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TABLETING PROCESS

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ABSTRACT OF THE DISCLOSURE

A two-cycle tableting process for producing compressed tablets containing a low-melting or adhesive active medicinal material which comprises introducing into the tablet die a first granulation containing an abrasive material, compressing and ejecting the resulting tablet, introducing into the same die a second granulation containing the low-melting or adhesive material, compressing and ejecting the resulting tablet. The cycle can be repeated until the desired number of tablets is obtained.

The present invention relates to a tableting process. More particularly, the invention relates to a novel tableting process which makes it possible to produce acceptable tablets from materials or combinations which, under standard operating conditions, would normally tend to adhere to the dies and punches of a tableting machine.

The problem of compressing low melting or adhesive pharmaceutical materials into tablets which are pharmaceutically acceptable and wherein the active material is physiologically available to the user has faced the pharmaceutical industry for years. If said low melting materials are compressed into tablets under high compression forces, the active ingredient tends to melt due to the heat generated on compression. Resolidification of the material after said melting usually results in tablets which have slow disintegration or dissolution rates and which, consequently, do not release the active material into the patient's system at a satisfactory rate. In addition, the melting caused by the high compression forces results in high percentages of fractured or laminated tablets, which are commercially unusable.

If, on the other hand, lower compression forces are used, some of the tableting granulation tends to adhere to the dies and punch faces of the tableting machine. Consequently, the resulting tablets are physically deformed.

Various methods of producing acceptable tablets containing low melting or adhesive materials have been proposed in the past. One of such methods comprises greatly increasing the amount of excipient customarily used in the tablet granulation. While, in some cases, it is possible to produce acceptable tablets by this method, such tablets are generally much larger than standard pharmaceutical tablets and due to their size, are unsatisfactory from a marketing standpoint.

It is an object of the invention to provide a method for producing acceptable tablets which contain one or more low-melting and/or adhesive materials. It is another object of the invention to provide a method of producing acceptable pharmaceutical tablets containing one or more low-melting and/or adhesive active materials whereby the resulting tablets have satisfactory disintegration or dissolution rates. It is a further object of the invention to produce acceptable pharmaceutical tablets containing tybamate. These and other objects of the invention will become apparent to those skilled in the art in the light of the instant specification.

In its broad aspect, the invention relates to a method of producing acceptable compressed tablets from a tablet granulation containing a low-melting or adhesive material, said method comprising the steps of:

(a) Introducing into a tablet die a first tablet granulation containing an abrasive material;

(b) Compressing said first granulation into an abrasive tablet under a high compression force;

(c) Ejecting said abrasive tablet from said tablet die;

(d) Introducing into said tablet die a second tablet granulation containing a low-melting or adhesive material;

(e) Compressing said second granulation into a production tablet under a low compression force;

(f) Ejecting said production tablet from said tablet die; and

(g) Repeating steps (a) to (f) until the desired number of production tablets are produced.

Among the low melting or adhesive materials which can be processed into acceptable pharmaceutical tablets according to the method of the present invention, there can be mentioned, for example, tybamate (chemically, 2-methyl - 2 - propyltrimethylene butylcarbamate carbamate), mephenesin, guaianesin, theophylline, meprobamate-aluminum hydroxide combinations, and the like.

As used herein and in the appended claims, the terms "low" and "high," as applied to the compression forces used during the tableting of, respectively, the production tablets and the abrasive tablets, signify compression forces which are lower or higher than those commonly used during standard tableting operations.

For example, it has been found that suitable tablets can be prepared from low melting or adhesive materials by employing a compression force, as measured at the punch face, in the range of from about 2 to about 8 tons per square inch and preferably about 4 tons per square inch. Said forces, which are unusually low by pharmaceutical tableting standards, would normally yield tablets which would adhere to the dies and punch faces of the tableting machine and which consequently, would be physically deformed. However, when such low compression forces are utilized in the process of the invention, there are produced elegant tablets which have suitable disintegration and dissolution rates.

The high compression forces used in the preparation of the abrasive tablets are in the range of from about 15 to about 25 tons per square inch and higher. The upper limit is generally determined by the physical capabilities of the tableting machine employed in the process since it has been found that, the higher the compression force, the better the cleaning effect will be on the punch and die walls.

In a preferred aspect of the invention, it has been found that optimum results can be obtained by varying the degree of penetration of the punch into the die cavity during the compression of the production tablets and the abrasive tablest. In compressing the production tablets a penetration of about ⅛ inch or less is preferred whereas in compressing the abrasive tablets a penetration of ⅜ inch or more is preferred. The deeper penetration used in compressing the abrasive tablets increases the amount of travel of the tablet along the die wall and, consequently, gives maximum die wall cleaning.

The abrasive materials which are used in the present process are materials which are sufficiently abrasive as to effectively clean the die walls and punch faces without damaging same. In addition, for the sake of avoiding contamination, it is preferred that said materials be non-toxic. Furthermore, for efficiency and economy, preferred materials should be easily compressible into coherent tablets, preferably without the need of complicated granulation stages.

Suitable abrasive materials useful in the practice of the invention include, for example, lactose, wood cellulose, magnesium hydroxide, tricalcium phosphate, dicalcium phosphate, and mixtures thereof.

The following are typical compositions which can be used in the practice of the present invention to produce abrasive tablets which will effectively clean the dies and punches. Compositions I–IV can be tableted directly after the components thereof are intimately admixed whereas composition V should be subjected to a stage-wise granulation prior to tableting in a manner known in the art. The percentages in parenthesis indicate the most preferred compositions.

Composition I

Components:	Weight percent
Anhydrous lactose (75)	65–90
Wood cellulose (24.5)	10–35
Magnesium stearate (0.5)	0.5–1.0

Composition II

Components:	Weight percent
Anhydrous lactose (75)	65–90
Magnesium hydroxide (24.5)	10–35
Magnesium stearate (0.5)	0.5–1.0

Composition III

Components:	Weight percent
Anhydrous lactose (75)	65–90
Wood cellulose (12.5)	5–18
Magnesium hydroxide (12.0)	5–18
Magnesium stearate (0.5)	0.5–1.0

Composition IV

Components:	Weight percent
Anhydrous latose (98)	97–99
Magnesium stearate (2)	1–3

Composition V

Components:	Weight percent
Tricalcium phosphate (50)	40–60
Lactose (monohydrate) (35)	30–40
Starch (10)	8–12
Acacia (3)	2–5
Magnesium stearate (2)	1–3

The low melting or adhesive materials are prepared for tableting in accordance with the present invention in manners well known to those skilled in the art by combining the active material with conventional excipients. A suitable granulation to be compressed into acceptable tablets according to the present teachings would contain at least 50 percent by weight of the low melting or adhesive material, from about 10 to about 30 percent by weight of a suitable filler, from about 5 to about 20 percent by weight of a disintegrating agent, from about 2 to about 15 percent by weight of a binding agent, and from about 1 to about 5 percent by weight of a lubricant.

In general, all conventional excipients are operable in the practice of the invention. It has been found, however, that wood cellulose is the preferred filler.

For example, a preferred granulation for compounding tybamate granules into tablets has the following composition:

Component:	Weight percent
Tybamate	67.0
Wood cellulose	16.0
Starch	12.0
Gelatin	3.5
Stearic acid	1 5

The process of the invention is conveniently carried out in a standard double rotary tablet press, with a plurality of dies arranged to compress and eject two tablets per die per revolution of the head. Two feed hoppers are provided, one filled with the abrasive composition and the other with the production granulation.

The press is adjusted so that, during the first half revolution of the head, each successive die is filled with the abrasive material which is then compressed into a tablet at a pressure of from about 15 to 25 tons per square inch and at a punch penetration of about ⅜ inch or more. The tablets thus formed are then ejected and collected into a suitable container.

The cycle is then repeated during the second half revolution of the head, using the production granulation and compressing same into tablets at a pressure of from about 2 to about 8 tons per square inch and with a punch penetration of about ⅛ inch or less.

The abrasive tablets produced can, of course, be crushed by any suitable means and the resulting material reused in the practice of the invention.

The following example is illustrative of the invention.

Tybamate tablets were produced according to the practice of the invention. The tybamate granulation was prepared by coating 67.0 parts of tybamate powder with 3.5 parts of gelatin (applied as a 10% solution). After the resulting granules were dried, they were admixed with 13 parts of wood cellulose and again coated with 1.5 parts of starch (applied as a paste having a 5% starch concentration). The final granulation was obtained by admixing the dried double-coated granules with 3.0 parts of wood cellulose, 10.5 parts of starch and 1.5 parts of stearic acid.

The granulation was compressed into tablets using a standard double rotary tablet press equipped with dies of 7/16 inch diameter.

The abrasive material used had the following composition.

Components:	Weight percent
Anhydrous lactose (75)	65–90
Wood cellulose (24.5)	10–35
Magnesium stearate (0.5)	0.5–1.0

Tablets were compressed from the tybamate granulation and from the abrasive material according to the present invention.

The punch penetration for the production tablets was maintained at ⅛ inch while the compression force was varied as indicated below. In tableting the abrasive material, the punch penetration and the compression force were maintained at ⅜ inch and 22 tons per square inch respectively.

The tybamate tablets thus produced were examined visually and samples thereof were then tested for disintegration using the U.S.P. XVI method for disintegration.

The tablets exemplified by Sample No. 1 were found to be too soft for commercial handling and use. The tablets exemplified by Samples Nos. 5–9 were observed to be fractured or laminated and, therefore, commercially unacceptable. Tablets produced in accordance with the present invention, and exemplified by Samples Nos. 2–4, were well-formed commercially acceptable tablets.

The results are as follows:

	Compression Force (Tons per square inch)	Disintegration Time
Sample No.:		
1	0	5 sec.
2	2.1	10 sec.
3	4.2	30 sec.
4	6.3	2 min.
5	14.0	10 min.
6	18.2	11 min.
7	22.4	8 min.
8	26.6	8 min.
9	30.8	8 min.

As will be apparent from the above table, the tablets produced in accordance with the present invention also possess excellent disintegration rates.

The invention in its broader aspect is not limited to the specific steps, methods and compositions described, but departure may be made therefrom within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its chief advantages.

For example, the present process will also permit the compression of other soft materials used in the pharmaceutical industry, such as suppositories. A suitable granu-

lation made of suppository medicaments and excipients may be compressed according to the claimed method by using suitable dies and punches to produce the conventional suppository shapes.

Suppository granulations to be compressed may contain, for example, a bismuth salt as an astringent, benzocain as a local anesthetic, and meprobamate as a tranquillizer. The medicaments may be granulated with a Carbowax-4000 to 6000 and suitable fillers as excipients.

Effervescent laxative suppository compositions containing Carbowax-6000, sodium bicarbonate and sodium biphosphate have been compressed according to the method of the present invention.

What is claimed is:

1. A method of producing compressed tablets from a tablet granulation containing a low-melting or adhesive active medicinal material, said method comprising the steps of:

(a) introducing into a tablet die a first tablet granulation containing an abrasive material selected from the group consisting of lactose, wood cellulose, magnesium hyydroxide, tricalcium phosphate, dicalcium phosphate, and mixtures thereof;

(b) compressing said first granulation into an abrasive tablet by means of a tablet punch at a compression force of from about 15 to about 25 tons per square inch and with a punch penetration into the die cavity of at least about ⅜ inch;

(c) ejecting said abrasive tablet from said tablet die;

(d) introducing into said tablet die a second tablet granulation containing at least 50 percent by weight of a low melting or adhesive active medicinal material;

(e) compressing said second granulation into a production tablet by means of said tablet punch at a compression force in the range of from about 2 to about 8 tons per square inch and with a punch penetration into the die cavity of up to about ⅛ inch;

(f) ejecting said production tablet from said tablet die; and

(g) repeating steps (a) to (f) until the desired number of production tablets are produced.

2. A method of producing compressed tablets from a tablet granulation containing tybamate, said method comprising the steps of:

(a) introducing into a tablet die a first tablet granulation containing an abrasive material selected from the group consisting of lactose, wood cellulose, magnesium hydroxide, tricalcium phosphate, dicalcium phosphate, and mixtures thereof;

(b) compressing said first granulation into an abrasive tablet by means of a tablet punch at a compression force of from about 15 to about 25 tons per square inch and with a punch penetration into the die cavity of at least about ⅜ inch;

(c) ejecting said abrasive tablet from said tablet die;

(d) introducing into said tablet die a second tablet granulation containing tybamate;

(e) compressing said second granulation into a tybamate tablet by means of a tablet punch at a compression force in the range of from about 2 to about 8 tons per square inch and with a punch penetration into the die cavity of up to about ⅛ inch;

(f) ejecting said tybamate tablet from said tablet die; and

(g) repeating steps (a) to (f) until the desired number of tybamate tablets are obtained.

3. The method of claim 2 wherein said second tablet granulation contains at least 50 percent by weight of tybamate.

4. The method of claim 3 wherein the tybamate content is about 67 percent by weight.

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