The Manufacture, Solubility and Stability of Hypodermic Tablets Containing Morphine Salts

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DEDICATION

The author dedicates this thesis to the memory of Dr. Andrew G. DuMez,* Dean of the School of Pharmacy, University of Maryland, from 1926 to 1948, who devoted his lifetime to the service of the profession of Pharmacy, and who initially approved the choice of the problem reported here.

* Died September 27, 1948.

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INTRODUCTION

Discoloration and slow solubility of hand molded hypodermic tablets containing morphine salts have long presented a problem to the manufacturing and dispensing pharmacist. Since 1861, when Dr. Robert M. Fuller (1) of Philadelphia first introduced the hand molded tablet triturate, undesirably discolored tablets have appeared on the market. The doctor and the nurse, who administered the tablets by hypodermic injection, experienced a delay in the administration of the drug because of the slow solubility of the tablet. The disturbance of the patient, psychologically at least, when confronted with a poorly made or grossly discolored tablet was another consideration.

An interest in studying this problem was influenced by three factors. The first was the appearance of unsatisfactory tablets in general practice. The second was experience in the manufacture of hand molded hypodermic tablets in industry. The third was encountered in the literature.

The difficulties encountered by technicians in the manufacturing field were observed in a pharmaceutical plant. Most alkaloidal salts when incorporated into tablets presented no problem. In working with morphine salts, however, varying degrees of discoloration were a common occurrence. The tablet composed of two morphine salts and scopolamine hydrobromide, the Schlesinger formula, showed discoloration shortly after the manufacture of the tablet.

In the plant attention also was given to the development of a tablet which would dissolve more readily in water than those formerly manufactured. The usual base (diluent), #100 powdered lactose, was replaced, first by beta-lactose and then, by "impalpable" lactose, a #170 powder. The finished product made with the "impalpable" lactose was smoother but the

tablets containing beta-lactose appeared to dissolve more readily. This difference is consistent with the fact that beta-lactose is more than twice as soluble as lactose (19).

All hand molded hypodermic tablets manufactured did not always discolor and become less soluble. Generally, hypodermic tablets containing salts of morphine were the prime offenders, with the Schlesinger tablet requiring greater study than the others.

The difficulties of discoloration and slow solubility have been reported in the literature. Malpass (2) outlined the methods of attack on the problems confronting the pharmaceutical worker engaged in tablet research. He recommended that research unhampered by the control laboratory or production staff was the only means of making real progress in the improvement of this important form of medication. At the time of his investigations, he found a dearth of literature on the subject. The literature is still scanty, probably because most manufacturers are unwilling to publish techniques which, since they were learned at an expense of both time and money, are treasured among their trade secrets.

The present study was undertaken in an effort to devise a technique for preparing hypodermic tablets containing morphine salts in such a manner that the tablets would be stable in color and readily soluble in water.

HISTORY

A review (3) of the history of tablet making shows that the two general methods of manufacture, compression and molding, have somewhat similar lines of evolution. In the beginning compressed tablets were made by subjecting the relatively dry medicament to compression in a suitable hand or power press. No foreign substance was added to give adhesiveness or bulk. Only substances adapted for compression in this way were employed. Gradually, however, as tablets grew in favor, it became desirable to compress other drugs. It was found necessary to add diluents and excipients to give the ingredients sufficient bulk and adhesiveness. At present, while some compressed tablets contain medicaments alone, most of the tablets upon the market contain medicaments, diluents and excipients.

In preparing molded tablets, the active drug was usually first mixed with lactose, the mixture made into a suitable mass with some liquid, and the moistened material pressed into molds. The molded forms of wet mixture were subsequently ejected as tablets and dried. Tablets made in this manner were usually designated as tablet triturates.

Some form of adhesive or excipient and some degree of pressure is used in both cases. Most tablets are made by one or the other of these methods. Today, tablets prepared by compressing relatively dry granules are called compressed tablets. Tablets prepared by pressing a moistened mixture into a suitable mold are called molded tablets. The homeopathic profession (6) has for years been using triturations and medications in the form of pellets which are saturated with liquid preparations and are called "tablet saturates."

The tablet triturate is an American idea. It is a direct ancestor of the hypodermic tablet (4). Kebler (5) conducted an investigation of

the evolution of the tablet. His paper presents Fuller as the originator of the tablet triturate, although Piffard (6), a contemporary, first recorded the compression of triturates into convenient doses.

Fuller's first paper (1) described "soluble tablets," "tablet triturates" and "tablet saturates." His "soluble tablets" were made by diluting the drug with lactose, moistening the mixture with alcohol or water and molding it into a form. He prepared "tablet saturates" in a manner similar to the one used by the homeopathic pharmacist.

His next paper (7) was an amplification of the work described earlier with a description of another form of tablet mold.

The term, hypodermic tablet, as it will be used in this paper, is defined as a hand molded tablet of water soluble ingredients, a solution of which is intended for injection. Sperandio and DeKay (8) reported that compression of a completely water soluble tablet is possible. They used aminoacetic acid as the diluent and found it to be satisfactory for most hypodermic tablets. According to their work, powdered boric acid in 12 per cent concentration was a satisfactory lubricating agent for aminoacetic acid granulations containing various medications.

The information found in the literature for the preparation of hypodermic tablets left many of the details to the individual worker. Bower (9, 10) investigated the factors causing variations in tablet yield. He reported that fineness of diluent, character of excipient and physical condition of the workman all influenced tablet yield.

Smithers (11) contributed a study of the manufacture of hand molded tablets. He made a survey of the methods in the literature and in the texts and studied in the laboratory the effect of variation of the alcohol

strength of the molding solution. He also determined the solubility of tablets molded with alcohol solutions of the following strengths: 25 per cent, 50 per cent, 75 per cent and 90 per cent. His tablet triturates consisted of lactose with small quantities of active ingredient. In all cases white tablets were obtained, but the yield, consistency and solubility varied. The yield was influenced by the volume of solution used in molding the tablets. The consistency of the tablets was most satisfactory when molded with 25 to 50 per cent alcohol (v/v), but 50 per cent alcohol was most suitable since the tablets made with this concentration of alcohol dried more quickly. Alcohol content of molding solution and temperature of drying the tablets affected the solubility. Smithers concluded that a low drying temperature, i.e. 45 to 60°C., was the most desirable for a satisfactory tablet.

The general outline of the method for preparing tablet triturates is well known, but details vary in different standard texts (4, 12, 13). Apparently the process for making hand molded tablets has changed very little since its inception. There is agreement that the tablet should permit (a) almost immediate disintegration, (b) complete solubility and (c) a perfectly clear solution.

Summarized from American Pharmacy (13), the method is as follows:

> The mold used in preparing these tablets is made of hard rubber or metal and consists of two parts. The upper portion, or the die, is a thin plate in which have been drilled, in regular alligment, a number of perforations of uniform diameter, the number varying from 50 to 200. At the end of each plate, there is one perforation considerably larger than the others. On one side of the die, the edges are beveled. The lower portion, or the base, is a fairly thick plate in which pegs are set conforming in pattern to the perforations in the die. For convenience in fitting the two parts of the apparatus together, both the base and the die have one square and one tapered end.
>
> When the mold is used, the perforations in the die are filled with moistened tablet material. The die is then placed on the base with beveled edge down and with the square and

the tapered ends matching. The two large pegs of the base are inserted into the two large perforations of the die. When the die is in proper position, it is pressed down firmly, and the pegs displace the tablets from the perforations. After the tablets have become partially dry by remaining for a few minutes on the pegs, they are removed by turning the mold on its side and lightly tapping it on a hard surface. The tablets are then transferred to a warm place and allowed to dry before dispensing.

The next step described in the procedure was the standardization of the mold by molding trial batches of blank tablets.

The base ordinarily used for molded tablets is lactose. Occasionally powdered sucrose in concentrations of from 5 to 20 per cent is incorporated with lactose as a base. The combination of the two sugars yields a firmer tablet. Lactose gives a fragile tablet, and powdered sucrose gives a very hard tablet. The use of the proper combination gives a tablet of the desired hardness, introduces adhesiveness into the mixture and results in a tablet that is readily soluble in water.

In preparing hypodermic tablets, the active ingredients are mixed with the diluent and moistened with the proper molding agent. The choice of a molding solution includes one that exerts a very slight solvent action upon the mixed material of the tablet. The molding solution most frequently encountered is diluted alcohol. The amount of solution used is as important as the kind. The powders must be thoroughly moistened but must not be pasty. The mass, when pressed into the mold, must be moist enough to hold the form of the molds. It must not show liquid on the surface, for the wetter the mass, the more compact and the harder the finished dry tablet. Then again, if the ingredients of the tablet are not sufficiently moistened, the tablet will not hold together but will crumble easily.

The actual molding of the tablet proceeds after the active ingredients and diluent are mixed by the method of geometric dilution, the trituration

of the mixture being done in a mortar. The mixture is moistened with the proper volume of molding solution and molded.

EXPERIMENTAL

A necessary adjunct to working with narcotics is the consideration of the U. S. Treasury Department, Bureau of Narcotics, Regulation No. 5, covering laboratories using narcotic drugs for the purpose of research, instruction, or analysis. It is required that such laboratory or institution obtain a class VI license. Further, records shall be kept, which shall be open at all times to the inspection of any duly authorized officer, employee or agent of the Treasury Department. This record shall include data similar to the samples shown in the following tables:

TABLE Ia

NARCOTICS USED

DATE	KIND	QUANTITY	PURPOSE
5.7.49	Morphine Sulfate	16.25 Gm.	Tablet Manufacture
5.9.49	Ethylmorphine HCl	10.84 Gm.	Tablet Manufacture
5.9.49	Morphine HCl	5.42 Gm.	Tablet Manufacture
1.7.50	Morphine HCl	8.125Gm.	Tablet Manufacture

TABLE Ib

IDENTIFICATION AND DISPOSITION OF NARCOTIC OR PRODUCTS

DATE	PRODUCT	QUANTITY	DISPOSITION
3.8.49	H.T. Morphine SO_4	2 tablets	Hardness Test
5.2.49	H.T. Schlesinger	31 tablets	Loss in Mf'g
6.1.49	H.T. M & A #9	20 tablets	Assay
7.3.49	H.T. Morphine HCl	10 tablets	Solubility Test

Standardization of the Mold. Although the manufacturer of a tablet triturate mold usually indicates its capacity, in terms of the weight of one tablet, this indication must be regarded as an approximation. The capacity of a mold is not an absolute quantity, but a relative value. The volume of material in the completely filled perforations is constant

but the weight varies with the nature of the material. It is then necessary to determine the capacity of a mold for each combination of substances which is to be molded.

Table II presents the mold capacity of the diluents used in this study. The average weight of one tablet is obtained by averaging ten weighings of ten tablets each. Batch #4, using sorbitol diluent, is omitted since satisfactory tablets were not obtained.

TABLE II

MOLD CAPACITY STUDY

Batch number		1	2	3
Diluent		LACTOSE	LACTOSE	MANNITOL
Weight of Groups of Ten Tablets	a	0.3285	0.3023	0.2410
	b	0.3301	0.3052	0.2388
	c	0.3273	0.3126	0.2376
	d	0.3244	0.3112	0.2395
	e	0.3300	0.3086	0.2398
	f	0.3268	0.3027	0.2387
	g	0.3255	0.3034	0.2402
	h	0.3331	0.3101	0.2390
	i	0.3312	0.3096	0.2384
	j	0.3298	0.3126	0.2376
Wt. 100 tablets		3.2956	3.7065	2.3906
Av. Wt. 10 tab.		0.3294	0.3706	0.2391
Av. Wt. 1 tab.		0.0329	0.0371	0.0239

Table III shows that when a high yield occurs, the average weight of the tablet is decreased. There was a decrease in weight varying from 2.23 per cent to 10.29 per cent below the calculated theoretical weight. The tablet weights listed in this table are the average of ten weighings of ten tablets each.

TABLE III

VARIATION STUDY

Batch No.	Tablets Theoretical	Tablets Actual	Weight Per Tablet Theor.	Weight Per Tablet Actual	% Weight Variation
5	1000	1163	0.0281	0.0261	6.79
6	500	522	0.0314	0.0307	2.25
7	500	560	0.0274	0.0246	10.22
8	500	526	0.0311	0.0279	10.29

In his study of a problem similar to the one reported here, Bower (9,10) experienced a significant variation in yield of tablets after standardization of the molds. It was therefore decided to express the assays in terms of per cent of active constituent in the tablet mixtures. The error due to variation in the weight of each tablet, or of yield, is eliminated by this procedure, providing there is complete distribution of the alkaloidal salts through the tablet mixture.

Deterioration Products. Morphine and its salts in powder form do not deteriorate under normal storage conditions (14). Deterioration does occur in the presence of moisture and under improper storage conditions. A consideration of the chemical formula of morphine indicates that deterioration may be attributed to hydration, oxidation, condensation or polymerization. It is generally believed that deterioration takes place through condensation at the phenolic hydroxyl with formation of oxydimorphine or pseudomorphine. This form of deterioration, which has been shown to be formed by oxidation of morphine with $K_3Fe(CN)_6$, requires the presence of oxygen. Deterioration in the absence of oxygen and in the presence of light is attributed to peroxidation or polymerization (dimerization), which can take place through the oxygen or the oxide

grouping which might be reactivated by ultraviolet light. This form of deterioration gives rise to the formation of bimorphine.

Hydrolysis or oxidation of the diluent might be another source of the discoloration which occurs with hypodermic tablets. Although this tendency is present to a lesser degree in tablets of this type, it has been demonstrated that tablets of morphine salts discolor more consistently than tablets of other alkaloids.

Antioxidants. Sodium metabisulphite was incorporated into some of the formulas to prevent oxidation by its inherent reducing property. Ascorbic acid, another powerful reducing agent, was chosen since it had been satisfactorily used in a study of oil solutions of epinephrine (20).

Tablet Diluents. The diluents included lactose, lactose with ascorbic acid, lactose with sodium metabisulphite and an alcohol sugar, mannitol. After several perliminary moldings with sorbitol and mannitol separately, mannitol was selected as the alcohol sugar of choice.

Molding Solution. Working with lactose containing no medicament at first, experiments were performed with various dilutions of alcohol. Sucrose was incorporated into the molding solution for its hardening quality. The ideal solution would lend adhesiveness to the mixture, afford ease in molding and permit the tablet to dry in an appreciably short time. A molding solution containing alcohol 30 per cent (v/v), sucrose 5 per cent (w/v) and distilled water seemed to approach these requirements. The water and the sucrose in solution acted as binding agents, and the alcohol hastened the drying. Another solution, used to moisten mixtures which had dried, contained alcohol 30 per cent (v/v) in distilled water.

Formulation and Manufacture. The values found in the mold capacity study were used as a guide for the manufacture of the medicated tablets. Table IV reveals the constituents of the control and modifications of the morphine sulfate hypodermic tablets.

TABLE IV

N. T. Morphine Sulfate
Tablets to contain 49.62 per cent of
Morphine Sulfate, $(C_{17}H_{19}O_3N)_2.H_2SO_4.5H_2O$.

INGREDIENTS	BATCH NUMBER			
	5	6	7	8
Morphine Sulfate, U.S.P., Powder	8.125	8.125	8.125	8.125
Lactose, U.S.P., Powder	8.250	8.234	8.234	
Mannitol, Powder, Atlas Pwd. Co.				8.250
Ascorbic Acid, U.S.P., Powder		0.016		
Sodium Metabisulphite, Gran.* Mallinckrodt Chem. Wks.			0.016	

* Reduced to #100 powder before using.

The ingredients were mixed, sieved five times through a #80 sieve and four gram portions, sufficient for one hundred tablets, were weighed. A 0.6 cc. quantity of the molding solution was added to each of these portions. The powder which remained from this molding was mixed with sufficient of the new mixture to bring the weight to four grams. Again 0.5 cc. of the molding solution was added. This molding and each subsequent one required from 0.1 to 0.2 cc. of the moistening solution to aid in a smooth operation.

The next group of tablets studied contained morphine and atropine sulfates. Table V presents the proportions of active ingredients, antioxidants and diluents.

TABLE V

H. T. Morphine and Atropine Sulfates
Tablets to Contain 49.62 per cent Morphine Sulfate.

INGREDIENTS	BATCH NUMBER			
	9	10	11	12
Morphine Sulfate, U.S.P., Powder	0.125	0.125	0.125	0.125
Atropine Sulfate, U.S.P., Powder	0.217	0.217	0.217	0.217
Lactose, U.S.P., Powder	0.033	0.017	0.017	
Ascorbic Acid, U.S.P., Powder		0.016		
Sodium Metabisulphite, Gran. Mallinckrodt Chem. Wks.			0.016	
Mannitol, Powder, Atlas Pwd. Co.				0.033

The materials were mixed by the geometric dilution method. In tablet #9, the atropine sulfate was first mixed with an equal weight of morphine sulfate. In tablet #10 the ascorbic acid and atropine sulfate were first homogeneously triturated before incorporating the morphine sulfate and diluent. Tablets #11 and #12 were also mixed by the geometric dilution method.

The third type of hypodermic tablet studied was the Schlesinger tablet. The quantities of alkaloidal salts, antioxidants and diluents appear in Table VI.

TABLE VI

Schlesinger Tablet
Tablets to contain 37.15 per cent alkaloids of morphine calculated as anhydrous morphine.

INGREDIENTS	BATCH NUMBER			
Scopolamine HBr, U.S.P., Powder	0.065	0.065	0.065	0.065
Ethylmorphine HCl, U.S.P., Powder	10.834	10.834	10.834	10.834
Morphine HCl, N.F., Powder	5.417	5.417	5.417	5.417
Lactose, U.S.P., Powder	16.315	16.283	16.283	
Ascorbic Acid, U.S.P., Powder		0.033		
Sodium Metabisulphite, Gran. Mallinckrodt Chem. Wks.			0.033	
Mannitol, Powder, Atlas Pwd. Co.				16.315

The "modus operandi" was the same for these combinations as for the previous tablets. A half cc. of the molding solution was added to four grams of the mixture, the moistened mixture was massed and fifty tablets molded. These tablets were made in molds which averaged 0.08 gram mixture per tablet. The previous tablets of morphine and morphine and atropine sulfates weighed approximately 0.08 gram per tablet.

In order to avoid the possible loss of narcotics, only the alcohol sugar, mannitol, which presented better workable mixtures and finer appearing finished tablets, was used in preparing the narcotic tablets. Sorbitol and sorbitol and mannitol in varying ratios were used in a later study, the results of which appear further on in this paper.

Drying and Storage. After the tablets were ejected from the mold by the pegs, they were allowed to remain resting on the pegs for a few minutes so that some of the molding solution evaporated. The tablets were removed from the pegs by lifting away the mold, inverting the mold over a piece of glassine paper, and gently but firmly tapping the mold to remove the

tablets. Making certain that only a single layer of tablets rested upon the paper, they were placed in a drying oven maintained at a temperature of 50° ± 2°C., and allowed to dry for two days. The tablets were then divided into two equal portions. One portion was stored in a calcium chloride desiccator and the other portion was stored at room atmosphere. The tablets were placed in amber colored glass vials having gauze closures. The gauze allowed access of the respective atmospheres. The average room temperature was 30°C. (22°-34°). During the course of the year of study, the tablets stored at room atmosphere were subjected to both extremes of humidity. An additional study was made of each tablet under conditions of accelerated aging. Samples of tablets were stored for one month at 50°C. both at room atmospheres and in a dry atmosphere. The original group of tablets was assayed at the beginning of this study and subsequently at the termination of three months', six months', and nine months' storage. Solubility and macroscopical studies were performed at the same time. In the case of the morphine sulfate tablets, samples were placed in a 50°C. oven for one month after their previous aging at room temperature for nine months. The tablets subjected to the accelerated aging were in most instances assayed only after one month's storage, but in some cases also after two months' storage.

Solubility Determination. The method for determining the solubility of the hypodermic tablets was a modification of the technique used by Smithers (11). His method is as follows:

> In order to compare relative ease of solubility, the following test was devised. Ten cc. of water was poured into a test tube, 4 inches in length by a ½ inch in diameter. The tablet was dropped into the test tube from the top of the tube and directly the tablet reached the bottom of the tube, the latter was inverted, and was reinverted every time the tablet settled to the bottom. The number of inversions necessary before complete solution was effected

was noted. The greater the number of inversions necessary, the less soluble, obviously, was the tablet.

Our modification of this method utilized a greater number of tablets in the same volume of water. We used a screw capped vial having the same dimensions described above. The vial was attached to the circumference of a coating pan having a diameter of 30 cm. The pan was caused to rotate at a speed of 40 R.P.M. The length of the vial was placed so as to travel in the direction of rotation. This system allowed the tablets to travel twice the length of the vial during each complete revolution. Ten cc. of distilled water, at room temperature, were placed in the vial and ten tablets were introduced. Immediately the vial was capped and the coating pan set in rotation. (Note: The time required to put the cap in place and the pan in motion, never more than two seconds, was a constant condition occurring in all solubility tests and was therefore eliminated in the final time calculation.) The number of revolutions made by the vial containing the water and tablets necessary for complete solution of the tablets was recorded. Using the angular speed of the system together with the number of revolutions recorded, the solubility time was calculated in seconds.

This method permitted solubility values which are more readily reproducible than the values obtained by Smithers' procedure.

Assay Methods. The tablets were assayed according to the methods outlined in the official compendia wherever the tablet was official. Morphine sulfate tablets were assayed by the U.S.P. XIII (18) method. Two modifications were made to this method. First, the tablets were placed in a 50 cc. volumetric flask, distilled water added to volume and an aliquot removed. Second, the alkaloid was completely extracted by shaking the mixture first with 30 cc., then with 20 cc., 15 cc., 10 cc., and 8 cc.

portions of solvent. A few cc. of the last extraction were placed in a micro test tube, 1 cc. of 0.02 N sulfuric acid was added and the solution heated on a water bath to evaporate the solvent and dissolve any alkaloid which might be present. Two drops of Valser's T.S. was added to the solution remaining after all solvent was removed. Absence of a white precipitate was indicative of completeness of extraction.

Morphine and strophine sulfates tablets were assayed according to the N. F. VIII (16). The tablets were weighed, transferred to a 50 cc. volumetric flask, sufficient distilled water added to volume and an aliquot of this solution withdrawn for assay. The same volumes of solvent were used in this extraction as in the previous one. Again the last few cc. of extraction were tested for completeness of extraction of the alkaloid. In this assay 0.02 N sulfuric acid and 0.02 N sodium hydroxide were used. Each cc. of the N/50 sulfuric acid was calculated to be equivalent to 7.585 mgm. of morphine sulfate.

The formulation of the Schlesinger tablet was adapted from Schlesinger solution (17). Ingredients and quantities for the solution follow:

Scopolamine Hydrobromide	0.25
Morphine Hydrochloride	20.00
Ethylmorphine Hydrochloride	40.00
Aseptol Water qs ad	1000.00

Morphine Hydrochloride

It was de Ethylmorphine Hydrochl containing the active principles of eight minims (0.5 cc. approximately) of the Schlesinger solution.

Schlesinger tablets were assayed essentially according to the method presented in the U.S.P. for morphine sulfate tablets. Ten tablets were weighed and transferred to a 50 cc. volumetric flask and an aliquot withdrawn equivalent to 120 mgm. of total alkaloidal salts of morphine. The U.S.P. method was followed from the directions "add 2 drops of hydrochloric acid" through "using methyl red T.S. as the indicator." Each cc.

of N/50 sulfuric acid was calculated to be equivalent to 5.707 mgm. of anhydrous morphine, $(C_{17}H_{19}O_3N)_2$.

The Schlesinger tablet not being official, it was decided to adapt the limits of strength specified by the N. F. VIII for Morphine and Atropine Sulfates Tablets. Schlesinger tablets would then be required to contain not less than 91 per cent and not more than 109 per cent of the theoretical amount of anhydrous morphine. Since the theoretical amount was 37.15 per cent, Schlesinger tablets must contain not less than 33.80 per cent and not more than 39.75 per cent anhydrous morphine.

RESULTS

Tables VII, VIII and IX present the results of almost a year of study of this problem. The solubility is expressed as time in seconds. The appearance expresses a macroscopic study; the results represent degree of discoloration. The figures appearing under assay represent per cent of active constituent in the tablet mixtures, and are the average of assays run in duplicate. If variances between the two assays differed by more than 2 per cent, additional assays were run in duplicate.

Results in Table VII. Tablets prepared with lactose base dissolved most readily. They maintained a relatively constant solubility over the period studied. Next in order of solubility were the tablets whose base was mannitol. The tablets containing sodium metabisulphite and ascorbic acid followed in that order. In all cases it was observed that the tablets stored in a dry atmosphere required a longer time for complete solution than did the tablets stored at room atmosphere.

The appearance of the tablets containing mannitol and sodium metabisulphite was "white" under all conditions of storage. The tablets prepared with lactose remained "white" in the desiccated atmosphere but were "slightly discolored" at room atmosphere. The tablets which contained ascorbic acid were the most undesirable of this group. They were "discolored" after only three months' aging.

Only in five of the forty assays performed did the morphine sulfate content of the tablets fall below the lower limit established by the U.S.P. This deficiency occurred with tablet #5 in both the desiccated and non-desiccated atmospheres after storage for nine months at normal plus one month at accelerated temperatures. The tablets with mannitol diluent appeared to have deteriorated the least of any of the tablets.

TABLE VII

H. T. Morphine Sulfate

Batch Number	5		6		7		8	
Diluent	Lactose		Lactose with Ascorbic Acid		Lactose with $Na_2S_2O_5$		Mannitol	
	A	B	A	B	A	B	A	B
	SOLUBILITY (IN SECONDS)							
Initial	7.5		22.5		18.0		10.5	
Three months	6.0	6.0	60.0	60.0	45.0	45.0	12.0	6.5
Six months	12.0	6.0	37.5	30.0	60.0	60.0	27.0	4.5
Nine months	6.0	6.0	45.0	51.0	60.0	54.0	15.0	9.0
	APPEARANCE (COLOR)							
Initial	W	W	W	W	W	W	W	W
Three months	W	+	W	++	W	W	W	W
Six months	W	+	W	++	W	W	W	W
Nine months	W	+	W	++	W	W	W	W
	ASSAY (PERCENTAGE)*							
Initial	50.04		50.41		50.09		51.63	
Three months	49.10	48.44	47.46	46.57	51.87	50.49	48.94	46.65
Six months	47.47	46.61	46.65	45.61	48.36	48.02	48.92	46.74
Nine months	46.19	46.49	47.06	46.98	46.27	48.20	48.08	49.06
Nine months normal plus one month accelerated	44.67	45.95	46.25	45.40	44.21	43.00	46.75	47.72

* 49.62% Theoretical Value.

Room Temperature Storage

A = In Desiccator
B = Room Atmosphere

Appearance

W = White; impart no color to solution.
+ = Slightly discolored; impart pale straw color to solution.
++ = Discolored; impart straw color to solution.

TABLE VIII

H. T. Morphine and Atropine Sulfates

Batch Number	9		10		11		12	
Diluent	Lactose		Lactose with Ascorbic Acid		Lactose with $Na_2S_2O_5$		Mannitol	
	A	B	A	B	A	B	A	B
	SOLUBILITY (IN SECONDS)							
Initial	7.5		21.0		7.5		18.0	
Three months	9.0	4.5	9.0	12.0	9.0	6.0	10.5	21
Six months	9.0	6.0	10.5	9.0	15.0	9.0	15.0	30
Nine months	4.5	15.0	24.0	9.0	13.5	12.0	15.0	15
	APPEARANCE (COLOR)							
Initial	W	W	W	W	W	W	W	W
Three months	W	+	W	+++	W	W	W	W
Six months	W	+	+	+++	W	W	W	W
Nine months	W	+	+	+++	W	W	W	W
	ASSAY (PERCENTAGE)*							
Initial	49.58		47.41		50.62		50.47	
Three months	51.01	49.17	51.89	50.14	52.03	50.55	53.73	51.97
Six months	45.64	45.30	47.85	46.93	46.92	46.50	46.41	46.86
Nine months	45.35	45.58	46.49	47.01	47.06	45.64	46.89	45.99

* 49.62% Theoretical Value

Room Temperature Storage

A = In Desiccator
B = Room Atmosphere

Appearance

W = White; impart no color to solution.
\+ = Slightly discolored; impart pale straw color to solution.
+++ = Grossly discolored; impart yellow color to solution.

However, deterioration was negligible regardless of storage or degree of discoloration.

Results in Table VIII. Tablets prepared with lactose diluent dissolved most readily. The tablets containing lactose with sodium metabisulphite were next most soluble. Those with mannitol and those with ascorbic acid were next in order of solubility.

Tablet #9 remained "white" under a dry atmosphere for almost a year. On the other hand, it was "slightly discolored" after three months' storage at room temperature and atmosphere.

Tablet #10 was "slightly discolored" after six months' aging even when stored in a desiccator. The tablets stored at room temperature and room atmosphere were "grossly discolored" at the end of three months' storage.

The tablets containing sodium metabisulphite and those containing mannitol remained "white" throughout the study.

Although the tablets which contained lactose as the base assayed slightly below 46.14 per cent after six months' storage under both dry and humid atmospheres, there is considerable doubt if this can be considered as significant deterioration since the deficiency could have been the result of a number of other factors.

The results with ascorbic acid and sodium metabisulphite were not indicative of any significant deterioration.

Results in Table IX. Of the various Schlesinger tablets, tablet #16 was the most soluble, with #15, #13 and #14 being the next most soluble in that order. The tablets with the mannitol base exhibited a property desired in a hypodermic tablet, i.e., it disintegrated in a manner similar to compressed tablets formulated with starch. The smaller particles of tablet material dissolved quite readily.

TABLE IX
H. T. Schlesinger

Batch Number	13		14		15		16	
Diluent	Lactose		Lactose with Ascorbic Acid		Lactose with $Na_2S_2O_5$		Mannitol	
	A	B	A	B	A	B	A	B
	SOLUBILITY (IN SECONDS)							
Initial	16.5		34.0		13.5		7.5	
Three months	7.5	9.0	7.5	18.0	6.0	9.0	4.5	7.5
Six months	15.0	16.5	18.0	30.0	10.5	9.0	7.5	7.5
Nine months	12.0	30.0	27.0	45.0	7.5	15.0	6.0	12.0
	APPEARANCE (IN COLOR)							
Initial	+	+	+	+	W	W	W	W
Three months	+	+	+	++	W	W	W	W
Six months	+	+	+	++	W	W	W	W
Nine months	+	+	+	++	W	W	W	W
	ASSAY (PERCENTAGE)*							
Initial	36.10		37.05		36.86		37.67	
Three months	37.22	36.69	36.49	35.72	37.39	37.55	38.45	37.90
Six months	35.92	34.98	35.63	35.51	35.85	34.97	36.34	35.96
Nine months	35.34	34.61	35.82	36.26	36.00	36.26	36.09	35.72

* 37.15% Theoretical Value

Room Temperature Storage

A = In Desiccator
B = Room Atmosphere

Appearance

W = White; impart no color to solution.
+ = Slightly discolored; impart pale straw color to solution.
++ = Discolored; impart straw color to solution.

Tablet #13, containing lactose base, was "discolored" at the completion of its manufacture. Apparently its discoloration did not increase on extended aging. Tablet #14, with ascorbic acid, also was "discolored" immediately after manufacture. The tablets stored in the desiccator presented no more advanced discoloration after three, six or nine months' storage. The tablets stored at room temperature and atmosphere advanced to the second stage of discoloration. The appearance of the tablets containing sodium metabisulphite and mannitol remained white throughout the period of study under both conditions of storage.

The potency limits previously established allowed Schlesinger tablets to contain not less than 33.80 per cent and not more than 39.75 per cent anhydrous morphine. At no time did the tablets of the Schlesinger formula fall below or go above these limits. Discoloration gave no indication of the degree of deterioration. More consistent assays were obtained here, although the tablets were generally more discolored than the other tablets studied.

Desiring to determine the component or components of the Schlesinger tablet responsible for this marked discoloration, tablets were prepared of variations of the ingredients in the formula and also of combinations of each. These variations would afford the opportunity for a more adequate study of the factors contributing to the marked discoloration reported here. Table X shows ingredients and the combinations used.

TABLE X

INGREDIENTS	BATCH NUMBER					
	17	18	19	20	21	22
Scopolamine HBr, U.S.P.			0.328		0.065	0.065
Ethylmorphine HCl, U.S.P.		8.125		5.417		
Morphine HCl, N.F.	8.125			2.709	8.125	
Lactose, U.S.P.	8.250	8.250	16.048	8.250	8.185	8.185

The tablets of morphine hydrochloride, ethylmorphine hydrochloride, morphine hydrochloride with scopolamine hydrobromide and ethylmorphine hydrochloride with scopolamine hydrobromide were all prepared to contain 49.62 per cent of the respective morphine salt. The tablets of scopolamine hydrobromide were prepared to contain 2 per cent active ingredient. The tablets containing the combination of morphine and ethylmorphine hydrochlorides were prepared to contain 37.15 per cent morphine alkaloids calculated as anhydrous morphine.

This series of tablets was prepared similar to the previous batches. The same quantities of molding and moistening solutions were used. The base used in the manufacture of these six tablets was lactose.

The tablets containing the morphine salts were assayed according to the method for Morphine Sulfate Tablets, U.S.P. XIII. The scopolamine hydrobromide tablets were assayed by the N.F. VIII method (18). The alkaloids were extracted with similar quantities of solvent used in the previous extractions reported in this paper.

The limits of purity allowed scopolamine hydrobromide tablets to contain not less than 88 per cent and not more than 112 per cent of the labeled amount of scopolamine hydrobromide. The results of this study appear in Table XI.

Results in Table XI. The results of this study indicate that morphine hydrochloride was the component of the Schlesinger tablet which was responsible for the discoloration encountered. The tablets containing morphine hydrochloride with lactose diluent "discolored" immediately after manufacture. It did not progress beyond this degree of discoloration when subjected to accelerated aging tests. The tablets which did not contain morphine hydrochloride remained "white" throughout the experiment. The

TABLE XI

STORAGE AT 50°C			INITIAL		ONE MONTH		TWO MONTHS		THEORETICAL
			A	B	A	B	A	B	VALUE
B	17	Appearance	++	++	++	++	++	++	
A		Assay	47.55		44.26	45.11	47.79	46.48	49.62
T	18	Appearance	W	W	W	W	W	W	
C		Assay	47.64		46.41	47.88	49.12	48.25	49.62
H	19	Appearance	W	W	W	W	W	W	
		Assay	2.02		2.17	2.17	xxx	xxx	2.00
N	20	Appearance	+		++	++	++	++	
U		Assay	35.64		35.22	34.90	35.21	35.29	37.15
M	21	Appearance	+		++	++	++	++	
B		Assay	48.29		46.83	45.85	47.00	47.58	49.62
E	22	Appearance	W	W	W	W	W	W	
R		Assay	48.65		48.74	48.20	49.08	48.11	49.62

Room Temperature Storage

A = In Desiccator
B = Room Atmosphere

Appearance

W = White; impart no color to solution.
+ = Slightly discolored; impart pale straw color to solution.
++ = Discolored; impart straw color to solution.

tablets containing both morphine and ethylmorphine hydrochlorides were initially only "slightly discolored." When stored at the higher temperature they became "discolored." Tablets of scopolamine hydrobromide and tablets of ethylmorphine hydrochloride did not discolor.

Solubility Study. A further experiment was conducted to investigate the solubilities of hypodermic tablets which did not contain narcotics. Table XII shows the ingredients and quantities used in the manufacture of these tablets. The solubility and the appearance of the finished tablets were noted. The results suggested the suitability of these bases for incorporation in other tablets intended for hypodermic injection.

Tablet #23 required 0.4 cc. of the molding solution for the molding of each one hundred tablets. Tablet #24 required 0.5 cc. of the molding solution plus 0.4 cc. moistening solution for each one hundred tablets. Tablet #25 molded with 95 per cent alcohol was very fragile. Formula #26 presented satisfactory tablets using 0.2 cc. molding solution and 0.8 cc. of 95 per cent alcohol. Tablet #27 was molded with 0.2 cc. molding solution, 0.1 cc. moistening solution and 1.5 cc. of 95 per cent alcohol. Tablet #28 required 0.3 cc. molding solution, 0.1 cc. moistening solution and 0.2 cc. of 95 per cent alcohol. Similar quantities of solutions were incorporated into tablets #29 through #40, inclusive, in which the bases were respectively identical.

These groups of tablets were observed for solubility and physical appearance at the beginning of the experiment, after storage in a dry atmosphere and at room atmosphere at 50°C. for one month and then again after two months.

Results in Table XIII. The solubility determinations indicate that tablets containing lactose were most soluble with mannitol next most

TABLE XII

Non-Narcotic Tablets

	STRYCHNINE NITRATE	ATROPINE SULFATE	ARSENIC TRIOXIDE	LACTOSE	MANNITOL	SORBITOL
23	1.0000			13.3645		
24	1.0000				13.3645	
25	1.0000					13.3645
26	1.0000				6.6822	6.6822
27	1.0000				3.3411	10.0234
28	1.0000				10.0234	3.3411
29		0.3000		14.0645		
30		0.3000			14.0645	
31		0.3000				14.0645
32		0.3000			7.0323	7.0323
33		0.3000			3.5141	10.5504
34		0.3000			10.5504	3.5141
35			1.0000	13.3645		
36			1.0000		13.3645	
37			1.0000			13.3645
38			1.0000		6.6822	6.6822
39			1.0000		3.3411	10.0234
40			1.0000		10.0234	3.3411

Numbers 23 through 40, inclusive = Batch Numbers.

soluble. In most cases the solubility did not vary from the original initial test.

Only in two instances of ninety observations of appearance was there "slight discoloration" of the tablets.

Discussion. The method for manufacturing hypodermic tablets is reviewed in detail in the text of this paper. A formula for a satisfactory molding solution is presented. The sucrose solution and water act as binding agents by virtue of their physical and chemical properties, respectively. The alcohol in the low concentration encountered in this formula enables quick drying. The incorporation of sodium metabisulphite into tablet formulas permits storage of such tablets under varying conditions of temperature and humidity without discoloration or considerable decrease in solubility. Mannitol is a satisfactory base for some tablets, since it facilitates the preparation of smooth, "white" tablets whose solubility is comparable to those made with lactose. Ascorbic acid apparently is not a suitable antioxidant for morphine preparations in which water is introduced in the process of manufacture.

The results of the variations showed morphine hydrochloride to be the component responsible for the discoloration of Schlesinger tablets. In the tablets omitting this ingredient no discoloration was observed even when stored at higher temperatures and in higher humidity.

Conclusion. All tablets prepared with only lactose as the base were readily soluble. Those prepared with mannitol, in most cases, were next in order of solubility. It was necessary to add an antioxidant, sodium metabisulphite, to mixtures containing lactose as the base. Tablets made with mannitol as the base did not require an antioxidant.

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TABLE XIII

	SOLUBILITY					APPEARANCE					
	I	VIII	IX	X	XI	I	VIII	IX	X	XI	
23	6	3	6	6	3	W	W	W	W	W	23
24	9	6	10½	6	12	W	W	W	W	W	24
25	21	60	27	51	48	W	W	W	W	W	25
26	21	30	18	18	24	W	W	W	W	W	26
27	27	45	42	48	54	W	W	W	W	W	27
28	42	72	45	30	36	W	W	W	W	W	28
29	6	3	6	3	4½	W	W	W	W	W	29
30	12	12	15	18	15	W	W	W	W	W	30
31	36	30	36	27	48	W	W	W	W	W	31
32	30	51	39	33	36	W	W	W	W	W	32
33	45	48	51	45	45	W	W	W	W	W	33
34	27	18	33	21	12	W	W	W	W	W	34
35	6	3	6	3	3	W	W	W	W	W	35
36	7½	12	18	12	9	W	W	+	W	W	36
37	54	60	63	66	48	W	W	W	W	W	37
38	18	12	24	9	15	W	W	W	W	W	38
39	54	52	53	36	39	W	W	W	W	W	39
40	24	12	9	12	12	W	W	+	W	W	40

I = Observations at Beginning of Experiment.
VIII = Observations after 1 month at elevated temperature in desiccator.
IX = Observations after 1 month at elevated temperature not in desiccator.
X = After two months at elevated temperature; desiccator.
XI = After two months at elevated temperature; not in desiccator.
W = White; impart no color to solution.
+ = Slightly discolored; impart pale straw color to solution.

Using the recommended quantities of molding and moistening solutions, the mixtures permitted satisfactory tablets to be molded. There was sufficient sucrose and water present in these solutions to bind the ingredients and give the finished dried tablet the desired hardness. The alcohol present in these formulas permitted quick drying.

Discoloration was evident to a greater degree when morphine hydrochloride was a constituent of a hypodermic tablet. It was noted that incorporating mannitol or sodium metabisulphite into such tablets eliminated the discoloration.

The solubility test method presented herein appears satisfactory for a comparative evaluation of the tablets studied. The results obtained by this method can be reproduced more readily than the results obtained by the hand inversion method of Smithers (11).

Summary. The unsatisfactory status of the hypodermic tablet prompted this study. An attempt was made to prepare a tablet which would not discolor or decrease in solubility on standing. For comparison, tablets were made with lactose as the diluent and with modifications intended to correct the undesirable properties encountered in hypodermic tablets. A molding solution containing alcohol 30 per cent (v/v), sucrose 5 per cent (w/v) and distilled water was formulated. A moistening solution was introduced containing alcohol 30 per cent (v/v) in distilled water. When sufficient of these solutions were used, elegant finished tablets were obtained.

The tablets prepared with mannitol as the base dissolved readily and did not discolor. All tablets stored in a dry atmosphere retained their original appearance, but had a tendency to be less rapidly soluble on aging. Sodium metabisulphite was found to be an effective antioxidant for tablets containing a lactose base.

The apparent deterioration of the tablets studied was not related to the degree of discoloration. There is considerable doubt whether the deterioration encountered in this work is significant, since the deterioration was small regardless of the conditions of storage or degree of discoloration.

BIBLIOGRAPHY

(1) Fuller, R. M., "Dose Dispensing Simplified," Med. Rec. 13:184 (1878)

(2) Malpass, G. N., "Tablet Manufacturing Research," Am. J. Pharm., 114:167 (1942)

(3) Kebler, L. F., "The Tablet Industry; Its Evolution and Present Status," J.A.Ph.A., 3:820-848 (1914).

(4) Scoville-Powers, The Art of Compounding, Sixth Edition, Pp. 235-240 (1937)

(5) Piffard, H. G., "The Use of Certain Triturations," Med. Rec., 12:756(1877)

(6) The U. S. Homeopathic Pharmacopoeia, First Edition, (1878)

(7) Fuller, R. M., "A Convenient Method of Dosage and Administration," Med. Rec., 21:511(1882)

(8) Sperandio, G. J., and H. G. DeKay, "The Manufacture of Hypodermic Tablets," J.A.Ph.A., Pract. Ed., 10:572-574(1949)

(9) Bower, S. Walley, "Why Hand Molded Tablets Vary," J.A.Ph.A., 23:36-40(1934)

(10) Ibid, "Variations in Hand Molded Hypodermic Tablets," J.A.Ph.A., 23:1207-1210(1934)

(11) Smithers, G. W. G., "The Preparation of Tablet Triturates for Use in Hypodermic Injections," Quart. Jour. and Yearbook of Pharmacy, 12:478-88(1939)

(12) Cook-Martin, Remington Practice of Pharmacy, Ninth Edition, Pp. 1286-1288(1948)

(13) Lyman, Rufus A., American Pharmacy, Vol. I, Pp. 457-459(1945)

(14) Ionescu-Matiu, Al. et al, "Determination of Morphine and Apomorphine by the Volumo-colorimetric Method," Ann. pharm. franc., 6:137-143 (1948

(15) United States Pharmacopoeia XIII, Pp. 331-332(1947)

(16) The National Formulary VIII, P. 346(1946)

(17) The Pharmaceutical Recipe Book, Second Edition, P. 223(1936)

(18) The National Formulary VIII, P. 455(1946)

(19) Merck Index, Fifth Edition, P. 308(1940)

(20) G. B. West, "Stability of Adrenaline," Pharm. J., 157:54(1946)