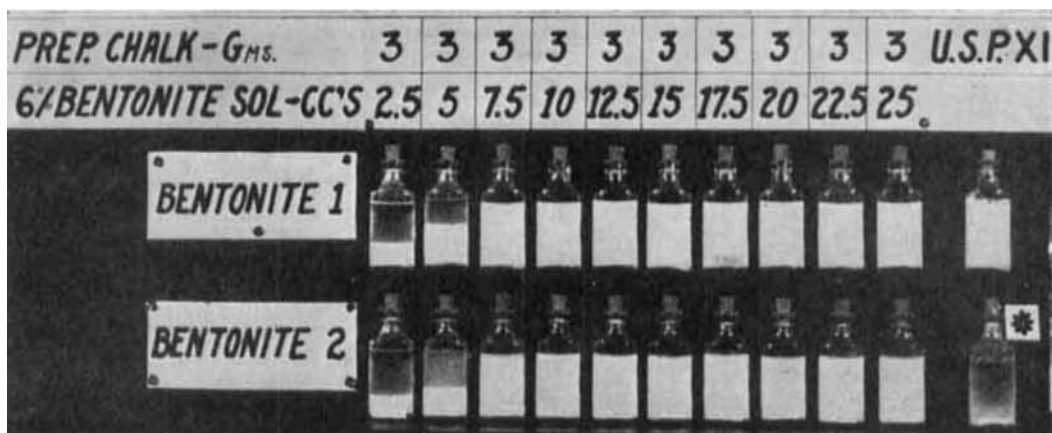


Fig. 1.—Photograph of Chalk Mixtures after One Hour (Preparation Containing Only Chalk and Cinnamon Water Indicated by Asterisk).

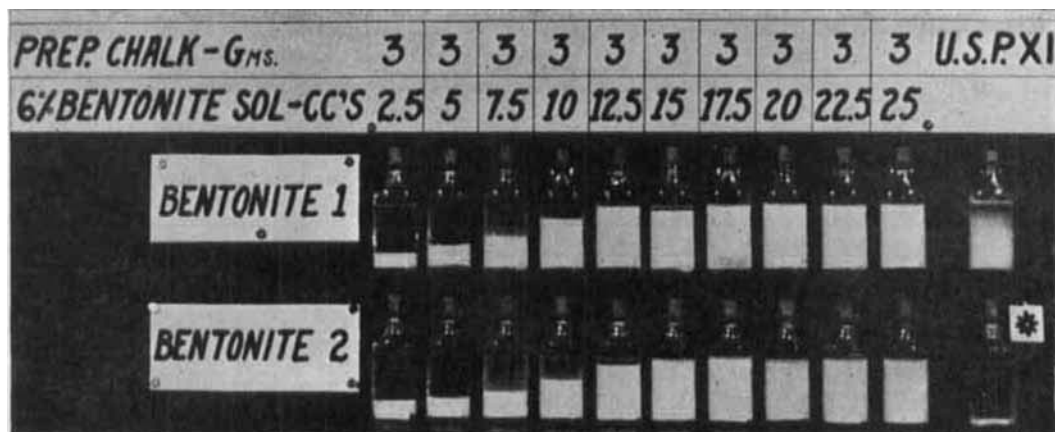


Fig. 2.—Photograph of Chalk Mixtures after Twenty Hours (Preparation Containing Only Chalk and Cinnamon Water Indicated by Asterisk).

hour, all resuspended easily on being shaken, even after standing for more than one year. Furthermore, in preparations containing bentonite in excess of about 2.4%, resuspension was slightly more difficult, though much less difficult than in the U. S. P. XI chalk mixture. For these reasons, a concentration of bentonite between about 0.9% and 2.4% seems most desirable.

The observation of Fantus and Snow on the production of a hydrogen sulfide odor in a mixture containing chalk, saccharin and cinnamon water was not confirmed, even after one year, although a toluene-like odor (perhaps the illuminating gas odor they described) was detected in all samples containing bentonite, especially in those samples containing larger proportions of bentonite magma. Two samples of this chalk mixture were set aside for more than a year, one in darkness and one exposed to sunlight; periodic examinations were made. The characteristic toluene-like odor developed in both within one to two months. Since this odor appears to depend upon the presence of cinnamon, the replacement of cinnamon by some other acceptable flavor seemed desirable.

Replacement of Cinnamon Water by Peppermint Water in Bentonite Formula.—A chalk mixture was prepared in which the cinnamon water in the above formula was replaced with peppermint water. The odor remained unchanged during the period of observation.

Suggested New Formula for Chalk Mixture.—On the basis of the foregoing results a chalk mixture containing 2% of bentonite was prepared as follows:

Prepared chalk	6.0 Gm.
Bentonite magma ²	40.0 cc.
Soluble saccharin	0.02 Gm.
Peppermint water	40.0 cc.
Distilled water, enough to make	100.0 cc.

² Bentonite magma was prepared as follows:

Bentonite	50.0 Gm.
Distilled water, enough to make	1000.0 cc.

Sift the bentonite on the surface of 900 cc. of distilled water contained in a suitable vessel. When the bentonite has become thoroughly wetted, mix well by vigorous stirring or by means of a mechanical agitator. Allow to stand for at least 12 hrs.; strain through muslin, and add enough water through the strainer to make 1000 cc. Mix thoroughly.

Place the prepared chalk in a mortar and triturate until free from lumps. Add bentonite magma in small portions, triturating thoroughly after each addition until a uniform mixture results. Then add the peppermint water in which the soluble saccharin has been dissolved; transfer this to a graduated vessel and rinse the mortar with enough distilled water to make the product measure 100 cc. Mix thoroughly.

This product is entirely palatable and yields satisfactory preparations when combined in prescription form with elixir of phenobarbital, elixir of Nembutal, compound elixir of pepsin, elixir of pepsin and rennin, Liquid Takadiastase, Caripeptic Liquid, camphorated tincture of opium, milk of magnesia, milk of bismuth, aluminum hydroxide gel, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, Kaomagma, Kaopectate and tincture of belladonna. Addition of tincture of opium causes excessive thickening.

SUMMARY AND CONCLUSIONS

1. Chalk mixtures containing prepared chalk, soluble saccharin, cinnamon water,

distilled water and variable amounts of bentonite were prepared. The bentonite seems superior to the more expensive acacia as a suspending agent for this purpose; concentrations between 0.9% and 2.4% are most suitable. Elimination of fermentable materials (sucrose and acacia) produced a biologically stable preparation, but some samples after long standing developed odors resembling toluene.

2. The toluene-like odor is not produced when cinnamon water is replaced by peppermint water.

3. An improved formula for chalk mixture containing prepared chalk, bentonite (magma), soluble saccharin, peppermint water and distilled water is suggested. This product is palatable and is compatible with many of the drug preparations that are prescribed with chalk mixture.

REFERENCES

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- (2) Reynolds, H. P., *Am. J. Pharm.* (Sept., 1870); through *PROC. A. PH. A.*, 19 (1871), 149.
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- (4) Jones, W. R., *Ibid.* (Sept., 1870); through *PROC. A. PH. A.*, 19 (1871), 149.
- (5) Rother, R., *Pharm.* (Oct., 1873), p. 308; through *PROC. A. PH. A.*, 22 (1874), 68.
- (6) Fantus, B., and Snow, C. M., *JOUR. A. PH. A.*, 11 (1922), 795.

The Toxicity of Benzoic Acid for White Rats*

By George P. Hager,† C. W. Chapman and E. B. Starkey

Benzoic acid is widely used in the preservation of food products (1) and pharmaceutical preparations (2), especially those with an acid reaction. Furthermore, because of its antiseptic action, it is used in ointments and dusting powders for the treatment of skin infections, in a 1% solution as a mouth wash (3), in a 0.5% solution for the treatment of chronic suppurating wounds (4) and in preparations for the treatment of tuberculosis, asthma and rheumatism (1).

In view of these many varied uses of benzoic acid, much interest attaches to its toxicity. It has been found that a rather broad

margin of safety attends its use in these instances—0.5 Gm. daily produced no demonstrable effects in healthy persons and even 4 Gm. was not injurious (5, 6). Amounts far in excess of the quantities likely to be consumed with food are required to produce ill effects or cause the death of human beings or experimental animals. However, benzoic acid, one of the least harmful of food preservatives, should be avoided by persons with gastro-intestinal or renal diseases (7). Many attempts have been made to prepare compounds related to benzoic acid with even greater margins of safety in the preservation of food. For the purpose of comparing the effect of benzoic acid with that of certain of its substitution derivatives, a preliminary study of the acute toxicity of these compounds for white rats was undertaken.

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