

United States Patent Office

3,102,845

Patented Sept. 3, 1963

1

3,102,845

PHARMACEUTICAL TABLET

John Richard Fennell, Lansdale, Pa., assignor to McNeil Laboratories, Incorporated, a corporation of Pennsylvania

No Drawing. Filed Nov. 18, 1960, Ser. No. 70,132
17 Claims. (Cl. 167—82)

This invention relates to a novel pharmaceutical tablet formulation and to methods for its preparation.

Numerous and highly intricate methods are currently being employed in the pharmaceutical industry for the preparation of pharmaceuticals having the peculiar property of exerting pharmacological activity over a controlled time period. The purpose for this, obviously, is to minimize the number of times a patient is required to take medication during a given day and, perhaps more importantly, to ensure constant absorption of therapy over a given time period, thus avoiding peaks and valleys in the control of chronic and acute maladies.

One of the most commonly employed methods for obtaining a so-called "prolonged" therapeutic effect from a pharmaceutical formulation is to combine the active ingredients during the manufacturing process with one or more inert components in such a fashion that the release of the active drug from the total pharmaceutical mass during its passage through the stomach and intestinal tract, is even and gradual. Among inert components which are presently being used for such purposes are high molecular weight waxes, used singly or in various combinations, either evenly distributed among the active ingredients or first melted and then carefully coated over small particles of the active components.

One disadvantage in the use of waxes for long-acting tablet formulations is that a relatively large mass of wax must be incorporated in the dosage form to give the desired long-acting effect. In other words, the ratio of wax to active component is a several-fold factor, thus requiring the manufacture of such a bulky tablet that its ingestion by patients is relatively difficult and uncomfortable.

It can readily be seen, therefore, that one of the prevailing problems in the pharmaceutical development field is the manufacture of controlled-release dosage forms which contain inert components that have large surface area, are nonabsorbable, and are devoid of toxicity and undesirable side effects.

The use of alkaline earth metal salts of fatty acids in tablet manufacture is known. These substances have been used for many years as tablet lubricants. That is to say, they are incorporated in the final tablet granulation just prior to compression in relatively small quantities in order to facilitate compression of the granules without their adherence to the punches and dies in the tableting machine.

It is also known that saturated fatty acids themselves, their esters, ethers and alcohols, can be pelletized with polyvinylpyrrolidone by converting the polymer, in the presence of the fatty acid or its derivative, into a molten mass, granulating the congealed mass, reheating, cooling, adding the therapeutic and pelletizing at a temperature near the set point.

Among the many disadvantages in using fatty acids or their derivatives in combination with polyvinylpyrrolidone to prepare prolonged action dosage unit forms is their physical similarity to high molecular weight waxes. In order to get uniform distribution in polyvinylpyrrolidone, the fatty acid derivatives must be melted in the presence of the latter, granulated, remelted and then pelletized. This not only constitutes an unwieldy, lengthy and expensive process but also, because of the dual high temperature involvement, limits the process to incorporation

2

only of those therapeutically active agents which can safely withstand elevated temperature exposure without decomposition. Thus, as in the case of most high molecular weight waxes, the long chain fatty acids and their derivatives are not susceptible to conventional wet granulation at room temperature.

The fatty acid derivatives above mentioned bear yet another similarity to high molecular weight waxes in their use as vehicle for long-acting dosage forms. Because of their physical character, large quantities of the fatty acid substances must be employed to obtain the desired effect. Thus the proportion of P.V.P. to fatty acid material must be about one to seven, or more. Moreover, it is known that the fatty acids themselves are inadequate as long-acting vehicle matrices, even though combined with P.V.P. Thus it is frequently necessary, in order to obtain the desired prolonged effect, to incorporate a quantity of high molecular weight wax such as candelilla, beeswax or carnauba in the formulation. This adds still further to the bulkiness of the dosage form, unnecessarily increasing the volume of the total mass and making the oral ingestion of the medication that much more difficult.

It has now been discovered that by combining an earth or alkaline earth metal salt of a fatty acid in certain proportions with polyvinylpyrrolidone, a result is obtained which, heretofore, defied successful accomplishment by those skilled in the art. The novel formulation of this invention embraces a dosage unit combination capable of releasing incorporated medication gradually over a controlled period of time. Among other advantages of the novel combination is that, depending upon the ratio of polyvinylpyrrolidone (P.V.P.) to fatty acid salt employed, the release of a drug from the tablet matrix can be predictably controlled over a desired, extended time span. The novel combination eliminates the use of waxes, does not need high temperatures for formulation, reduces the total number of steps in the manufacturing operation and requires no special machinery or equipment. In other words, by simple variation of P.V.P.:fatty acid salt proportions within the prescribed limits, one can regulate drug release from a relatively short (1 to 2 hours) to long (24 hours) time interval. In addition, the novel combination permits the use of the wet granulation process without alteration of the hydrophobic nature of the fatty acid salt. This is accomplished by taking advantage of the unique water soluble, film-forming properties of P.V.P. through its incorporation with the fatty acid salt in the prescribed ratios.

The novel combination of the present invention comprises, as the principal constituents of an oral tablet formulation, therapeutic ingredient(s) distributed throughout a molecularly dispersed P.V.P. phase, and forming a film network about a water insoluble, hydrophobic, fatty acid salt macrophase, the P.V.P.-fatty acid salt constituents being in a ratio of from about 1 to about 0.5 to 4. It will be observed that although the ratio of P.V.P. to fatty acid salt is critical, it may be varied over a substantial range, depending upon the rate of release of medicament desired. Thus, when the ratio is from about 1 to about 0.5 to 1, release of the medicament is obtained in approximately one to three hours. When the ratio is from about 1 to about 1.5 to 2.0, the incorporated medicament is released over a period of from about seven to twelve hours. When the ratio is from about 1 to about 3 to 4, release is obtained in a period of from about fourteen to twenty-four hours.

Although the mechanism whereby gradual release of medication is attained over an extended time period from the novel combination of this invention has not been absolutely determined, it can be postulated with reasonable certainty that the desired effect is gained be-

cause of the peculiar physical combination of components, and their co-action during absorption in the gut. This unusual combination is accomplished through the manufacturing process which comprises, in a general way, the addition of a sufficient volume of water to wet the dry powdered mass containing the prescribed quantity of fatty acid salt, P.V.P. and therapeutic components as well as other tablet constituents, if desired. The medicament dissolves in the added water and becomes evenly distributed throughout the P.V.P. The medicament-P.V.P.-water system then flows freely about the hydrophobic fatty acid salt macroparticles. Upon drying, a plasticized, molecular film layer of P.V.P. and medicament is deposited about the fatty acid salt particles. The dried granules and, consequently, the final tablet are composed of a network of hydrophobic fatty acid salt particles, enveloped by a hydrophilic, medicated P.V.P. film. The granules are uniformly distributed throughout the tablet mass, hence the drug molecules are also uniformly distributed throughout the mass.

When the above-described dosage form comes in contact with digestive juices, the aqueous medium infiltrates the hydrophobic fatty acid salt mass at a slow, constant rate by following the network path of the hydrophilic P.V.P. film through capillary action. The molecules of medicament are dissolved in the juice at the point of contact of the latter with the drug-containing P.V.P. film. The dissolved medicament is then free to diffuse into the body of the surrounding medium and is available for absorption. Because of this method of diffusion of drug out of the tablet, there is no rupture of the fatty acid salt mass, and the tablet functions as an inert matrix whose shape remains substantially intact after prolonged agitation in fluid media.

It is to be observed that two competing forces are operating within the tablet as it tumbles in the intestinal tract and is bathed in the aqueous fluid—namely, the hydrophobic barrier of the fatty acid salt and the surrounding hydrophilic film of P.V.P. and medicament. As a result, the dissolution of water soluble therapeutics is readily controlled by increasing or decreasing the quantity of hydrophobic material in the tablet. In other words, by having a relatively high proportion of fatty acid salt, as compared to P.V.P. content, the medicament will be released over a long period of time. On the other hand by decreasing the ratio, the therapeutic component is released over a shorter period of time. Advantage is thus taken of the unique hydrophilic, nonswelling film properties of P.V.P. as contrasted to the action of other commonly used binders which do not possess such physical properties.

The polyvinylpyrrolidone component which is preferred in the novel combination of this invention is one having a K-value of from about 24 to about 40 and having an average molecular weight of from about 20,000 to about 100,000, preferably about 40,000 to about 80,000. As the fatty acid salt, any one of the nontoxic, pharmaceutically acceptable earth, alkaline earth metals may be employed, as for example calcium, magnesium or aluminum.

Although the novel formulation is peculiarly adapted to the use of "water soluble" medicaments, it may be readily modified to include "water insoluble" therapeutics, singly, in combination with each other or in combination with water soluble medicaments, and it is intended that this modification be included within the scope of the present invention. Inasmuch as a water insoluble drug can be made available for absorption from the intestinal tract only by being directly exposed to the intestinal mucosa, such exposure can be accomplished by incorporating in the formulation an appropriate amount of hydrophilic gum. The quantity of the hydrophilic gum should be such that the tablet matrix erodes slowly while tumbling through the intestinal tract, thereby rendering the water insoluble drug available for absorp-

tion. The exact amount of hydrophilic gum may be varied depending upon the nature of the water insoluble constituent and its quantity in relation to the total tablet mass. In practice one may employ from about 0.1% to about 10% of the gum, preferably from about 0.5% to about 5%. Gums suitable for this purpose include gelatin, the methylcelluloses, including the carboxymethylcellulose, and their salts such as the sodium salt, acacia and the alginates.

In a general way, therefore, the novel tablet formulation comprises a water soluble or water insoluble therapeutic component in intimate dispersion throughout a molecular P.V.P. phase which is uniformly distributed in layer form about macroparticles of a water insoluble fatty acid salt. It will be readily apparent, therefore, that the novel tablet formulation lends itself to a wide variety of applications in the pharmaceutical field since it provides a means for administering water soluble and water insoluble therapeutics singly, in admixture with each other or with other substances, over a controlled period of time with predictable regularity and time lag. Drugs which are suitable for use in the novel tablet formulation include antihistaminics, such as carbinoxamine and rotoxamine; antispasmodics, such as poldine; central nervous system depressants, such as phenobarbital, butylbarbital; central nervous system stimulants, such as methamphetamine; vasodilators, such as phenylpropanolamine, phenylephrine; vitamins, such as thiamine and pyridoxine; antibiotics, such as tetracycline, chlortetracycline, oxytetracycline, penicillin and derivatives thereof, such as potassium α -phenoxyethyl penicillin. These may be incorporated in the novel formulation either in the form of their water insoluble bases or as their water soluble salts, depending upon the particular modification selected and found most advantageous.

It is to be emphasized that, although a fatty acid salt is used as a critical component in rendering the tablet mass long acting, this quantity of salt is incorporated during the wet granulation process. That is to say, it is included in the powdered mass during that step of tablet manufacture whereby it is, along with other ingredients, wetted with water and becomes an integral component of the dried granules. However, those who are familiar with tablet manufacturing process know that fatty acid salts, especially calcium stearate, are used routinely as tablet lubricants. In this capacity, the fatty acid salts are incorporated at that stage of tablet manufacture just prior to compression and after drying and reduction of granules to the appropriate size. Accordingly, although fatty acid salts, such as calcium stearate, are used in the present formulation as the critical components which render the tablet long acting, these same salts may also be used as lubricants by incorporating them in appropriate additional small quantities in the dried granulation just before compression. In some cases it may be desirable to employ other lubricants in the tablet granulation, such as, for example, the fatty acids themselves, i.e. stearic acid, talc or mixtures thereof.

There is no restriction on the inclusion of other commonly employed excipients in the formulation of the novel combination of this invention. Thus, one may employ as diluents, in whatever quantities are indicated, such components as dibasic calcium phosphate, lactose, mannitol and others. One may also include as binders, to ensure additional cohesive properties over and above those exerted by P.V.P., such gums as acacia or tragacanth.

The unique time-controlled properties of the novel combination of this invention are readily demonstrable by subjecting the formulated tablets to release-rate studies in accordance with the method described in the United States Pharmacopeia (U.S.P. XV) or the method described by Souder et al., Drug Standards, 26, 77 (1958). Table I, below, shows the results obtained in release-rate studies employing the U.S.P. tablet disintegration appa-

5

ratus with discs. Table II, below, shows the release rates obtained with various drugs over a twenty-four-hour period, employing the Souder et al. method. It will be readily seen from the results of these studies that the rate of release of the therapeutic component can be accurately controlled over whatever periods of time are desired by incorporating, in proper proportion, P.V.P. and a fatty acid salt in the tablet granulation. Finally, Table III shows results obtained, in terms of cumulative percent of drug released with respect to time, when a water-insoluble drug is incorporated in the novel formulation together with specific quantities of carboxymethylcellulose salts (Examples IV and VII). In order to demonstrate the effectiveness of gums such as the methylcelluloses when used for this purpose, i.e. in combination with water-insoluble therapeutics, comparison is made with a formulation wherein such gum is absent (Example VIII). The tablet disintegration apparatus used was that described in United States Pharmacopeia, XV, revision.

TABLE I

Ratio of P.V.P. to Calcium Stearate	Drug	Cumulative Percent of Drug Released								
		1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	7 hrs.	8 hrs.	24 hrs.
(a) 1:1.....	Rotoxamine D-tartrate.....	54	90	100	-----	-----	-----	-----	-----	-----
(b) 1:1.5.....	do.....	37	50	63	-----	90	-----	-----	-----	-----
(c) 1:2.....	do.....	28	38	46	56	63	72	78	87	97
(d) 1:2 with 2% CMC.....	Chlorzoxazone (water insoluble).....	11	26	33	-----	-----	-----	71	-----	-----
(e) 1:3.....	Rotoxamine D-tartrate.....	25	33	40	47	-----	56	60	-----	91
(f) 1:4.....	Phenylephrine HCl.....	28	36	-----	48	56	60	64	-----	74

TABLE II

Ratio of P.V.P. to Calcium Stearate	Drug	Cumulative Percent of Drug Released					
		1 hr.	3 hrs.	5 hrs.	6 hrs.	7 hrs.	24 hrs.
(a) 1:1.5.....	Poldine Methylsulfate.....	38	66	-----	84	-----	100
(b) 1:1.5.....	Carbinoxamine Maleate.....	42	70	-----	86	-----	100
(c) 1:1.75.....	Poldine Methylsulfate.....	33	63	-----	84	-----	100
(d) 1:2.0.....	do.....	26	65	-----	80	-----	100
(e) 1:2.5.....	do.....	29	56	-----	79	-----	86
(f) 1:4.0.....	do.....	24	44	61	-----	-----	87

TABLE III

Cumulative Percent of Drug Released vs. Time—U.S.P.
Tablet Disintegration Apparatus

	A*	B**	C***
1 Hour.....percent.....	3.3	11	56
2 Hours.....do.....	-----	26	100
3 Hours.....do.....	5.7	33	-----
7 Hours.....do.....	15.6	71	-----

Manner of tablet disintegration:

A*—Tablet substantially unchanged after seven hours. (Formulation of Example VIII.)

B**—Slow "erosion" of tablet. (Formulation of Example IV.)

C***—Fast "erosion" of tablet. (Formulation of Example VII.)

The following examples are intended to illustrate but not to limit the scope of the present invention.

EXAMPLE I

Formula:

	Percent
(1) Poldine methylsulfate.....	1.545
(2) Polyvinylpyrrolidone	10.0
(3) Calcium stearate.....	15.0
(4) Dibasic calcium phosphate, hydrous....	72.955
(5) Calcium stearate.....	0.5

(1) (2) (3) (4) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (5) is admixed, and the entire mass is compressed into tablets.

6

EXAMPLE II

Formula:

	Percent
(1) Rotoxamine D-tartrate.....	1.1370
(2) Polyvinylpyrrolidone.....	5.0
(3) Calcium stearate.....	10.0
(4) Dibasic calcium phosphate, hydrous....	83.363
(5) Calcium stearate.....	0.5

(1) (2) (3) (4) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (5) is admixed, and the entire mass is compressed into tablets.

EXAMPLE III

Formula:

	Percent
(1) Phenylephrine HCl.....	1.875
(2) Polyvinylpyrrolidone	5.0
(3) Calcium stearate.....	20.0
(4) Dibasic calcium phosphate, hydrous....	72.625
(5) Calcium stearate	0.5

(1) (2) (3) (4) are wetted with water and pressed

through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (5) is admixed, and the entire mass is compressed into tablets.

EXAMPLE IV

Formula:

	Percent
(1) Chlorzoxazone	62.5
(2) Sodium carboxymethylcellulose	2.0
(3) Calcium stearate.....	20.0
(4) Polyvinylpyrrolidone	10.0
(5) Dibasic calcium phosphate, hydrous....	5.0
(6) Calcium stearate.....	0.5

(1) (2) (3) (4) (5) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (6) is admixed, and the entire mass is compressed into tablets.

EXAMPLE V

Formula:

	Percent
(1) Rotoxamine D-tartrate.....	1.1370
(2) Polyvinylpyrrolidone	10.0
(3) Calcium stearate.....	15.0
(4) Lactose	73.363
(5) Calcium stearate.....	0.5

(1) (2) (3) (4) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (5) is admixed, and the entire mass is compressed into tablets.

7

EXAMPLE VI

Formula:	Percent
(1) Carbinoxamine maleate-----	1.5
(2) Polyvinylpyrrolidone-----	10.0
(3) Calcium stearate-----	15.0
(4) Dibasic calcium phosphate, hydrous----	73.0
(5) Calcium stearate-----	0.5

(1) (2) (3) (4) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (5) is admixed, and the entire mass is compressed into tablets.

EXAMPLE VII

Formula:	Percent
(1) Chlorzoxazone-----	62.5
(2) Polyvinylpyrrolidone-----	10.0
(3) Calcium stearate-----	20.0
(4) Sodium carboxymethylcellulose-----	4.0
(5) Dibasic calcium phosphate, hydrous----	3.0
(6) Calcium stearate-----	0.5

(1) (2) (3) (4) (5) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (6) is admixed, and the entire mass is compressed into tablets.

EXAMPLE VIII

Formula:	Percent
(1) Chlorzoxazone-----	62.5
(2) Polyvinylpyrrolidone-----	10.0
(3) Calcium stearate-----	20.0
(4) Dibasic calcium phosphate, hydrous----	7.0
(5) Calcium stearate-----	0.5

(1) (2) (3) (4) are wetted with water and pressed through a screen. The resulting granules are air dried at about 100° F., again passed through a screen; (5) is admixed, and the entire mass is compressed into tablets.

EXAMPLE IX

Formula:	Percent
(1) Potassium α -phenoxyethyl penicillin----	49.5
(2) Polyvinylpyrrolidone-----	10.0
(3) Calcium stearate-----	40.0
(4) Calcium stearate-----	0.5

(1) (2) (3) are mixed, wetted with a solution containing equal parts of isopropyl alcohol and water, screened, dried, (4) is added, and the mixture is compressed into tablets.

What is claimed is:

1. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt and therapeutically active material, the composition containing a ratio of 1 part polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

2. A composition as set forth in claim 1 wherein the therapeutic component is water soluble.

3. A composition as set forth in claim 1 wherein the therapeutic component is water insoluble.

4. A composition as set forth in claim 1 wherein the fatty acid salt is an alkaline earth metal salt.

5. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt, therapeutically active material and a hydrophilic gum, the composition containing a ratio of

8

1 part of polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

6. A composition as set forth in claim 5 wherein the therapeutic component is water soluble.

7. A composition as set forth in claim 5 wherein the therapeutic component is water insoluble.

8. A composition as set forth in claim 5 wherein the hydrophilic gum is a methylcellulose.

9. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt, a mixture of water soluble and water insoluble therapeutically active materials and a hydrophilic gum, the composition containing a ratio of 1 part of polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

10. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt and poldine methylsulfate, the composition containing a ratio of 1 part polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

11. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt and rotoxamine D-tartrate, the composition containing a ratio of 1 part polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

12. A time-controlled oral pharmaceutical dosage composition in tablet form comprising polyvinylpyrrolidone and a hydrophobic fatty acid salt in a ratio from about 1 to about 0.5 to 4 and phenylephrine hydrochloride.

13. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt and phenylephrine hydrochloride, the composition containing a ratio of 1 part polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

14. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt, chlorzoxazone and a hydrophilic gum, the composition containing a ratio of 1 part of polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

15. A composition as set forth in claim 14 wherein the hydrophilic gum is a methylcellulose.

16. A compressed pharmaceutical preparation for time-controlled oral administration consisting essentially of the following components: polyvinylpyrrolidone, a hydrophobic fatty acid salt and carbinoxamine maleate, the composition containing a ratio of 1 part polyvinylpyrrolidone to from about 1 part to about 4 parts hydrophobic fatty acid salt, the quantity by weight of polyvinylpyrrolidone being at least about 5% of the total weight of the composition.

17. A composition as set forth in claim 16 wherein the methylcellulose is carboxymethylcellulose.

(References on following page)

References Cited in the file of this patent

UNITED STATES PATENTS

2,385,920	Jenkins	Oct. 2, 1945
2,606,195	Tilford et al.	Aug. 5, 1952
2,776,924	Martin	Jan. 8, 1957
2,811,483	Aterno et al.	Oct. 29, 1957
2,819,981	Schornstheimer et al.	Jan. 14, 1958
2,820,741	Endicott et al.	Jan. 21, 1958
2,841,528	Myhre	July 1, 1958
2,887,437	Klioze et al.	May 19, 1959
2,887,439	Klioze et al.	May 19, 1959
2,890,985	Marsh et al.	June 16, 1959
2,894,289	Harper et al.	July 14, 1959
2,895,877	Marsh	July 21, 1959
2,897,120	Cronin et al.	July 28, 1959
2,897,121	Wagner	July 28, 1959
2,918,411	Hill	Dec. 22, 1959
2,957,804	Shuyler	Oct. 25, 1960
2,991,226	Millar et al.	July 4, 1961
3,018,221	Millar et al.	Jan. 23, 1962

OTHER REFERENCES

"Clistin," T.M. 587,051, Mar. 16, 1954.
 "Clistinal," T.M. 613,458, Oct. 4, 1955.

Kwan et al., "Factors Affecting Tablet Disintegration," J.A.Ph.A. (Sci. Ed.), vol. 46, No. 4, pp. 236-239, April 1957.

"Parafon," T.M. 681,397, July 7, 1957

"Nacton," T.M. 668,255, Oct. 14, 1958.

"Paraflex," T.M. 668,920, Oct. 28, 1958.

"Poldine," File No. 6753, recorded in T.M. search room December 17, 1958, by British Pharmacopoeia Comm.; for 2-benzilcyloxymethyl-1-methylpyrrolidine.

Stempel, "Prolonged Drug Action," J.A.Ph.A. (Prac. Phy. Ed.), 20(6), June 1959, pp. 334-336.

Stempel, "Prolonged Drug Action," J.A.Ph.A. (Prac. Phy. Ed.), 20(7), July 1959, pp. 393-395.

"American Drug Index—1960," Wilson et al., J. B. Lippincott Co., Philadelphia, Pa. © 1960—Lc-55-6286, pp. 152-153, 167, 174-175, 411-412, 472, 509-511, and 596, June 23, 1960.

"Nactisol," trademark application S.N. 109,719, July 27, 1960.

"Twistussin," trademark application S.N. 106,211, July 27, 1960.

"Twiston," T.M. 702,155, Aug. 2, 1960.