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TABLETS AND METHOD OF PRODUCING SAME

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This invention relates to medicinal tablets of the type formed by pressing in a die and has for its object the provision of improved tablets having one or more coatings pressed thereover and a method of making the tablets. The improved tablets of my invention comprise a center or core tablet of compressed granular material and one or more coatings of a dry granular material pressed thereover and in good bonding contact therewith.

One of the important characteristic features of my invention is the firm bonding of the coating layer to the core tablet. The tablets will withstand rough handling, as by dropping to the floor, and the wear and impact the tablets must receive in their packages during transportation without the coatings shelling or peeling off. Coating material does not just envelop the core tablet, the coating granules are actually embedded in, or intermingled with, the granules of the core tablet at the interface. On breaking or shattering a tablet of my invention, there is no consistent preferential severance of the coating at the interface, the breakage usually being non-selective in this respect.

The methods proposed heretofore for compressing coatings on previously formed core tablets have not been successful because the materials would not bond or intermingle at the interface with the result that the coatings would peel off like the shell of an egg. If dropped to the floor or jarred in the bottle, the coating would shatter and separate cleanly from the core tablet. After extensive investigations, I found that the core tablet must undergo an appreciable reduction in thickness while the coating is being compressed to effect adequate bonding. I achieve the adherence of the coating to the core tablet by using core tablets that approach 75% of the predetermined compression ratio, so that when the coating of loose granular material is compressed over the core tablet, the core tablet undergoes an appreciable diminution in thickness, say, from around 8% to 20% and for repeated compressions where two coatings are applied around 26% and higher.

My invention is applicable to the production of duplex tablets comprising a core tablet consisting of a medicinal ingredient and a coating which may be merely an inert flavored or colored granular material, a so-called sugar-base coating, or a granular formulation containing another medicament. The coating may be an enteric formulation to assure that the core tablet will be protected from the stomach action for assimilation in the intestines.

The invention is also applicable to the production of multiplex tablets comprising, for example, a medicinal core tablet, an enteric coating, and a third coating for disguising or protecting the inner medicaments, such as a sugar-base coating.

Moreover, I found that the granular coating material must meet certain requirements. The coating is formed of a free-flowing granular material preferably of carefully screened particles so that it will flow into the die mold and not bridge across the die and inadequately fill the die, giving an imperfect tablet.

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The coating material must possess natural inherent bonding and plasticizing characteristics or these characteristics must be imparted to the coating material. I have found that a good bond is created when the surface of the core or the contact surface of the coating is penetrated or preferably when both surfaces become enmeshed so that the granules are anchored one to another. Such bonding is further insured when a cohesive agent such as acacia is present (two percent of which has been found very satisfactory) or when as aforementioned the material is cohesive per se. To prevent cracking with sudden temperature changes the coating must possess natural plasticizing properties or a plasticizer such as for example gelatin should be employed (1.75% has been found to be satisfactory). The usual disintegrators such as corn starch may be used if necessary to achieve a rapid and controlled disintegration of the coating.

The following examples illustrate typical granular formulations for core tablets and coatings:

EXAMPLE 1

Core tablet formulation

25	Alpha chloralose	1 oz.	25.5 gr.
	Delvinal acid	2 oz.	51.0 gr.
	Lactose	1 oz.	30.0 gr.
	Dicalcium phosphate		230.0 gr.
	Corn starch paste 7-1, 2 oz. allow		101.0 gr.
30	Distilled water, q. s. about ½ fl. oz.		
		5 oz.	

Additives:

35	Corn starch dried	250 gr.
	Talc	45 gr.
	Magnesium stearate	17.5 gr.
		5 oz. 312.5 gr.

The first 4 powders were mixed together and the mixture passed through a fine screen. The screened mixture was granulated with the starch paste to form wet granules which were passed through a 16-mesh screen, dried at 120-130° F., and then reduced in size to pass through a 20-mesh screen. The dried corn starch, talc, and magnesium stearate were incorporated in the screened mixture, and this mixture was compressed in a press having 5/16 inch dies with standard curvature punches, producing tablets having an average weight of 2.5 gr. with a thickness of 0.157 inch and a hardness of 3-3.5 kg.

Coating formulation

SUGAR-BASE COATING—PEACH COLORED

	Lactose	4 lb. 3 oz.
	Powdered sugar with 3% starch	4 lb. 3 oz.
55	Acacia powdered	2 oz. 385 gr.
	Corn starch	5 oz. 350 gr.
	Solution D & C Red #19 (1-300), used 120 minims.	
	Alcohol S. D. 3A 95%, 2 fl. oz.	
	Gelatin solution, 20% allow	1 oz. 140 gr.
60	Distilled water, q. s.	
		9 lb.

The first 4 powders were mixed together with some color solution. The mixture was passed through a very fine screen and the screened material was granulated with the gelatin solution to form damp granules which were passed through a 12-mesh screen. The granules were spread on trays and air dried for 24 hours and finally dried at 140° F. for 2 hours. The granules were passed through a 30-mesh screen. To this screened material was added 0.5% magnesium stearate just prior

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to compression. The mixture was fed to a tablet-forming press having $\frac{13}{32}$ inch dies with standard curvature punches and uniformly distributed around the core tablets of Example 1. The coated tablets had an average weight of $\frac{5}{4}$ gr. with an outside thickness of 0.168–0.170 inch, a core thickness after coating of 0.131–0.133 inch and a hardness of 10 kg. During compression, the core tablets were reduced in thickness an average of 0.025 inch (16% reduction).

EXAMPLE 2

Core tablet formulation

Aspirin powder	7 oz. 179 gr.
Phenacetin	2 oz. 422 gr.
Caffeine alkaloid	1 oz. 49 gr.
Corn starch	350 gr.
Starch paste 7-1, 3 oz. allow	152.5 gr.
Distilled water to granulate, q. s.	

12 oz. 277.5 gr.

Additives:

Corn starch dried	1 oz. 35.0 gr.
Talc dried	300.0 gr.

14 oz. 175.0 gr.

The first 4 powders were mixed together and the mixture passed through a fine screen. The screened mixture was granulated with the damp starch paste to form wet granules which were passed through a 10-mesh screen, dried at 120–130° F., and then reduced in size to pass through a 16-mesh screen. The dried corn starch and talc were incorporated in the screened mixture, and this mixture was compressed in a press having $\frac{13}{32}$ inch dies with standard curvature punches, producing tablets having an average weight of 5.5 gr. with a thickness of 0.190 inch and a hardness of 3–4 kg.

Coating formulation

Propadrine hydrochloride	1 oz. 49 gr.
Powdered sugar	7 oz. 286.5 gr.
Lactose	15 oz.
Corn starch	2 oz.
Acacia powder	220.0 gr.
D & C Red No. 19 (1-300), 35 minims.	

Gelatin solution 20%, 9 drachms.
Distilled water, q. s. to granulate.

1 lb. 10 oz. 118.0 gr.

Additive:

Magnesium stearate	57
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2 lb. 8 oz. 350.0 gr.

The first 5 powders were mixed together with the color solution. The mixture was passed through a very fine screen and the screened material was granulated with the gelatin solution to form damp granules which were passed through a 12-mesh screen, and dried at 120° F. The granules were passed through a 30-mesh screen. To this screened material was added the magnesium stearate just prior to compression. The coating mixture was fed to a tablet-forming press having $\frac{1}{2}$ inch dies with standard curvature punches and uniformly distributed around the core tablets of Example 2. The coated tablets had an average weight of 8.5 gr. with an outside thickness of 0.217 inch, a core thickness after coating of 0.161–0.164 inch and a hardness of 12 kg. During compression, the core tablets were reduced in thickness an average of 0.028 inch (15% reduction).

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EXAMPLE 3

Core tablet formulation

Ascorbic acid powder	4 oz. 121.5 gr.
Antioxidant G4 conc.	8.0 gr.
Lactose	2 oz. 110.0 gr.
Potato starch	1 oz. 346.0 gr.
Charcoal	1.5 gr.
Confectioner's glaze, 10 drachms allow	80.5 gr.
Alcohol S. D. 3A anhydrous, q. s.	

8 oz. 230.0 gr.

Additives:

Talc, dried	215.0 gr.
Calcium stearate	24.0 gr.

9 oz. 31.5 gr.

The antioxidant was incorporated in the ascorbic acid and the remaining powdered materials mixed therewith. This mixture was passed through a fine screen and intermixed and granulated with the confectioner's glaze, adding alcohol as necessary to form granules. These granules were passed through a 16-mesh screen and then dried at 120° F. The dried material was reduced in size and passed through a 20-mesh screen. The dried talc and calcium stearate were mixed with the granules and the mixture was compressed in a press having $\frac{1}{32}$ inch dies with standard curvature punches, producing tablets having an average weight of 1.8 gr. with a thickness of 0.125 inch, and a hardness of 3 kg.

Coating formulation

Vitamin B ₁₂ 0.1% trituration in sodium chloride	374 gr.
Corn starch dried	131.5 gr.
Sodium chloride powder	4 oz. 390.5 gr.
Alcohol S. D. 3A 95%, 8 parts	used 12 drachms
Distilled water, 2 parts	

15 oz. 52.5 gr.

The powders were intermixed and granulated by dampening, then passed through a 16-mesh screen, and dried at 110° F. The dried material was reduced to pass through a 30-mesh screen. The sodium chloride is self-lubricating and the screened mixture was compressed over the core tablets of Example 3 in a press having $\frac{5}{16}$ inch dies with standard curvature punches. The coated tablets had an average weight of 3.0 gr. with an outside thickness of 0.155 inch, a core thickness after coating of 0.111–0.113 inch, and a hardness of 8 kg. During compression, the core tablets were reduced in thickness 0.013 inch (10.4% reduction).

EXAMPLE 4

Core tablet formulation

Lactose	18 lb. 8 oz.
Dicalcium phosphate	7 lb. 7 oz.
Corn starch	2 lb.
Acacia powder	9 oz.
Starch paste 7-1, 6 pints allow	12 oz.
Distilled water, a sufficient quantity.	

29 lb. 4 oz.

Additives:

Talc	10 oz.
Magnesium stearate	2 oz.

30 lb.

The powders were mixed together and the mixture passed through a fine screen. The screened mixture was granulated with the starch paste to form wet granules which were passed through a 12-mesh screen, dried at 120° F., and then reduced in size to pass through a 20-mesh screen. The dried talc and magnesium stearate

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were incorporated in the screened mixture, and this mixture was compressed in a press having $\frac{5}{16}$ inch dies with standard curvature punches, producing tablets having an average weight of 3.0 gr. with a thickness of 0.155–0.157 inch, and a hardness of 3.5–4.5 kg.

Coating formulation

A sugar-base coating similar to that of Example 1 was used and applied to the core tablets of Example 4 in the same manner. The press had $\frac{13}{32}$ inch dies with standard curvature punches. The coated tablets had an average weight of 5.2 gr. with an outside thickness of 0.168–0.170 inch, a core thickness after coating of 0.131–0.133 inch and a hardness of 8–10 kg. During compression, the core tablets were reduced in thickness an average of 0.024 inch (15% reduction).

EXAMPLE 5

Core tablet formulation

Aspirin powder, USP	14 oz. 357 gr.
Lactose	11 oz. 157.5 gr.
Corn starch	1 oz. 192.5 gr.
Corn starch paste (7-1), 6 oz. allow.	368.0 gr.
Distilled water—a sufficient quantity.	

Additive:

Talc with magnesium stearate 2%.	1 lb. 12 oz. 200.0 gr. 30
	150.0 gr.

1 lb. 12 oz. 350.0 gr. 35

The first 3 powders were mixed together and the mixture passed through a fine screen. The screened mixture was granulated with the damp starch paste to form wet granules which were passed through a 10-mesh screen, dried at 120–130° F., and then reduced in size to pass through a 16-mesh screen. The talc and magnesium stearate were incorporated in the screened mixture and this mixture was compressed in a press having $\frac{13}{32}$ inch dies with standard curvature punches, producing tablets having an average weight of 6.0 gr. with a thickness of 0.190 inch, and a hardness of 4.5–5.0 kg.

Coating formulation

Propadrine hydrochloride	1 oz. 49 gr.
Powdered sugar	7 oz. 286.5 gr.
Lactose	15 oz.
Corn starch	2 oz.
Acacia powder	220.0 gr.
D & C Red No. 19 (1-300), 35 minims.	
Gelatin solution 20%, 9 drachms.	
Distilled water to granulate.	

Additive:

Magnesium stearate	1 lb. 10 oz. 118.0 gr.
	57.0 gr.

3 lb. 7 oz. 87.5 gr. 65

The core formulation was processed as in Example 2. The press had $\frac{1}{2}$ inch dies with standard curvature punches. The coated tablets had an average weight of 11.5 gr. with an outside thickness of 0.215 inch, a core thickness after coating of 0.149–0.154, and a hardness of 15 kg. During compression, the core tablets were reduced in thickness an average of 0.036 inch (19% reduction).

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EXAMPLE 6

Core tablet formulation

	Grams
5 Methapyrilene hydrochloride	810.0
Lactose	100.0
Dextrin white	100.0
Corn starch	80.0
Distilled water, sufficient to granulate.	

Additive:

Corn starch, dried	126.0
Talc with magnesium stearate, 2%	44.0

1260.0

The core formulation was processed as in Example 2 and the mixture was compressed in a press having $\frac{7}{32}$ inch dies with standard curvature punches, producing tablets having an average weight of 1.2 gr. with a thickness of 0.125–0.127 inch, and a hardness of 2.5–3.5 kg.

First coating formulation

Aspirin as pink granulation containing:

	Grams
16% corn starch	6250
Talc dried	50

7560

The granulated pink aspirin and dried corn starch were passed through a 20-mesh screen and dried talc mixed therewith and the mixture fed to a tablet-forming press having $\frac{13}{32}$ inch dies with standard curvature punches and uniformly applied over the core tablets of Example 6. The coated tablets had an average weight of 7.2 gr. with an outside thickness of 0.190 inch, a core thickness (not determined), and a hardness of 5–5.5 kg.

Second coating formulation

	Grams
40 Propadrine hydrochloride	243.25
Powdered sugar	1674.5
Lactose	3281.25
Corn starch	437.5
45 Acacia powder	110.0
Gelatin solution 20%, 4.5 drachms.	
Distilled water to granulate.	

5746.5

Additive:

50 Magnesium stearate	28.5
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13335.0

This second coating formulation was processed in a manner similar to the coating formulation of Example 2 and was fed to the tablet-forming press and pressed over the first coating. The press had $\frac{1}{2}$ inch dies with standard curvature punches. The second coating resulted in tablets having an average weight of 11.5 gr. with an outside thickness of 0.230 inch, a core thickness of 0.100–0.104 inch, and a hardness of 10 kg. (19% reduction). The thickness of the tablet beneath the outer coating after recompression was 0.168–0.172 inch, a reduction of 0.020 inch (10%). During both compressions the core tablets were reduced in thickness 0.024 inch.

EXAMPLE 7

Core tablet formulation

70 Chloral hydrate granular, USP	8 oz. 322.0 gr.
Talc, dried	246.75 gr.

9 oz. 131.25 gr.

The granular chloral hydrate was passed through a 75 20-mesh screen, the dried talc incorporated therein, and

the mixture was compressed in a press having $\frac{5}{16}$ inch dies with standard curvature punches, producing tablets having an average weight of 3.8 gr. with a thickness of 0.155 inch, and a hardness of 2.5–3.0 kg.

First coating formulation

Glyceryl tristearate.....	Grams
Aluminum monostearate.....	9,600
	400
	10,000

The coating materials were fused and stirred until congealed. The cooled mixture was passed through a 16-mesh screen and then reduced to pass through a 20-mesh screen. To each 850 grs. was added 150 grs. of dried corn starch and the mixture was compressed around the core tablet in a press having $\frac{13}{32}$ inch dies with standard curvature punches. The tablets had an average weight of 6.0 gr. with an outside thickness of 0.183–0.185 inch, a core thickness after coating of 0.128–0.132 inch, and a hardness (not determined). During compression, the core tablets were reduced in thickness an average of 0.025 inch (16% reduction).

Second coating formulation

Lactose	19 lbs.	6 oz.	200 gr.
Corn starch.....	1 lb.	12 oz.	
Acacia powder.....		10 oz.	
D & C red No. 19, 7.75 gr.			
Distilled water, $2\frac{1}{2}$ fluid ounces.			
Alcohol 3 A 95%, $2\frac{1}{2}$ fluid ounces.			
Gelatin solution 20%, 2 pints allow		3 oz.	237.5 gr.
Alcohol 3A			
95%, 1 part.	sufficient to granulate.		
Distilled water, 1 part.			
	22 lbs.		

The second coating formulation was processed as in Example 1. Just prior to feeding the granular coating formulation to the press about 0.5% magnesium stearate was incorporated in the material which was compressed over the aforementioned coating in a press having $\frac{1}{2}$ inch dies with standard curvature punches, producing tablets having an average weight of 11 gr. with a thickness of 0.225 inch, and a hardness of 5 kg. The thickness of the inner core after two recompressions was 0.128–0.130 and the outside thickness of the first coating was 0.170 inch which was reduced in thickness about 0.014 inch in the second compression.

In the foregoing examples, the hardness was measured on the Strong Cobb hardness tester, the reading having been taken at the time of shattering of the tablets.

The core forming and coating application may be carried out in any suitable tablet-forming machine such as a rotary press. I prefer to form the core tablets by customary practices and to apply the coating or coatings using the apparatus and the method of the copending application of John Edward Wolff and Paul W. Wilcox,

Serial Number 277,436, filed March 19, 1952, now Patent No. 2,700,938.

I claim:

1. The method of coating medicinal tablets which comprises compressing a core tablet of granular material to a firm condition but which is still capable of further appreciable compression, applying a uniform layer of free-flowing dry granular material having bonding characteristics over the core tablet in a die, and applying to the granular coating material such a compressive force as to compress the coating on the core tablet and diminish the thickness of the core tablet at least 8%, whereby the particles of granular material are intermingled at the interface resulting in a firm bonding of the coating to the core tablet.

2. In the method of claim 4, compressing the coating material sufficiently to result in a reduction in the thickness of the core tablet of at least 10%.

3. The method of coating a medicinal tablet which comprises compressing a core tablet of granular material to a firm condition but which is still capable of further appreciable compression, applying a layer of dry granular material having plasticizing characteristics over the core tablet in a die, and applying to the granular coating material such a compressive force as to compress the coating on the core tablet and diminish the thickness of the core tablet at least 8%, whereby the particles of granular material are intermingled at the interface resulting in a firm bonding of the coating to the core tablet.

4. An improved medicinal tablet comprising a core tablet of granular medicinal material, a compressed coating of originally free-flowing granular material having bonding and plasticizing characteristics, said medicinal tablet being characterized by having the granules of the core tablet and the granules of the coating at their interface enmeshed and anchored one to another, said medicinal tablet being further characterized in that on breaking the tablet the coating does not shell off but remains bonded to the core tablet, said medicinal tablet having been produced by the method defined in claim 1.

5. An improved medicinal tablet according to claim 4 which comprises an enteric coating of granular material having bonding and plasticizing characteristics over the core tablet and a sugar coating of granular material also having bonding and plasticizing characteristics compressed over the enteric coating, said medicinal tablet being further characterized by having the granules of the sugar coating and the granules of the enteric coating intermingled at their interface.

References Cited in the file of this patent

UNITED STATES PATENTS

207,013	Carter	Aug. 13, 1878
701,438	Whyte	June 3, 1902
1,881,197	Kirk	Oct. 4, 1932
2,517,513	Vaernet	Aug. 1, 1950
2,656,298	Loewe	Oct. 20, 1953

FOREIGN PATENTS

471,116	Great Britain	Aug. 24, 1937
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