A STUDY OF GLYCERIN SUPPOSITORIES.*,[1]

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INTRODUCTION.

The combination of glycerin and soap, melted and molded into suppositories was reported by the Pharmaceutical Society of Great Britain as early as 1873 (1). It was not, however, until 1890 that a monograph for Suppositories of Glycerin found its place in the Seventh Revision of the United States Pharmacopœia. This preparation is still widely utilized as is demonstrated by its retention in four revisions of the pharmacopœia.

In comparing the formulas of Suppositories of Glycerin in the four revisions of the Pharmacopœia, some few slight changes have been made. When monohydrated sodium carbonate replaced the dekahydrated sodium carbonate in the United States Pharmacopœia VIII, a similar change was made in the Suppository formula.

The United States Pharmacopœia.	VII.	VIII.	IX.	X.
Glycerin	60	30.0	30.0	80
Sodium Carbonate	3	..	..	..
Sodium Carbonate Monohydrated	..	0.5	0.5	2
Water	..	5.0	5.0	10
To Make Suppositories No.	10	10.0	10.0	30

EXCESS OF ALKALI IN VARIOUS FORMULAS FOR GLYCERIN SUPPOSITORIES.

It is interesting to note the excess of alkali employed in the manufacture of Glycerin Suppositories throughout many parts of the world. Several formulas have been compared and summarized in the following table:

United States Pharmacopœia, Seventh Revision:			
Sodium Carbonate	Actual	3.0	
	Theoretical	2.5	(ten suppositories)
	Excess	0.5	
United States Pharmacopœia, Eighth and Ninth Revisions:			
Sodium Carbonate Monohydrated	Actual	0.50	
	Theoretical	0.43	(ten suppositories)
	Excess	0.07	
United States Pharmacopœia, Tenth Revision:			
Sodium Carbonate Monohydrated	Actual	0.66	
	Theoretical	0.58	(ten suppositories)
	Excess	0.07	
Japan, Third Edition, 1907:			
Sodium Carbonate	Actual	3.00	
	Theoretical	2.51	(ten suppositories)
	Excess	0.49	

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British Pharmacopœia Codex, 1932:

Sodium Carbonate	Actual	1.50	
	Theoretical	1.25	(ten suppositories)
	Excess	0.05	

Norway (1913):

Sodium Carbonate	Actual	5.0	
	Theoretical	4.53	(ten suppositories)
	Excess	0.47	

Scoville (2) did extensive work on glycerin suppositories and his formula was adopted and became official in the United States Pharmacopœia X. The main objection to the present formula is that it does not always produce a transparent preparation.

There has been recommended a change in the present formula for Suppositories of Glycerin to be made in the forthcoming revision of the Pharmacopœia. The following formula was proposed:

Glycerin	91.00 Gm.
Sodium Hydroxide, 50 per cent	2.52 Gm.
Stearic Acid	9.00 Gm.
Monohydrated Sodium Carbonate	0.09 Gm.
Water	0.5 cc.

To make about 30 suppositories.

Place the glycerin in a suitable vessel and heat on a water-bath, keeping the vessel well immersed in the boiling water, until the temperature is about 85° C. Add the sodium hydroxide 50 per cent or its equivalent of an approximately 50 per cent solution to the hot glycerin with thorough mixing. Melt the stearic acid in a small vessel and pour at once into the hot alkaline glycerin mixture, stirring thoroughly. Maintain the temperature at from 85° C. to 90° C. for twenty to thirty minutes. Dissolve the monohydrated sodium carbonate in 0.5 cc. of distilled water, contained in a test-tube and add to the hot mixture just finished. Mix thoroughly, pour the melted mass into suitable molds. Remove the suppositories when they are completely cold and preserve in tightly stoppered glass vessels in a cool place.

One of the most important prerequisites of a United States Pharmacopœial formula is that wherever possible, it may be prepared easily by both the pharmacist and the manufacturer. When the above formula is critically examined, it will readily be seen that from the standpoint of small scale production, it presents serious difficulties. It is a well-known fact that the strength of sodium hydroxide cannot be relied upon. Consequently a titration must be carried out to determine its strength before it may be used. Obviously in using a strong alkali the slightest excess would greatly increase the alkalinity of the product. On the other hand, if an insufficient amount was used, the suppositories would be opaque.

The object of this study was to develop the most simple and efficient formula possible for the preparation of glycerin suppositories. Inasmuch as sodium stearate may now be obtained of a high degree of purity, it was thought that the most logical procedure would be to formulate the suppositories by the direct incorporation of sodium stearate with glycerin rather than attempt the chemical reaction in the mass. Such a method would eliminate all the inherent errors that must be guarded against wherever a chemical reaction is involved.

With this idea in mind, a series of experiments was conducted, *first*, to deter-

mine the feasibility of such a method, and *second*, a ratio of ingredients resulting in the most desirable product from the standpoint of clarity and consistency.

EXPERIMENTAL PART.

All the materials used in this study were carefully checked for their purity and strength. The sodium stearate (Merck) was found to contain no free alkali.

DETERMINATION OF CONTENT OF WATER.

The per cent of water present in the finished product was determined by the use of the Toluene Distillation Method. This method has been adopted for inclusion in the Eleventh Revision of the United States Pharmacopœia. Ten grams of the suppository mass was placed in a flask and sufficient toluene added to cover the mass completely. The receiving tube was filled by pouring the toluene through the top of the condenser. The toluene in the flask was heated until it boiled and distilled slowly, about two drops per second, until most of the water had passed over; then the rate of distillation was increased to about four drops per second. When all the water was apparently over, the condenser was washed down by pouring toluene in at the top and the distillation continued for a short time to ascertain whether or not any water remained in the flask. The receiving tube was allowed to stand at room temperature and the volume of water read and calculated to determine the percentage.

DETERMINATION OF CONSISTENCY OF THE SUPPOSITORY MASS.

The consistency of each suppository mass was determined by means of the Asphalt Penetrometer. The degree of penetration in the different masses was measured; time, temperature, pressure and volume of mass were held constant. The time chosen for the penetration was five seconds. A mass of twenty grams in weight was poured into a standardized cup of 3.5-mm. depth and 4.1-mm. diameter and allowed to solidify at room temperature.

DETERMINATION OF p_H.

The determination of p_H of each suppository mass was made colorimetrically. A definite quantity (two rectal suppositories) was melted in a standardized test-tube, the indicator added and then the mass allowed to cool. Comparison was then made in the usual manner with the proper color standards.

The following experiments were carried out to decide the optimum ratio of ingredients necessary to provide the most desirable product and furthermore to determine if an added amount of excess alkali was necessary to bring about the proper degree of clarity.

Exp. No.	Gm. Glycerin.	Gm. Sodium Stearate.	Gm. Sod. Carb. Monohyd.	p_H.	Per Cent Water.	*Consistency.	[1] Appearance.
A-1	90	10	0.1	9.8	2.1	9	O
A-2	90	10	..	9.8	2.0	12	O
B-1	91	9	0.1	9.8	2.2	12	O
B-2	91	9	..	9.8	2.0	14	O
C-1	92	8	0.1	9.8	2.4	18	T
C-2	92	8	..	9.8	2.4	18	T
D-1	93	7	0.1	9.8	2.6	25	FT
D-2	93	7	..	9.8	2.8	28	FT
E-1	94	6	0.1	9.8	3.0	35	VT
E-2	94	6	..	9.8	3.2	32	VT
F-1	95	5	0.1	9.8	3.4	40	VT
F-2	95	5	..	9.8	3.6	38	VT

* Relative figures obtained with the Asphalt Penetrometer.

[1] VT—Very Transparent. FT—Fairly Transparent. T—Transparent. O—Opaque. VO—Very Opaque.

On the basis of the above results: Group C was chosen as the ratio providing the best consistency. When smaller amounts of sodium stearate were used, the suppositories became somewhat clearer but in consistency, they were not sufficiently firm.

There was not enough difference in the clarity C-1 with added monohydrated sodium carbonate and C-2 to warrant its inclusion in the formula.

The probable explanation of the similarity in p_H of both formulas with and without added alkali lies in the absence of sufficient water to enable the hydrolysis of the carbonate to take place.

The following experiments were undertaken to determine the effect of increased amounts of distilled water upon the clarity of Glycerin Suppositories made with glycerin and sodium stearate.

To 100 Gm. of a melted mass consisting of 95 Gm. of glycerin and 5 Gm. of sodium stearate, the following amounts of distilled water were added and the results tabulated:

Expt. No.	Cc. Water Added per 100 Gm. Mass.	p_H.	Per Cent Water.	*Appearance.
A	1 cc.	9.5	5.2	FT
B	2 cc.	9.8	5.8	FT
C	3 cc.	9.8	6.0	FT
D	4 cc.	10.0	6.2	FT
E	5 cc.	10.0	6.5	T
F	6 cc.	10.2	6.6	T
G	7 cc.	10.2	6.8	O
H	8 cc.	10.2	6.9	O
I	9 cc.	10.5	7.0	VO
J	10 cc.	10.6	7.2	VO

* Symbols previously explained.

DETERMINATION OF THE HYGROSCOPICITY OF GLYCERIN SUPPOSITORIES.

A series of experiments was carried out with different Glycerin Suppositories in order to determine the hygroscopic properties over a period of time.

The suppositories were weighed and placed in a desiccator containing water to furnish a high relative humidity. At stated periods, the suppositories were removed, weighed and the increase in moisture content noted. Fairly consistent results were obtained as will be noted as follows:

U. S. P. X.		B. P. C., 1932.		Developed Formula.	
Glycerin	80.0	Glycerin	90.0	Glycerin	92
Sod. Carb. Monohyd.	2.0	Sod. Carb.	4.5	Sod. Stear.	8
Stearic Acid	8.0	Stearic Acid	7.5	Water	5
Water	10.0				

Time.	Gain in Weight.	Gain in Weight.	Gain in Weight.
2 hours	0.1201	0.1244	0.1216
4 hours	0.2101	0.1618	0.1764
6 hours	0.2491	0.2150	0.2243
10 hours	0.3751	0.3462	0.4032
24 hours	0.7739	0.4282	0.9883
30 hours	0.9027	0.8842	1.4652
48 hours	1.3345	1.2748	2.1574
1 week	3.2327	3.0092	3.2849

There was approximately an increase of 192 per cent moisture over the entire period of one week.

THE EFFECT OF PROLONGED HEATING OF THE SUPPOSITORY MASS.

The experiments were undertaken to determine the effect of prolonged heating of a suppository mass in a covered vessel (double-boiler). Ten-minute periods of heating at 95° C. elapsed between pouring of the mass, with the exception of the last period which was of an hour duration. The following formula was chosen for these experiments:

Glycerin	92
Sodium Stearate	8
Water	5

Ten-Minute Periods of Heating at 95° C.	Per Cent of Water at End of Each Pouring.
First	6.8 per cent
Second	6.4 per cent
Third	6.2 per cent
Fourth	6.0 per cent
Fifth	5.8 per cent
Sixth	5.6 per cent
Seventh	5.4 per cent
Eighth	5.2 per cent
Ninth (one hour of heating)	4.8 per cent

As was expected, the per cent of water gradually decreased until along about the sixth pouring, when the percentage remained fairly constant.

From the standpoint of clarity, consistency and ease of manufacture, the following formula was chosen as the most desirable to produce an ideal suppository for both adult and infant types:

Glycerin	92
Sodium Stearate	8
Distilled Water	5

To make about 30 rectal suppositories.

Heat the glycerin to 95° C. in a double boiler. Add the sodium stearate, stirring very gently occasionally until a clear solution is effected. Then add the distilled water, mix thoroughly and pour the mass into suitable molds. Remove the suppositories when they are completely cold and preserve them in tightly stoppered glass bottles in a cool place.

CONCLUSIONS.

1. A study has been made of various formulas which have been proposed for glycerin suppositories.
2. The difficulties encountered with certain formulas have been enumerated.
3. A new formula in which sodium stearate is directly incorporated with glycerin is submitted as a practical method for their preparation.
4. A comparison of the various characteristics of suppositories made by this method with those made by other methods is presented.

REFERENCES.

(1) *Am. J. Pharm.*, 45, 189 (1873).
(2) Scoville, Wilbur, JOUR. A. PH. A., 13, 818 (1924).