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CONTINUOUS PHARMACEUTICAL FILM COATING PROCESS

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ABSTRACT OF THE DISCLOSURE

A continuous spray of a highly volatile solvent containing methyl cellulose or hydroxypropyl methyl cellulose is directed on a tumbling bed of tablets which are kept at a uniformly high temperature by a continuous blast of hot air, an exhaust being continuously operated.

This invention relates to novel compositions and methods for the production of coated solid dosage units containing pharmaceutical ingredients.

The coating of solid dosage units containing pharmaceutical compositions such as pellets, pills, or tablets, is well known. In the pan process of sugar coating, for example, the usual procedure is to first apply a water repellent resinous material, such as zein, shellac, cellulose acetate phthalate, or fatty material, which forms a protective barrier against the moisture later applied. Next are applied subcoating materials, such as gelatin and acacia, which materials are dusted when wet with powders. This subcoating is required in the sugar process to round out the edges of the dosage unit prior to the application of a basically plain syrup which is deposited as a crystalline layer of sugar. The coated dosage unit is finally colored and polished. The process is time consuming, requiring from two to six days, and is also expensive. The process adds considerably to the size of the core of the dosage unit. Attempts have been made to improve sugar coatings by the addition of minor amounts of such compounds as sodium carboxymethyl cellulose to the syrup, thereby reducing the number of charges required. The process is still lengthy when compared to film coating processes.

Thin film coatings have been described wherein a "stop and go" process of application of substances, such as the cellulose derivatives, the polyethylene glycols, the prolamines, and the acetylated monoglycerides, or mixtures and modifications of the above were applied. Such applications have been variously described in (1) Drug Standards, p. 29, January-February 1958; (2) U.S. Patent No. 2,881,085; (3) Drug Cosmetic Inds. 75, p. 466; and (4) J. Amer. Pharm. Assoc., Sci. Ed. 43, 433 (1954), the disclosures thereof being incorporated herein by reference and made a part hereof.

The lengthy process of the sugar coatings combined with the large build-up in tablet size suggests room for improvement. The film coating processes described in the literative are those wherein the film is applied in charges by pouring a solution of the film former onto a rolling bed of tablets. As the tablets rotate, the material is distributed over the surface, thereof, and there is a material transfer from tablet to tablet. In a few minutes time usually aided by the application of heat, the solvents evaporate leaving a random deposition of film on the tablets. The cycle is then repeated until the coating is judged to be satisfactory. This is what is known in the trade as a "stop and go" process. In the above process, some tablets are actually overwet by the film coating solution and a continuous homogeneous film is dependent upon the transfer of film from tablet to tablet, and therefore a film of uniform thickness and composition is difficult to attain.

While pharmaceutically acceptable film coatings have been thus formed, the production of a continuous film coating which has a glossy, noncrazing surface has been unobtainable in a single step operation. Interrupted applications or charges and a stepwise build-up have generally been required to avoid tackiness. Polishing operations have always been required. The "stop and go" pouring process has the added disadvantage of making it difficult, if not impossible, to apply an even deposition of film of uniform thickness to indentations in the tablet such as might be caused by the desirability of symbols, score marks, and identification markings. These indentations usually become obliterated to some extent, especially in attempting to coat mottled tablets containing indentations or other tablets where a larger than normal concentration of pigments is required to cover the tablets.

It is an object of this invention to obviate the above mentioned disadvantages by the development of the novel dosage unit compositions of this invention which when prepared by the novel coating process of this invention will produce the desired results. The production of the novel coated dosage units of this invention lends itself to automation and does not require the use of a skilled operator, thereby taking the coating process out of the "art" category.

It is another object of this invention to provide a method of coating scored, engraved, or embossed tablets so that these markings and the tablet are uniformly covered without obliterating the desired markings.

It is still another object of the invention to provide an inexpensive and efficient method of coating tablets which will materially shorten the coating time.

It is yet another object of this invention to provide a one cycle continuous process requiring no drying or polishing cycles or steps.

It has now been found that a continuous non-toxic film coating may be produced on shaped cores containing pharmaceutical ingredients by the deposition thereon of a composition consisting essentially of a continuous film of a compound selected from the class consisting of methyl cellulose and hydroxypropyl methyl cellulose. Methyl cellulose is essentially the dimethyl ether of cellulose, and hydroxypropyl methyl cellulose constitutes methyl cellulose in which varying ratios of propylene glycol ether substiuttion to methoxyl substitution exist. The film forming composition is applied to the shape cores containing pharmaceutical ingredients by the process of this invention which comprises the steps of (1) establishing a rolling bed of shaped dosage units of a pharmaceutical ingredient, (2) continuously spraying said dosage units with a solution of a compound selected from the class consisting of methyl cellulose and hydroxypropyl methyl cellulose in substantially equal amounts of ethanol and chloroform in an atomized state, (3) continuously evaporating said ethanol and chloroform from said sprayed dosage units at a rate such that said dosage units maintain a substantially dry appearance and wherein there is materially no transfer of film per se or of film forming solution from tablet to tablet, and (4) continuing the simultaneous rolling, spraying and evaporating, and controlling the relative spray rate and evaporation in such a manner as to prevent transfer from tablet to tablet until a continuous film of the desired thickness and quality has been established on the dosage unit.

In using the composition of the present invention it is possible to use a conventional pear shaped rotating coating pan and to spray it on the tumbling tablets. However, best results are obtained if one uses the specifically designed rotating coating pan and its associated equipment which are described in my patent application Ser. No.

357,804 filed on Apr. 6,1964. That description is incorporated herein by reference.

It is to be understood that the coating process being novel in its concept and new in its application is an integral part of the invention. In this novel process it becomes necessary to achieve a fairly high degree of turbulence in the tablet mass and it is a requisite that each tablet pass beneath the spray in several positions. In conventional coating procedures, the film is transferred from tablet to tablet so agitation need not be as severe. The upper limit of turbulence is that which causes abrasion and breakage of the tablet. The weight of the tablet bed upon the coating aids in molding the film into a smooth continuous coating, but is not a requisite in all cases and other methods of imparting movement to the tablets could be used. The pressure of the spray is sufficient to noticeably indent a portion of the agitated tablet mass, an action which significantly contributes to the mixing of the tablets since it involves a change of direction in a portion of the mass. The preferred method of obtaining the requisite turbulence is the rolling of the tablets in a coating pan equipped with an air supply and exhaust.

The most important factors contributing to the process are the particle size of the suspended particles and spray droplet and the impact velocity. These are controlled by regulating the orifice sizes of both the air and fluid nozzles, the pressure on the atomized material which flows through the fluid orifice, and the pressure of the atomizing air if such is used. They are also controlled by regulating the viscosity and solids content of the coating composition, the number of nozzles, the spray distance, the size and shape of the spray pattern, the direction of the spray in relation to the travel of the tablets, and the spray angle. The number of nozzles does not vary directly as the weight of the pan load.

An equally important factor is the ratio of spray rate to drying rate. This is readily controlled by the use of flow meters and the control of bed temperatures which is a function of solvent evaporation rate. The temperature of the bed is monitored and kept within specified limits. At no time in the coating process are the tablets allowed to become "wet." The tablets feel quite dry at the end of the spraying cycle.

The average drop diameter is 18 microns for the process recommended which produces the type of coating desired. However, if a small change in drop diameter is desired, the following equation (Kirk-Othmer, "Encyclopedia of Chemical Technology") can be used as a guide toward adjusting flow ratios and the physical properties of the spray solution:

D_0=surface mean diameter in microns
v=relative velocity of air to liquid in meters per second
σ,η_1,ρ_1=surface tension, viscosity and density of liquid in c.g.s. units
Q_1/Q_a=volume flow of liquid/volume flow of air

$$D_0=\frac{585}{v}\left(\frac{\sigma}{\rho_1}\right)^{0.5}+597\left(\frac{\eta_1}{\sqrt{\sigma\rho_1}}\right)^{0.45}\left(1000\,\frac{Q_1}{Q_a}\right)^{1.5}$$

The drying rate can be controlled by regulating the temperature and volume of the drying air and by regulating the rate, direction, and volume of the exhaust air. The air can be directed to flow through or over the bed in any direction by diverse mechanical means. The particle size of the suspended particles and the viscosity of the coating composition are rigidly controlled.

The following examples are presented in order to describe the invention more fully, but it should be understood that the invention is not intended in any way to be limited in its scope by these specific examples.

EXAMPLE 1

60.75 liters of anhydrous ethanol (SD3A) were placed into a stainless steel container equipped with a high speed air-driven agitator. While stirring, 2.673 kilograms of hydroxypropyl methyl cellulose, N.F., 50 cps., were added slowly to avoid clumping. Then there was added in order, 0.668 kilogram of diethyl phthalate and 60.75 liters of chloroform U.S.P., the contents then being mixed until the hydroxypropyl methyl cellulose was dissolved. After solution had been effected, and while stirring, 3.645 kilograms of titanium dioxide, U.S.P., 1.215 kilograms of talc, U.S.P., and 0.365 kilogram of tartrazine FD&C Yellow No. 5, aluminum lake were added, and the stirring continued until a uniform suspension was obtained. This suspension was then passed through a Manton-Gaulin SMD homogenizer at 5000 p.s.i., at a rate of 73 g.p.h., 25 lbs./sq. in. suction.

Coating procedure

40.5 kilograms of compressed cores containing 0.25 gm. 1-α-methyldopa each were placed in a 42 inch stainless steel coating pan equipped with an air blower and exhaust system. The exhaust was turned on and drying air was directed toward the bottom of the tablet bed and adjusted to a temperature of approximately 190° F. The pan was then rotated at approximately 19 r.p.m., which caused the cores to take on a uniformly tumbling motion. A manifold of 4 No. 2050 fluid nozzles (Spray Systems) equipped with a No. 120 air nozzle and cleanout assembly was arranged to continuously coat the full area of the pan occupied by the cores. The previously prepared suspension was contained in a reservoir located ten inches above the manifold and fed by siphon to the nozzles. 40.5 liters of the suspension were sprayed from the nozzles using an atomizing air pressure of 46 p.s.i. pressure. The spray was directed at an angle to the face of the pan impinging to the left and in the opposite direction to the tablet flow. The average distance between the spray nozzles and the pan load was in the range of from about 7 to about 8 inches. The suspension flow rate was in the range of from about 0.225 to about 0.250 kilogram per minute, and the pan load was maintained at a temperature in the range of from about 28° C. to about 33° C. with the exhaust damper completely open. After completing the spraying the film coated tablets were transferred by plastic scoops to lined drying trays and dried in a forced-air cabinet for approximaely 18 hours at approximately 135° F. The resulting tablets had a clear colored continuous film coating formed thereon, which coating took a high polish when tumbled in carnauba wax.

EXAMPLE 2

75.25 liters of anhydrous ethanol (SD3A) were placed into a stainless steel container equipped with a high speed stainless steel, air-driven agitator. While stirring, 3.311 kilograms of hydroxypropyl methyl cellulose, N.F., 50 cps., were added to avoid clumping. Then there was added in order, 0.828 kilogram of diethyl phthalate and 75.25 liters of chloroform, U.S.P., the contents then being mixed until the hydroxypropyl methyl cellulose was dissolved. 30.0 liters of this solution were, then removed to a second mixing kettle equipped with a stainless steel, air-driven agitator and while stirring, there was added 4.515 kilograms of titanium dioxide and 1.505 kilograms of talc, U.S.P. The mixing was continued until a uniform suspension had been achieved, which was then passed through a Manton-Gaulin SMD homogenizer at 5000 p.s.i. pressure. The thus milled suspension was added to the remainder of the hydroxypropyl methyl cellulose solution and mixed well therewith. The resulting material was divided into two equal parts labelled Film Coating Suspension "A" and Film Coating Suspension "B." To 10.0 liters of Film Coating Suspension "B" was added 0.219 kilogram of Mapico Red No. 347 (color) with stirring until uniform suspension was achieved, and the suspension then passed through the homogenizer at 8000 p.s.i. pressure. The thus milled suspension was then added to the remainder of Film Coating Suspension "B" and mixed until uniform.

Coating procedure

50.00 kilograms of compressed cores containing a combination of .250 mg. 1-α-methyldopa and 15 mg. hydro-

chlorothiazide each were placed in a 42 inch stainless steel coating pan equipped with an air blower and exhaust system. The exhaust was turned on and drying air was directed toward the bottom of the bed of cores and adjusted to a temperature of approximately 190° F. The pan was then rotated at approximately 19 r.p.m., which caused the cores to take on a uniformly tumbling motion. A manifold of 4 No. 2050 fluid nozzles (Spray Systems) equipped with a No. 120 air nozzle and cleanout assembly was arranged to continuously coat the full area of the pan occupied by the cores. Film Coating Suspension "A" was contained in a reservoir located ten inches above the manifold and fed by siphon to the nozzles. 25.00 liters of Film Coating Suspension "A" were sprayed from the nozzles using an atomizing air pressure of 46 p.s.i. pressure. They spray was directed at an angle to the face of the pan impinging to the left and in the opposite direction to the tablet flow. The average distance between the spray nozzles and the pan load was in the range of from about 7 to about 8 inches. The suspension flow rate was in the range of from about 0.225 to about 0.250 kilogram per minute, and the pan load was maintained at a temperature in the range of from about 28° C. to about 33° C. with the exhaust damper completely open. After this spraying step, 25.00 liters of Film Coating Suspension "B" were sprayed on the tumbling cores in like manner. The cores were then transferred by plastic scoops to lined drying trays and dried in a forced-air cabinet for approximately 18 hours at approximately 135° F. The resulting tablets had a clear colored continuous film coating formed thereon, which coating took a high polish when tumbled in carnauba wax.

EXAMPLE 3

20.0 liters of the following film coating suspension, prepared essentially in the manner of Example 1, were sprayed onto approximately 33.0 kilograms of compressed cores containing 50 mg. indomethacin in the manner of Example 1.

Ingredient:	Amount
50 cps. ---kg---	0.435
Hydroxypropylmethyl cellulose, 50 cps. ---kg---	0.435
Titanium dioxide, U.S.P. ---kg---	0.593
Diethyl phthalate ---kg---	0.109
Talc, U.S.P. ---kg---	0.197
Mapico Black (color) ---kg---	0.016
Ethanol (SD3A), anhydrous ---l---	9.90
Chloroform, U.S.P. ---l---	9.90

The resulting tablets had an opaque continuous film coating formed thereon, which coating took a high polish when tumbled in carnauba wax.

The utilization of diethyl phthalate in the film coating composition of this invention is to provide the properties of a plasticizer, but such an ingredient is not critical to the effectiveness of the hydroxypropyl methyl cellulose without a plasticizer.

The incorporation of talc in the spraying solution is preferred for the reason that it prevents undue sticking of the cores to each other during the coating process.

The particular non-toxic coloring agents disclosed in the above examples are only exemplary of the use of such coloring agents in the coating composition, and any compatible non-toxic coloring agent may be used effectively.

Following the procedures described specifically in Examples 1–3, 700 gram batches of 5/16" standard curvature placebo tablets were coated in accordance with the following Examples 4–13.

EXAMPLE 4

Coating solution:	Amount
Methyl cellulose, 25 c.p.s. ---gm---	4
Alcohol SD3A, anhydrous ---ml---	100
Chloroform ---ml---	100
FDC Yellow No. 3 ---gm---	0.01

A continuous spray without drying air was successfully used to coat the tablets.

EXAMPLE 5

Coating solution:	Amount
Methyl cellulose, 50 c.p.s. ---gm---	4
Methylene chloride ---ml---	100
Isopropanol ---ml---	100
DC Yellow No. 11 ---gm---	0.01

A continuous spray without drying air was successfully used to coat the tablets.

EXAMPLE 6

Coating solution:	Amount
Methyl cellulose, 50 c.p.s. ---gm---	6
Toluene ---ml---	120
Alcohol, anhydrous ---ml---	120
Water ---ml---	15
FDC Red No. 4 ---gm---	0.01

A continuous spray with continuous application of hot drying air was successfully used to coat the tablets.

EXAMPLE 7

Coating solution:	Amount
Methyl cellulose, 25 c.p.s. ---gm---	6
Water ---ml---	15
Dioxane ---ml---	285

An intermittent spray with continuous application of hot drying air was successfully used to coat the tablets.

EXAMPLE 8

Coating solution:	Amount
Methyl cellulose, 50 c.p.s. ---gm---	6
Carbon tetrachloride ---ml---	135
Isopropanol ---ml---	135
Water ---ml---	24
FDC Yellow No. 5 ---gm---	0.01
DC Yellow No. 11 ---gm---	0.01

A continuous spray with continuous application of hot drying air was successfully used to coat the tablets.

EXAMPLE 9

Coating solution:	Amount
Methyl cellulose, 50 c.p.s. ---gm---	6
Carbon tetrachloride ---ml---	150
Isopropanol ---ml---	150
Water ---ml---	16
FDC Yellow No. 5 ---gm---	0.01

An intermittent spray with continuous application of hot drying air was successfully used to coat the tables.

EXAMPLE 10

Coating solution:	Amount
Methyl cellulose, 25 c.p.s. ---gm---	8
Alcohol, anhydrous ---ml---	100
Chloroform ---ml---	100
DC Yellow No. 11 ---gm---	0.01

A continuous spray with continuous application of hot drying air was successfully used to coat the tablets.

EXAMPLE 11

Coating solution:	Amount
Methyl cellulose, 15 c.p.s. ---gm---	10
Alcohol, anhydrous ---ml---	100
Chloroform ---ml---	100
Iron oxide brown ---gm---	1

A continuous spray formed by 5 lbs. pressure on the coating solution was used with continuous application of hot drying air to successfully coat the tablets.

EXAMPLE 12

Coating solution:	Amount
Methyl cellulose, 25 c.p.s. ---gm---	4
Chloroform ---ml---	100
Alcohol, anhydrous ---ml---	100
TiO_2 ---gm---	0.5

A continuous spray with continuous application of hot drying air was successfully used to coat the tablets.

EXAMPLE 13

Coating solution:	Amount
Methyl cellulose, 25 c.p.s. ---gm---	4
Alcohol, anhydrous ---ml---	100
Chloroform ---ml---	100
TiO_2 ---gm---	0.5
FDC Yellow No. 5 ---gm---	0.05

The FDC Yellow No. 5 was first dissolved in water and that solution was incorporated into the titanium pigment. The resulting slurry was dried and the dry product reduced to 100 mesh before it was incorporated into the coating solution. The final solution was sprayed continuously with continuous application of hot drying air to successfully coat the tablets.

The following Examples 14–23 represents batches of tablets containing active pharmaceutical ingredients which were coated in accordance with the procedures described in the previous examples:

EXAMPLE 14

A 5,000 gram batch of 130 mg. tablets containing as an active ingredient amitriptyline hydrochloride, 25 mg., was successfully coated by spraying continuously with intermittent application of hot drying air the following solution:

	Amount
Methyl cellulose, 25 cps. ---gm---	50
Alcohol, anhydrous ---ml---	1,250
Chloroform ---ml---	1,250
FDC Yellow No. 5 ---mg---	250
DC Yellow No. 11 ---gm---	1

EXAMPLE 15

Using the procedure and solution described in Example 14, a 5,000 gram batch of 130 mg. tablets containing as an active ingredient imipramine hydrochloride, 25 mg., was successfully coated, 3 mg. of resultant coating being formed on each tablet.

EXAMPLE 16

Using the procedure and solution described in Example 14 (except that FDC Blue No. 1 in the amount of 0.003 percent by weight of the total solution was substituted for the FDC Yellow No. 5 and the DC Yellow No. 11), a 5,000 gram batch of 130 mg. tablets containing as an active ingredient methscopolamine bromide 1.25 mg. was successfully coated.

EXAMPLE 17

Using the procedure and solution described in Example 14, a 5,000 gram batch of 130 mg. tablets containing as an active ingredient nor-amitriptyline hydrochloride, 25 mg., was successfully coated.

EXAMPLE 18

A 1,650 gm. batch of 130 mg. tablets containing as an active ingredient nor-amitriptyline hydrochloride, 10 mg., was successfully coated using the procedure described in Example 14 with the following solution:

	Amount
Methyl cellulose, 25 cps. ---gm---	40
Chloroform ---ml---	640
Alcohol, anhydrous ---ml---	640
FDC Blue No. 1 ---mg---	40

EXAMPLE 19

Using the procedure described in Example 14, a 5,000 gram batch of 130 mg. tablets containing as an active ingredient amitriptyline pamoate, 25 mg. was successfully coated with the following solution:

	Amount
Methyl cellulose, 25 cps. ---gm---	20
TiO_2 ---gm---	4
DC Yellow No. 11 ---mg---	20
Alcohol, anhydrous ---ml---	500
Chloroform ---ml---	500

EXAMPLE 20

Using the procedure described in Example 14, a 5,000 gram batch of 190 mg. tablets containing as an active ingredient amitriptyline hydrochloride, 10 mg.-ethinyl estradiol, 0.02 mg., was successfully coated with the following solution:

	Amount
Methyl cellulose, 25 cps. ---gm---	140
FDC Yellow No. 6 ---gm---	0.5
Methanol ---l---	2.85
Chloroform ---l---	2.85

EXAMPLE 21

Using the procedure described in Example 14, a one kilogram batch of 130 mg. tablets containing as an active ingredient amitriptyline hydrochloride, 25 mg.-perphenazine, 1 mg., was successfully coated with the following solution:

	Amount
Methyl cellulose, 25 cps. ---gm---	31
FDC Yellow No. 6 ---gm---	0.125
Methanol ---ml---	500
Chloroform ---ml---	500

EXAMPLE 22

Using the procedure described in Example 14, a 13.5 kg. batch of 130 mg. tablets containing as an active ingredient amitriptyline hydrochloride, 25 mg.-d-amphetamine sulfate, 5 mg., was successfully coated with the following solution:

	Amount
Methyl cellulose, 25 cps. ---gm---	343
DC Yellow No. 11 ---gm---	2.28
Chloroform ---l---	5.7
Alcohol, anhydrous ---l---	5.7

EXAMPLE 23

Using the procedure described in Example 14 and the solution described in Example 22, a 13.5 kg. batch of 130 mg. tablets containing as an active ingredient d-amphetamine sulfate, 5 mg., was successfully coated.

Having thus described my invention, I claim:

1. In a process for forming a continuous nontoxic film coating on a plurality of shaped pharmateutical ingredient containing cores, the steps which comprise (1) establishing a continuous tumbling movement of said cores, (2) continuously spraying said moving cores with an atomized solution of a compound selected from the class consisting of hydroxypropyl methyl cellulose and methyl cellulose in a solvent mixture selected from the group consisting of ethanol-chloroform, methylene chloride-isopropanol, toluene-alcohol, carbon tetrachloride-isopropanol, and methanol-chloroform, the spraying solution being applied at a rate of 0.225 to 0.250 kg./min. relative to a tablet volume of 40.5 kg., (3) continuously evaporating said solvent from said sprayed cores by directing a blast of hot air on the cores at a rate such that said cores maintain a temperature of 28°–33° C. and thereby a substantially dry appearance, and (4) continuing the simultaneous rolling, spraying and evaporating until a continuous film has been established on said shaped cores.

2. The process according to claim **1** in which the atomizing air pressure is about 46 p.s.i.

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