METHYLCELLULOSE AS A TROCHE BASE

by

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INTRODUCTION

Troches are a form of medication to be held in the mouth where they slowly dissolve, liberating the medicinal ingredients which exert a desired therapeutic effect on the mucous membranes of the oral cavity. They are not intended to be chewed or swallowed, but to be dissolved in the oral secretions, where the mucous membranes are bathed with the resultant solution for a considerable period of time. Troches are usually flat and hard, and may be round or oval shaped in form. They are generally made to weigh about 0.6 gram.

Although there are few official forms of this medication in the compendia, they enjoy wide employment as a proprietary form of medication which combines drugs that elicit antiseptic, astringent, or anesthetic actions.

Two methods are used for making troches. The first involves mixing the ingredients to form a pliable mass with a moistening agent. The mass is rolled flat and cut into round flat discs. On a commercial scale, power-driven machinery is used for both the rolling and cutting processes.

The second method involves procedures used in tablet making. These troches are made by compression. This method finds wide application in industry and is the method chosen for this research study.

Sugars, either granulated or powdered, comprise the base of most troches. Natural gums, acacia and tragacanth, as well as gelatins, are incorporated to give adhesiveness to the sugar base. The dry

sugars and gums are mixed. A binding agent, usually in solution, such as a 50 percent glucose solution, a 10-20 percent solution of the gums (acacia or tragacanth) or 10-20 percent gelatin, is added to the powders to form a dough-like mass. The mass is dry enough to crumble but moist enough to form a lump when pressed in the hand. The damp powders are then forced through a screen, spread out on a tray and placed in an oven to dry. After the drying is complete, the coarse granules are again passed through a screen of a mesh size commensurate with the size of the troche to be made. The granules obtained after this second screening operation are then mixed with a lubricant (talc, light mineral oil, calcium, or magnesium stearates, etc.) and are ready for the compression into a tablet form of troche.

Producing troches by tablet compression methods was followed throughout using the accepted procedures for tablet making with one exception, i.e., the elimination of a disintegrating agent from the formula for a troche. A disintegrating agent is a substance which is added to the tablet granulation to help break the tablet apart after administration or to hasten solution in water. Starch is used for this purpose as it absorbs water, causing tablets to burst. The disintegrating agent is eliminated because it would cause rapid breaking up of the troche. This would tend to promote solution and swallowing of the resultant particles with a loss of the desired characteristic of prolonged dissolution of the mass in the mouth.

A balanced formula for producing a good compressed troche must possess these essential properties[1,2]: (1) materials used should

be free flowing to fill the die cavity uniformly; (2) it should have binding properties; (3) it should compress into a hard troche without excessive pressures; (4) it must eject readily and not stick to the punches.

With a formula possessing such characteristics a finished troche should be produced which is very hard and possesses uniform weight and appearance. The combination of ingredients that can be processed to yield the properties outlined, should also dissolve slowly, release any medicament over a longer time period and increase the viscosity of the oral fluid[3,4] when administered as a therapeutic agent. The increase in viscosity of the oral secretions by the base enhances the spread of the dissolved drug in the areas of the mouth. This results from the drug's remaining at the site over a longer period as the resistance to flow or wash away is reduced by the increase in viscosity of the salivary secretions.

The commonly used formulas utilizing sugars, gelatin and mucilages for troche bases do not fully meet the requirements listed above[3,4,5]. Methylcellulose, a synthetic gum, with its controlled viscosity types and inertness, seemed to possess properties for improvement over the usual sugar types.

Seven viscosity types of methylcellulose*, official in the National Formulary IX, possess the unique properties of giving a uniform viscous final product when dissolved in water and are stable over a wide pH range from pH 2 to 12. Methylcellulose solutions are

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* Methylcellulose is available from the Dow Chemical Co., Midland, Michigan, as "Methocel".

neutral, colorless, tasteless, completely inert[5-8], stable to light, heat, and aging, and retain their viscosity over the wide pH range previously mentioned. It was decided that methylcellulose should be investigated to determine whether a product could be obtained which would possess the properties previously outlined for an ideal compressed troche base.

EXPERIMENTAL

Formulation and Methods of Preparation.

The methylcellulose used in formulation of various troches was in the form of a moderately coarse white powder (40 mesh particle size) of the viscosity types 15 cps, 25 cps, 50 cps, 100 cps, 1500 cps, and 4000 cps. Each type was assigned the following letter designations for batch number controls:

I	MC-T 15	Methylcellulose	15 cps
II	MC-T 25	"	25 cps
III	MC-T 50	"	50 cps
IV	MC-T 100	"	100 cps
V	MC-T 400	"	400 cps
VI	MC-T 1500	"	1500 cps
VII	MC-T 4000	"	4000 cps

The Model E* single punch tablet compression machine, using a 1/2-inch standard concave punch and die assembly adjusted to make 0.5 gram troches, was used throughout this study.

Direct Compression Method.

The procedure used for direct compression was to compress each methylcellulose viscosity type directly in the tablet compression machine, after weighed amounts had been dried in an oven at 38° - 40° C. The troche obtained by this first compression would be in a rough

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* F. J. Stokes Machine Company, Philadelphia 20, Pennsylvania.

form of tablet or "slug". The "slugs" are then broken down into a granulation of uniform size that is then compressed into finished troches.

This procedure was carried out with the methylcellulose types listed above, without the addition of any moistening agent or lubricant. The above procedure was also attempted with the seven viscosity types of methylcellulose with the addition of several lubricants, i. e., on three different runs with 3 percent Talc, 3 percent Calcium Stearate and 3 percent Stearic Acid.

It was found that, with or without a lubricating agent, none of the batches could be compressed into a suitable "slug". They had poor flow characteristics causing bridging of the powders in the hopper and shoe (feed and ejection mechanism of the tablet machine). It was apparent that methylcellulose was not applicable to the pre-compression method of tableting.

Direct compression was then attempted using 70 percent methylcellulose, 25 percent Superfine Granulated Sugar and 5 percent Magnesium Trisilicate. The procedure, essentially the same as above, was used to compress the mixture directly into a finished troche.

The troches prepared by this formula seemed to be satisfactory, as indicated in Table I.

TABLE I.

Characteristics of Compression of Methylcellulose Troche Base Formulas

Batch No.	Flow	Compression	Ejection	Appearance of Troche
MC-T 15	Good	Hard troche with minimal pressure	Good	Smooth
MC-T 25	Good	Hard troche with minimal pressure	Good	Smooth
MC-T 50	Good	Hard troche with minimal pressure	Good	Smooth
MC-T 100	Poor	Hard troche with maximum pressure	Good	Smooth
MC-T 400	Very poor	Not compressible with maximum pressure	Very poor	Rough
MC-T 1500	Very poor	Not compressible with maximum pressure	Very poor	Rough
MC-T 4000	Very poor	Not compressible with maximum pressure	Very poor	Rough

Wet Granulation Method.

A weighed amount of methylcellulose and powdered sugar was dried in an oven at 38° - 40° C. for six hours. Granulating solutions were added to dampen the mixed powders, using distilled water in the first series of batches. In subsequent trials a 2 percent methylcellulose solution corresponding to the viscosity type used in the formula and a 50 percent glucose solution were used as the granulating agents. The moistened mixtures were forced through a No. 8 mesh screen, spread out in a thin layer and placed in an oven at 35° - 38° C. until dried. The dried granules were then forced through a No. 14 mesh screen and lubricated. Each batch was then compressed in the tablet machine.

This general procedure was then carried out with the seven different viscosity types of methylcellulose using 3 percent Calcium Stearate as a lubricant. The amount of powdered sugar in this basic formula was varied at 0, 25, 50, and 60 percent for each viscosity type.

It was found that all of the troches made by the wet granulation method were too soft, crumbling with slight pressure of the fingers. The troches were greyish-white in color and none were uniformly smooth. It was also found that maximum pressure of the tablet machine was required to punch these troches. It was apparent that the wet granulation method did not seem to be the best procedure for making a compressed troche.

Controls.

To serve as controls in the testing procedures, two sugar base troches were produced by the same tablet machine used in making the

methylcellulose base troches. The formulas were obtained from two sources[1,2], each utilizing the general sugar base formulas commonly employed at the present time.

The first formula, designated PSG-T 1, consisted of:

Powdered Sugar	435.0 grams
50 percent Glucose Solution	q.s.
Calcium Stearate	4.5 grams

and was made by forcing the powdered sugar through a No. 40 mesh screen to break down lumps and remove foreign matter. The sugar was weighed and dampened with the glucose solution. The moistened mass was then forced through a No. 8 mesh screen and spread out in a thin layer and placed in an oven at 37° - 39° C. After drying, the coarse granules were forced through a No. 14 mesh screen and mixed with the calcium stearate; it was then compressed.

This formula had good flow characteristics. The tablet machine, however, required constant attention with frequent checks and adjustments to maintain uniformity in weight. The ejection properties were fair, indicating the need for more, or a change of, lubricant used. The finished troche had a smooth glossy surface free of pits.

The second sugar base troche, SA-T 1, consisted of:

Sucrose	465.0 grams
Powdered Acacia	15.4 grams
20 percent Acacia Solution	q.s.
Talc	15.4 grams

and was made by weighing the sugar and powdered acacia and mixing in a tumbling mixer for thirty minutes. The mixture was then moistened

with the 20 percent acacia solution, the mass then forced through a No. 8 mesh screen, and spread out in a thin layer and dried in an oven at 37° - 39° C. The dried granulation was then forced through a No. 14 mesh screen and lubricated with the talc. The mixture was then compressed into troches.

The above formulation had good flow characteristics. Difficulties were experienced in the ejection of the troches. There was some binding and lamination after ejection. As with formula PSG-T 1, constant checking and adjustment of the machine for weight of the troche was found necessary. The final appearance of the troche was satisfactory.

EVALUATION

The methylcellulose batches which seemed to make a suitable troche by the direct compression method, as shown in Table I, were MC-T 15, MC-T 25, MC-T 50, and MC-T 100. These were chosen to be evaluated against the standard sugar base types made by the wet granulation procedures.

The MC-T 400, MC-T 1500, and MC-T 4000 were not satisfactory and were eliminated from the evaluation studies to follow.

Tests included in the evaluation of the troches were for hardness, release of phenolsulfonphthalein, viscosity, and *in vitro* and *in vivo* dissolution times.

Hardness

Hardness is the physical property of compressed dosage forms which is a measure of resistance to chipping, abrasion, or breakage under conditions of storage, transportation and handling before usage[8]. The Strong-Cobb Hardness Tester* [9] was used to obtain an indication of the relative degree of hardness for each batch of troches. With this instrument, the degree of hardness is measured on an arbitrary scale and is the force required to break a tablet. The range of the gauge is from 0 to 28. A reading near the maximum hardness of the gauge was desired for the troches. With this degree of hardness, troches cannot be readily broken with the fingers or

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* Strong-Cobb Company, Incorporated, Cleveland, Ohio.

when shaken in a container. This would seem to indicate that the troches would be sufficiently hard to meet the requirements as defined for the property of hardness. The results of this test are presented in Table II, representing an average reading for 40 troches selected at random from each batch.

Table II

Strong-Cobb Hardness Tester

Readings

	MC-T 15	MC-T 25	MC-T 50	MC-T 100	PSG-T 1	SA-T 1
Percentage Break of Each Sample at the Average Gauge Reading	0	0	30	60	100	100
Average Gauge Reading	28	28	25	23	16	5

It has been demonstrated in Table II that the methylcellulose troches all possessed higher degrees of hardness as compared to the sugar base troches.

Release of Phenolsulfonphthalein From the Various Bases.

A colorimetric procedure[10] was adopted for determining the amount of phenolsulfonphthalein released at various intervals from the different troche bases. Before compressing each batch a weighed amount (50 grams) of the base was mixed with 50 milligrams of phenolsulfonphthalein which had been passed through a No. 80 mesh screen before weighing. With the completion of the compression procedure for each

type of the troches made, a portion of the formula containing the dye was then compressed. Thus, each troche base containing the dye was compressed with the same pressure adjustment of the tablet machine for each batch.

A constant temperature of 37° C. was maintained by the use of a heating mantle, regulated by a variac. The mantle was secured to a mechanical shaker*, which agitated the troches placed in a 500 milliliter flask held in place in the heating mantle.

From preliminary tests, it was determined that for the methylcellulose troches a time interval of 5 minutes for removing aqueous samples would be satisfactory for determining the amount of dye released. It was also determined that the sugar base troches, which dissolve more rapidly, would require for PSG-T 1 and SA-T 1, a one minute and a 45 second time interval, respectively, for collection of samples.

A random sample of 12 troches was taken from each batch containing the incorporated dye. The sample was placed in a 500 milliliter flask to which 30 milliliters of distilled water at 37° C. was added, and the flask shaken for the time interval previously determined for the batches. The 37° C. temperature was maintained during the agitation by the heating mantle. The aqueous portion was drawn off after agitation for the specified time and treated drop-wise with a 10 percent sodium hydroxide solution until maximum red color was developed. The sample was then diluted to one liter with distilled

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* Eberbach Corporation, Ann Arbor, Michigan

water, mixed thoroughly, and 10 milliliters placed in a colorimetric tube, 18 mm. outside diameter, and reserved for subsequent reading in the Lumetron Photoelectric Colorimeter*. The procedure of adding 30 milliliters of distilled water, agitating the samples on the mechanical shaker and reserving the 10 milliliter sample in the Lumetron tube was continued until all of the troches were dissolved. Each sample was read for percent transmission, and the milligrams of the dye released were obtained from a calibration card opposite the reading for percent transmission. The colorimeter was operated on ordinary house current stabilized by means of 110 volt 60 cycle voltage stabilizer.

A colorimeter tube containing a troche dissolved in distilled water was used as a blank to adjust the colorimeter. A series of 5 determinations was taken for each of the batches. The results were tabulated showing the cumulative weight of phenolsulfonphthalein recovered over the time interval for each sample of 12 troches for the 5 determinations of each batch, with an average weight in milligrams calculated for one troche. These are presented in Tables III - VIII inclusive.

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* Model 400-A, Photovolt Corporation, New York, N.Y.

Table III

Batch No. MC-T 15

Cumulative Weight in Milligrams of Phenolsulfonphthalein Released During 5 Minute Intervals for 12 Troches per Sample With a Cumulative Weight Average for 1 Troche*.

	Minutes							
Sample No.	5	10	15	20	25	30	35	40
I	0.3	0.9	1.7	2.4	3.1	3.8	4.3	4.6
II	0.7	1.6	2.4	2.7	3.4	4.0	4.4	5.0
III	1.1	2.2	3.1	3.8	4.4	4.9	5.2	5.4
IV	0.9	2.2	3.2	3.9	4.4	4.7	4.9	5.1
V	0.5	1.0	1.7	2.6	3.4	4.0	4.5	4.8
Total	3.5	7.9	12.1	15.4	18.7	21.4	23.3	24.9
Cumulative Average Weight (mg.) for 1 Troche	0.06	0.13	0.20	0.26	0.31	0.36	0.39	0.41

* Each troche contained approximately 0.5 milligram phenolsulfonphthalein.

Table IV

Batch No. MC-T 25

Cumulative Weight in Milligrams of Phenolsulfonphthalein Released During 5 Minute Intervals for 12 Troches per Sample With a Cumulative Weight Average for 1 Troche*.

	Minutes							
Sample No.	5	10	15	20	25	30	35	40
I	0.7	1.7	2.8	3.7	4.6	5.3	5.5	5.7
II	0.6	1.5	2.6	3.4	4.2	4.8	5.2	5.5
III	0.6	1.8	2.8	3.7	4.6	5.3	5.8	6.0
IV	0.5	1.5	2.4	3.3	4.1	4.8	5.3	5.6
V	0.6	1.7	2.8	3.7	4.5	5.2	5.8	6.0
Total	3.0	8.2	13.4	17.8	22.0	25.4	27.6	28.8
Cumulative Average Weight (mg.) for 1 Troche	0.05	0.14	0.22	0.30	0.34	0.42	0.46	0.48

* Each troche contained approximately 0.5 milligram phenolsulfonphthalein.

Table V

Batch No. MC-T 50

Cumulative Weight in Milligrams of Phenolsulfonphthalein Released During 5 Minute Intervals for 12 Troches per Sample With a Cumulative Weight Average for 1 Troche*.

	Minutes					
Sample No.	5	10	15	20	25	30
I	0.8	1.9	3.0	4.1	4.9	5.2
II	0.8	2.2	3.4	4.5	5.3	5.7
III	0.7	2.0	3.2	4.4	5.3	5.7
IV	0.9	2.3	3.8	4.9	5.7	6.0
V	0.7	1.9	3.1	4.1	5.0	5.6
Total	3.9	10.3	16.5	22.0	26.2	28.2
Cumulative Average Weight (mg.) for 1 Troche	0.06	0.17	0.28	0.37	0.44	0.47

* Each troche contained approximately 0.5 milligram phenolsulfonphthalein.

Table VI

Batch No. MC-T 100

Cumulative Weight in Milligrams of Phenolsulfonphthalein Released During 5 Minute Intervals for 12 Troches per Sample With a Cumulative Weight Average for 1 Troche*.

	Minutes					
Sample No.	5	10	15	20	25	30
I	0.5	1.4	2.4	3.5	4.4	5.0
II	0.3	1.3	2.4	3.4	4.3	4.8
III	0.7	1.8	3.0	4.1	4.8	5.1
IV	0.7	1.9	3.3	4.6	5.3	5.5
V	0.7	2.1	3.4	4.6	5.5	5.7
Total	2.9	8.5	14.5	20.2	24.3	26.1
Cumulative Average Weight (mg.) for 1 Troche	0.048	0.14	0.24	0.34	0.41	0.44

* Each troche contained approximately 0.5 milligram phenolsulfonphthalein.

Table VII

Batch No. PSG-T 1

Cumulative Weight in Milligrams of Phenolsulfonphthalein Released During 1 Minute Intervals for 12 Troches per Sample With a Cumulative Weight Average for 1 Troche*.

	Minutes			
Sample No.	1	2	3	4
I	2.7	4.7	5.6	5.8
II	2.3	4.1	5.0	5.2
III	2.1	3.7	4.6	4.8
IV	2.7	4.8	5.7	5.9
V	2.2	3.9	4.6	4.8
Total	12.0	21.2	25.5	26.5
Cumulative Average Weight (mg.) for 1 Troche	0.20	0.35	0.43	0.44

* Each troche contained approximately 0.5 milligram phenolsulfonphthalein.

Table VIII

Batch No. SA-T 1

Cumulative Weight in Milligrams of Phenolsulfonphthalein Released During 45 Second Intervals for 12 Troches per Sample With a Cumulative Weight Average for 1 Troche*.

	Seconds			
Sample No.	45	90	135	180
I	2.6	4.6	5.7	6.0
II	2.8	4.7	5.7	6.0
III	2.3	4.0	4.9	5.1
IV	2.4	4.2	5.4	5.7
V	2.3	3.9	4.8	5.0
Total	12.4	21.2	26.5	27.8
Cumulative Average Weight (mg.) for 1 Troche	0.21	0.35	0.44	0.46

The cumulative weight averages of milligrams of phenolsulfonphthalein released were plotted against the time required for complete solution of a compressed troche. These are shown in Figures 1 and 2.

* Each troche contained approximately 0.5 milligram phenolsulfonphthalein.

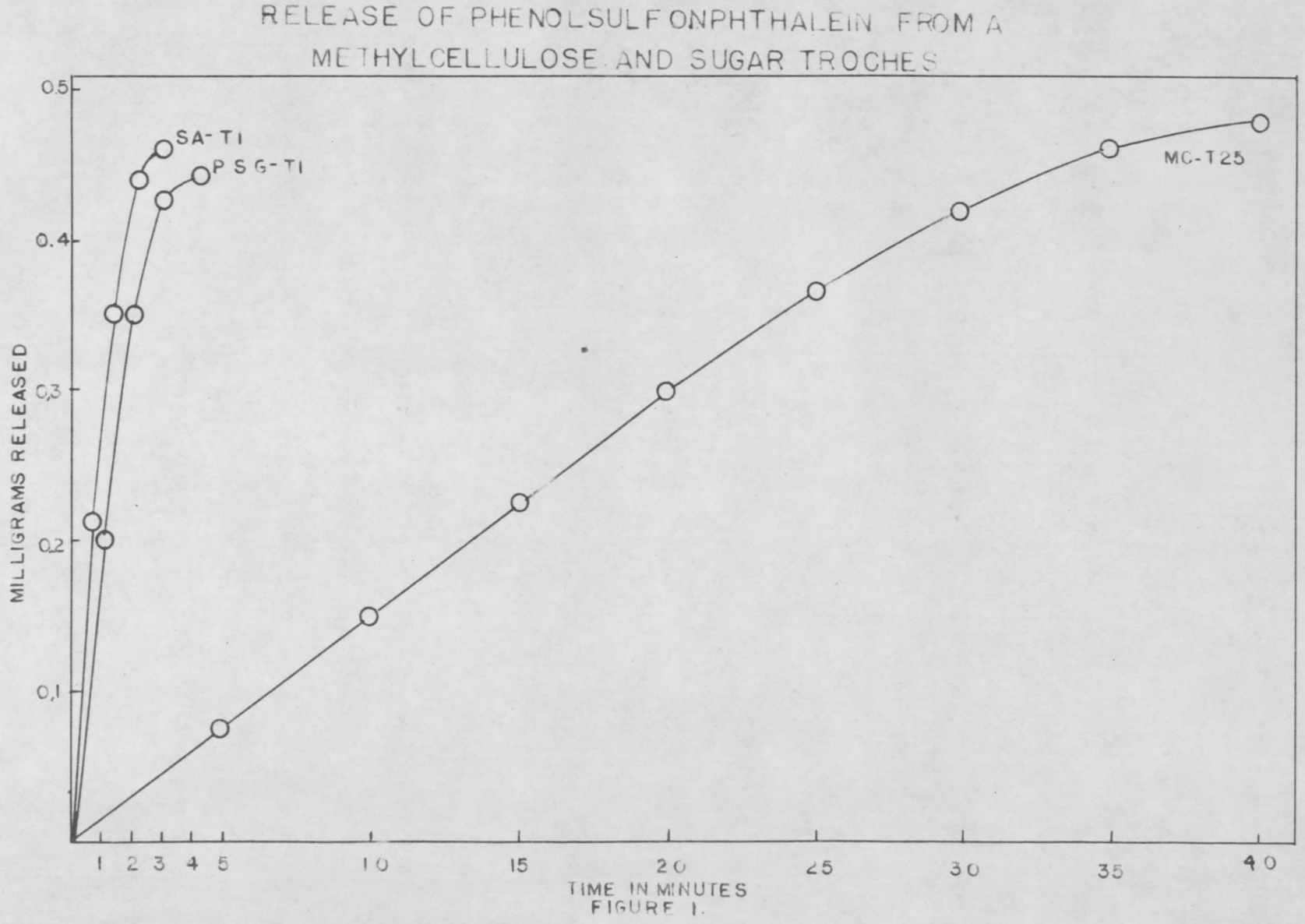
RELEASE OF PHENOLSULFONPHTHALEIN FROM A
METHYLCELLULOSE AND SUGAR TROCHES
MILLIGRAMS RELEASED
0.5
0.4
0.3
0.2
0.1
SA-TI
PSG-TI
MC-T25
1 2 3 4 5 10 15 20 25 30 35 40
TIME IN MINUTES

FIGURE 1.

RELEASE OF PHENOLSULFONPHTHALEIN FROM METHYLCELLULOSE TROCHES

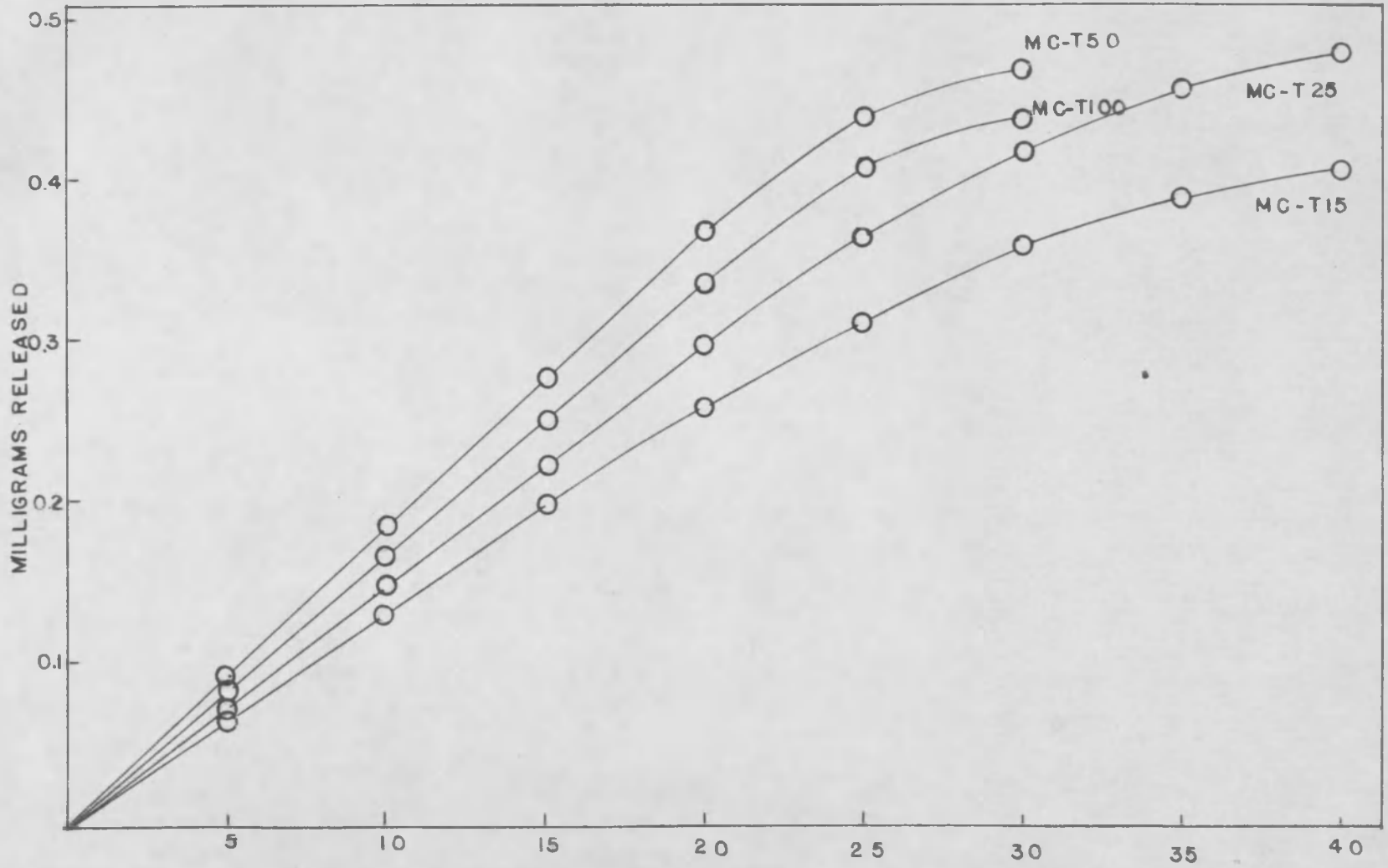

FIGURE 2.

As shown in Figure 1, the methylcellulose troches released the phenolsulfonphthalein over a longer period of time. The lower viscosity type, MC-T 25, lasted 40 minutes as compared to the powdered sugar bases, SA-T 1 and PSG-T 1, which lasted 3 and 4 minutes respectively.

The ratio of a methylcellulose troche to a sugar troche for duration of release of the dye, therefore, was at least 10 to 1, comparing the best of each type of troche base as illustrated in Figure 1.

Viscosity Produced by Dissolution of the Various Troches.

With an increase in the viscosity of the oral secretions caused by the dissolving of a troche base, a drug so released is held at the site of the areas being treated for a longer time and a greater spread of the drug in the oral cavity is obtained.

Since the change in viscosity of oral fluid[4] is effected by the base of a troche, it was decided to make viscosity determinations under the same conditions used for the colorimetric determinations.

The mechanical shaker, heating mantle and constant temperature of 37° C. were used to agitate 50 troches from each batch in 125 milliliters of distilled water for two and one-half minutes. The aqueous solutions were maintained at 37° C. while densities were determined using a Mohr-Westphal balance. The density readings are presented in Table IX.

Table IX

Densities for Solutions of Troche Batches and Distilled Water at 37° C.

Batch No.	Densities
MC-T 15	0.998
MC-T 25	0.9985
MC-T 50	0.999
MC-T 100	1.002
PSG-T 1	1.057
SA-T 1	1.0575
Distilled Water	0.993

An Ostwald-Fenske Viscosimeter*, D 393, size 300, was used for viscosity determinations. A constant temperature (37° C.) water bath was provided with a bracket to hold the viscosimeter submerged. The bath was equipped with glass sides presenting an unobstructed view of the viscosimeter.

The viscosimeter was calibrated by using the known values[11] for distilled water at 37° C.; the time in seconds for distilled water to pass from the upper mark to the lower mark of the viscosimeter was determined. Using the formula[12]

* Kimble Glass Co., Toledo, Ohio.

$v = kdt$,

where v = viscosity of the liquid in centipoise

k = specific gravity of the liquid

t = time in seconds

The viscosimeter constant k for the viscosimeter used was found to be

$$k = \frac{0.6947}{(0.993)(4.6)}$$

$$k = 0.1513$$

For the calibration of the viscosimeter 10 milliliters of distilled water was used in the instrument. In the subsequent determinations for the various batches of troches, identical volumes of 10 milliliters were used in each test. The time in seconds for the liquids to pass from the upper to the lower mark of the viscosimeter was recorded by the use of a stop watch. After introducing the 10 milliliters of solution into the viscosimeter, the instrument was lowered into the constant temperature bath and allowed to remain for 10 minutes to assure the solutions were at 37° C. A trial series of time runs were made for practice on each solution tested, followed by four recorded runs, the average of which was used for the calculation of the viscosity for each batch. The results are shown in Table X.

Table X

Viscosities (Centipoises) of Solutions of Troches After Shaking in Distilled Water for $2\frac{1}{2}$ Minutes at 37° C.

MC-T 15	MC-T 25	MC-T 50	MC-T 100	PSG-T 1	SA-T 1
1.993	2.295	2.418	17.838	0.891	1.080

The viscosities of solutions for the several troches made indicate that the methylcellulose types all produced solutions of a higher viscosity than the sugar base troches.

Dissolution Time for the Various Troches.

The approximate time of dissolution was found by *in vitro* and *in vivo* studies. The approximate time required for the troches to completely dissolve at a temperature of 37° C. was found by using the mechanical shaker. A 500 milliliter flask containing a troche in 90 milliliters of distilled water was placed in the heating mantle. The time was recorded from the start of the shaking operation until the troche was dissolved. The troches were selected at random from each batch and the average time taken for 5 determinations for each batch. The results of the dissolving time by mechanical agitation are shown in Table XI.

Table XI

Average Time in Minutes for Dissolution of a Troche by Mechanical Agitation in Distilled Water at 37° C.

MC-T 15	MC-T 25	MC-T 50	MC-T 100	PSG-T 1	SA-T 1
30	35	28	28	3	2.5

The *in vivo* study was carried out with a group of 30 students who were given samples of the compressed troches. They knew mothing of the composition of each of the samples distributed. They were instructed to place the troche on the tongue and allow it to dissolve. In the group of 30, 5 individuals were testing samples of the same type troche bases. The author supervised the testing and recorded the time when the troches were completely dissolved. In Table XII the results are presented as the average time for dissolution of the various troche bases tested.

Table XII

Average Time in Minutes for Dissolution of a Troche by Humans

MC-T 15	MC-T 25	MC-T 50	MC-T 100	PSG-T 1	SA-T 1
51	53	30	53	4.5	4.4

By comparing the times of dissolution of a methylcellulose (MC-T 25) and a sugar (PSG-T 1) troche, in both the *in vitro* and *in vivo* studies, it is apparent that the methylcellulose troche lasted 10 times as long as a sugar type troche.

DISCUSSION

A procedure for the manufacture of compressed troches with a methylcellulose base has been presented. The method consisted of determining by experimental procedures how methylcellulose, in the form of a moderately coarse powder, should be processed in order that a suitable troche could be produced by compression.

Of the seven viscosity types of methylcellulose used, the higher viscosity types, the 400 cps, 1500 cps, and 4000 cps were not adaptable for compression using the standard formula developed because they did not possess the property of flowing readily into the feed mechanism of the tablet machine and could not be compressed. The lower viscosity types were all found to have the property of flowing in this powdered form. The problem was to process the powders to enable the material to flow readily from the hopper and feed mechanism of the tablet machine into the die cavity, in the same amounts each time, to give a uniform weight of the troche throughout production. It was required that the material have the properties of compressing into a sufficiently hard product to enable it to withstand the handling of packing and shipping, as well as to maintain its form during dispensing and administration. It was also required that the material be compressible without the use of excessive pressures and be readily ejected after compression. The final appearance was to be smooth, even, without surface markings, and free of adherent powders.

The crystalline nature of sucrose possessed the ability of supplying the necessary flow characteristic when mixed with the methylcellulose powders. Sucrose produces harder tablets, and as a base it will harden with age[2]. These properties were desirable, and the use of sugars in the formulation was not entirely discarded. It was found that the sucrose facilitated the flow and compressibility of the formulations when used as the binding agent for the methylcellulose.

The method of processing--simply mixing weighed quantities of methylcellulose and the binder, superfine powdered sugar, followed by the addition of a lubricant, magnesium trisilicate, with necessary mixing to assure complete distribution throughout the mixture--required minimum equipment. Of equal importance was the reduction in time and the number of steps necessary to prepare the mixtures for the compressing operation. Difficulty was experienced with the sugar base troches in maintaining uniform weight and ejection of the troches from the machine. The sugar base troches were both made by the wet granulation method. This method required the use of additional equipment and two screening operations which involves both time and labor. The method of manufacture of the methylcellulose base troches, in addition to producing a product comparable in appearance and other physical characteristics desired, is also favorable in effecting savings in time, labor, and equipment necessary to produce a satisfactory product. It has been established that synthetic gums are not suitable for producing a tablet form of medication utilizing the wet granulation methods.[5]

The choice of lubricant for the methylcellulose troches varied from the chemicals generally used. Magnesium trisilicate was chosen for its property of providing greater motility to the mixture of the methylcellulose and sugar. The use of this material for a lubricant was determined after experimental tests were made using the more common substances, such as talc, stearic acid, and magnesium and calcium stearates. Magnesium trisilicate is also completely innocuous when it is taken by mouth[13].

The testing procedures adopted were devised to compare the physical properties of the methylcellulose and presently used sugar troches. The methods, with the exception of the determination using humans for the dissolution time, employed mechanical devices to eliminate any bias or variability that may be present when physiological agents are used for testing purposes. All tests were prefaced by trial runs to standardize the procedures to insure the identical treatment of each batch of troches as tested by the various methods described.

Tests conducted for the property of hardness indicate that the methylcellulose base is capable of being readily controlled to produce a product of a desired hardness as tested with the Strong Cobb hardness tester. The data collected shows that methylcellulose troches had hardness readings of 23, 25 and greater-than-28 on the gauge for the different viscosity type troches, as compared to the two sugar base troches which had hardness readings of 16 and 5.

Preliminary work using this testing machine on commercial varieties of troches showed that the degree of hardness varied with

the manufacturer, from hardness readings of 8 up to the maximum reading on the Strong Cobb hardness tester.

The colorimetric determination to ascertain the duration of release of phenolsulfonphthalein shows that methylcellulose bases are capable of prolonged release of the dye (see Figure 2). The curves in Figure 1 compare a methylcellulose troche with the two sugar base types and show that the methylcellulose troche released the dye more slowly and over a greater period of time.

It is of interest to compare the average time of complete solution, shown by the in vivo study for the methylcellulose and the sugar base troches, which were 45 and 4½ minutes, respectively. This indicates that one methylcellulose troche is equivalent on a time basis to 10 of the sugar type troches. The total effect of 10 sugar troches could be obtained from one methylcellulose troche, by increasing the concentration of the medicinal ingredient in the latter.

SUMMARY

A method has been presented for preparing methylcellulose, as a moderately coarse powder, for compression into a tablet form of troche using a tablet compression machine.

Seven viscosity types of methylcellulose were processed for making a compressed troche using a standard formula. Of the seven viscosity types used, the lower viscosity types, 15, 25, 50 and 100 cps, were compressed into satisfactory products, while the higher viscosity types, 400, 1500 and 4000 cps, were not compressible.

Sugar and sugar-gum base troche types were made using standard techniques to serve as controls for comparative tests with the methylcellulose troches.

Tests for hardness, duration of release of phenolsulfonphthalein, viscosity and dissolution time were made.

In the test for hardness the methylcellulose troches were compressible to the attainment of maximum gauge readings of 28 on the Strong Cobb tablet hardness tester, as compared to only 16 for the hardest sugar base troche.

For the test of duration of release of phenolsulfonphthalein, the methylcellulose troches released the dye over a time period 10 times greater than that of the sugar troches.

The methylcellulose troches when dissolved in distilled water were found to yield solutions more viscous than those of the sugar base types, and in the tests for the time of dissolution using

in vitro and *in vivo* methods, the ratio of methylcellulose to sugar type troches was 10 to 1.

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