United States Patent Office 3,518,346 Patented June 30, 1970

3,518,346

TABLETING

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No Drawing. Filed Jan. 2, 1968, Ser. No. 694,890
Int. Cl. A61j 3/10
U.S. Cl. 424—44 5 Claims

ABSTRACT OF THE DISCLOSURE

An improvement in the process of compressing powdered tabletable compositions is gained by mixing fumaric acid with said composition prior to compression. The fumaric acid acts as a surface lubricant and as an internal compression lubricant for said tabletable compositions. The powdered tabletable compositions lubricated with fumaric acid can be those intended for internal employment such as for alkalizing of the stomach or intended for external use such as for general cleaning of solid surfaces.

This invention relates to tableting and provides a new tableting lubricant which can be mixed with a powdered tabletable composition to aid during the compression thereof into tablets.

Tableting lubricants perform the general functions of providing (1) surface lubrication for the punch and die surfaces which come into contact with one another and with the compressed composition and (2) internal compression lubrication in order to lend pliability to the composition being compressed. Both of these lubrication functions must be satisfied if the powdered tabletable composition of interest is to be tableted at commercially acceptable rates in tableting machines operated at high speeds. Some prior lubricants have provided only one of these two necessary lubrication functions and hence have necessitated the use of a second lubricant. A general problem with these prior lubricants has been their insolubility which causes a tablet formed from an otherwise soluble composition to give a cloudy suspension rather than a clear solution when dissolved in water. Talc and magnesium stearate are examples of such lubricants. The use of other lubricants is restricted because of their toxicity. Examples are boric acid, benzoic acid and polyethylene glycol. Some tableting lubricants such as sodium benzoate have therapeutic effects and therefore alter the pharmacological acceptability of tablets in which they are included.

It has not been found that fumaric acid provides the necessary tableting lubrication for powdered tabletable compositions and enables tablets to be compressed therefrom at high speeds. Fumaric acid does not impart additional toxicity of pharmaceutical activity to such compositions and has the advantage of being water soluble.

Accordingly, it is an object of this invention to provide a process for making a tablet which comprises compressing a mixture of fumaric acid and a powdered tabletable composition.

The fumaric acid tableting lubricant can be used with a wide range of powdered tabletable compositions to allow high speed tableting thereof. While various amounts of fumaric acid can be mixed with such compositions depending upon the presence therein of ingredients which impart some lubrication and upon the tableting speed desired, it is usually sufficient to use at least 5% fumaric acid based on the total weight of the fumaric acid and the composition being tableted, when no other lubricants are used. If desired, fumaric acid may be used in large amounts, approaching the total tablet weight, since it is cohesive when compressed.

Fumaric acid is generally available as minute colorless monoclinic prisms which can be used in the present invention without further modification. If desired, these small prisms can be comminuted to any desired fineness. Mesh sizes of 40 (United States Standard) and finer are particularly preferred for use with most powdered compositions. Fumaric acid has low toxicity and hence may be used for tablets which are intended to be taken internally. It appears to be unique in its tableting lubrication properties since its metal salts and homologous acids do not exhibit these properties. It has also been found that its stereo-isomer, maleic acid, does not show the same lubrication properties.

The tabletable compositions which can be lubricated for tableting with fumaric acid can be any compositions which are cohesive enough when compressed to form and retain a table shape. Such compositions can be composed of powdered detergents, disinfectants, and/or abrasives which disintegrate when placed in water to form cleaning solutions of various types. The preferred compositions are effervescent mixtures, comprising an alkali metal carbonate or bicarbonate and an acid such as malic, citric or tartaric acids, which are capable of rapidly releasing carbon dioxide upon addition of water thereto. When the carbon dioxide has been released, the solution formed is useful for its alkalizing properties when taken orally. The compositions can also be composed of at least one therapeutic agent, a water-soluble excipient, and any necessary coloring or flavoring agents, diluents, binders, or disintegrators. In such compositions the therapeutic agent may be, e.g., acetylsalicylic acid, acetyl p-aminophenol or other analgesic. If necessary, binders may be added to the base composition to promote cohesion. All such compositions are tabletable in that they are cohesive when compressed; however, most of such compositions can be tableted only by hand since they cause binding and scoring of the punches and dies of power driven tableting machines. In order to attain commercial production speeds a tableting lubricant must be employed to reduce surface friction and internal compression friction.

The fumaric acid of the present invention may be used as the sole lubricant or may be employed in conjunction with another lubricant included in the tabletable composition. More particularly the fumaric acid lubricant can be substituted for various materials which function as tablet lubricants during compression.

In effervescent tablets, fumaric acid provides the additional effect of taking part in the effervescent action. When the fumaric acid does form part of the effervescent couple it is neutralized to a metal salt, if a sufficient amount of an alkaline material is employed, and in salt form is more highly soluble than is the free fumaric acid. Hence, when greater solubility than that for free fumaric acid is desired, a source of alkali metal ions may be included in the pharmaceutical composition, so that upon dissolution of the composition in water the alkali metal salt of fumaric acid is formed and any solubility limitations of fumaric acid are eliminated. Generally, however, this is not necessary because the fumaric acid is used in amounts low enough so that the volume of water normally used for dissolution of the tablets is sufficient to dissolve all the fumaric acid employed.

Amounts of at least 5% fumaric acid based on the total weight of the lubricated tabletable composition are generally sufficient to allow high-speed tableting when fumaric acid is used as the sole lubricant. When it is used as one of at least two tableting lubricants a proportionately smaller amount may be used. Amounts of from 5% to 14% fumaric acid allow tableting of effervescent mixtures at rates up to about 5,000 tablets per minute on rotary tablet machines containing 47 punch and die

sets. Each punch and die set produces approximately 106 tablets per minute in such machines. On a rotary machine containing 33 punch and die sets, tablets may be compressed at a rate of 76 tablets per minute per set for a total production of about 2,500 tablets per minute.

The following examples illustrate the invention. The concentrations of components are stated as weight percent of the weight of the lubricated composition as tableted.

EXAMPLE 1

Component:	Amount, gm.
Sodium bicarbonate	500
Citric acid (anhydrous)	150
Fumaric acid	100

The above components in the amounts stated were dried and reduced to 30 mesh screen size and thoroughly mixed. The fumaric acid in the composition was present in an amount of 13.3 weight percent of the weight of the mixture. The citric acid was present in an amount of 20 weight percent and the sodium bicarbonate was present in an amount of 66.6 weight percent, both based on the total weight of the mixture.

The mixture was placed in a hopper of a hand-operated punch rotary tableting machine from which the mixture was fed to the dies of the punch and die sets of the machine. The compression pressure was set at 8–10 tons/in.^{2}. The tablets produced weighed approximately 3.6 gm. each.

Upon completion of the run the tablets were found to be smooth-surfaced and elegant in appearance. Upon dropping the same into about 100 ml. of room temperature water the tablets quickly effervesced and dissolved to give a sparkling clear solution with no sediment. Such a solution can be taken orally to provide an alkalizing effect in the user's stomach.

EXAMPLE 2

Component:	Amount, gm.
Sodium bicarbonate	500
Malic acid	150
Fumaric acid	100

The above components were dried, reduced to 30 mesh screen size and mixed. The mixed composition was then added to the hopper of a hand-operated punch rotary tableting machine and tablets were made. Each tablet weighed approximately 3.6 gm.

The tablets had the same dissolving and effervescent characteristics as the tablets of Example 1.

EXAMPLE 3

Component:	Amount, gm.
Sodium bicarbonate	4000
Citric acid (anhydrous)	1200
Fumaric acid	800

The sodium bicarbonate was dried and then mixed with both the citric acid and the fumaric acid and the resulting mixture then passed through a mill operating at 4500 r.p.m. containing an 8 mesh screen and compressed into three gram tablets on a single punch, one station machine set for 8 to 10 tons per square inch pressure. The tablets produced were uniform and smooth-surfaced, and were one inch in diameter and 0.2 inch thick. A first portion of these tablets was stacked in capped bottles and stored at 40° C. for one month and a second portion was similarly stored at 50° C. for the same period of time. The tablets from both portions appeared to be unchanged upon testing after these stability studies. Both before and after storage under the accelerated storage conditions the tablets dissolved in about 100 ml. of 43° C. water in about 25 seconds to produce a completely clear solution.

EXAMPLE 4

Component:	Amount, gm.
Sodium bicarbonate	4380
Citric acid (anhydrous)	1320
Fumaric acid	300

The sodium bicarbonate was dried and then blended with a mixture of the citric acid and the fumaric acid. Three (3) gram tablets of 1.0 inch diameter and 0.14 inch thickness were run on a single punch, one station tableting machine. These tablets showed slight scoring but were otherwise of good quality, indicating that 5% fumaric acid based on the total tablet weight provides sufficient tableting lubrication. The tablets showed a one minute dissolution time in 180 ml. of water at 16° C.

EXAMPLE 5

Component:	Amount, gm.
Sodium bicarbonate	2190
Citric acid (anhydrous)	660
Fumaric acid	100
Acetylsalicylic acid	81

The sodium bicarbonate was dried and the materials were then mixed in order of increasing amounts. Tablets of 1.0 inch diameter and 0.20 inch thickness weighing 3.03 gm. each were run on a single punch, one station tableting machine. These tablets were of elegant appearance and exhibited an 80 seconds dissolution time when placed in 180 ml. of water at 16° C. Upon dissolution of one tablet 1.25 grains of aspirin (acetylsalicylic acid) were released into the water, which amount is that recommended for children.

EXAMPLE 6

Component:	Amount, gm.
Dicalcium phosphate dihydrate	340
Confectionery cane sugar	56.7
Gelatin, U.S.P.	3.3
Fumaric acid	100

The first three above components were mixed with the fumaric acid to make an initial mixture containing 20% fumaric acid. Two hundred (200) gm. of this composition were formed into placebo tablets on a single punch tableting machine at a rate of about 125 tablets per minute. The tablets had diameters of about 0.375 inch and thicknesses of about 0.22 inch and disintegrated slowly in room temperature water.

An additional three hundred (300) gm. of the first three components in the same proportions as given above were then mixed with an equal amount of the initial mixture and 400 gm. of the resulting mixture tableted as above. These tablets contained 10% fumaric acid based on the total tablet weight and showed the same slow disintegration rate as the above tablets. The remaining 200 gm. of the composition used for these tablets was then mixed with an additional 200 gm. of the first three components in the same proportions as given above. The resulting mixture containing 5% fumaric acid was tableted as above and the tablets exhibited similar properties.

All of the tablets produced were hard surfaced and elegant in appearance.

In summary, fumaric acid can be used as a tableting lubricant for powdered tabletable compositions. Generally at least 5% fumaric acid on the basis of the total tablet weight is used, although lesser amounts are usable.

What is claimed is:

1. A tablet producing a clear aqueous solution and being free from insoluble tablet lubricants or other tablet excipients or components which cause a tablet formed from an otherwise soluble composition to produce a clouded suspension having undesirable surface scum rather than a uniform solution when dissolved in water consisting essentially of a compressed, essentially free-flowing mixture of a powdered, water-soluble, tabletable essential active ingredient and, as the essential tablet lubricant, a dry-mixable tableting lubricant comprising fumaric acid.

2. The tablet of claim **1** wherein said powdered, water-soluble, tabletable essential active ingredient is an internal use oral therapeutic agent, effervescent couple alkalizer,

or clear solution-forming, powdered detergent, disinfectant and/or abrasive which disintegrates when placed in water.

3. The tablet of claim 1 wherein said fumaric acid is present in an amount of at least about 5% based on the total tablet weight.

4. The tablet of claim 2 wherein said effervescent couple alkalizer is a fumaric acid-free effervescent mixture of a base and an acid.

5. The tablet of claim 4 wherein said fumaric acid is present in an amount of about from 5% to 14% based on the total weight of said fumaric acid and said effervescent couple alkalizer.

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U.S. Cl. X.R.

252—1, 9, 10, 11, 106, 350; 264—39, 300, 338; 424—230