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PROCESS FOR PREPARING A DELAYED RELEASE MEDICINAL TABLET

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ABSTRACT OF THE DISCLOSURE

A process in which medicament particles are mixed with a wax or wax-like substance and compressed into tablet form. The tablet is then coated with a material which retains its shape at the wax melting point. Sufficient heat is then applied to the tablet to melt the wax therein while at the same time the coating material preserves the shape of the tablet, which is then cooled.

This invention relates to a method of preparing pharmaceutical compositions and particularly to tablet preparations which upon ingestion are capable of prolonging the release of the contained medicine or drug over extended periods of time.

This prolonged or sustained release of a medicine or drug is important for several reasons. In the first place it serves to provide the body with medication over a long time and thereby eliminates the need for swallowing an ordinary tablet at frequent intervals. The treatment of any disease with a medicine requires a fairly constant high body titre of the medicine. If the medicine is metabolized, or otherwise eliminated quickly from the body it would be necessary to swallow an ordinary tablet quite often to maintain the desired therapeutic level. The sustained release tablet of this invention makes it possible to swallow the tablet at considerably less frequent intervals.

Some medicines have such a narrow therapeutic ratio that slightly more of it than is necessary to achieve a therapeutic effect, will cause adverse toxic symptoms. If an ordinary tablet is taken, the rapid release of its medical content may cause such a high body level that undesirable side reactions will occur. The prolonged release tablet of this invention prevents the sudden release of a large amount of medicine and thereby prevents the onset of toxic symptoms.

Some medicines are inherently irritating to the alimentary mucosa and their rapid release from the ordinary tablet may cause damage at the loci of high concentrations of the medicine. The tablet of the present invention prevents the build-up of such a noxious or toxic concentration.

Tablets have been prepared in the past which will prolong the release of the contained medicine but they have not been entirely satisfactory. Some of them have been too expensive to make either because of the expensive ingridents or the complicated apparatus or process to make them or they have been too large because of the necessary additives to obtain the delayed release. Other tablets have been unsatisfactory because they have poorly reproducible release patterns although made in exactly the same way. The tablets of the present invention employ inexpensive tableting material and achieve an exceptionally uniform release of the medicine. These tablets can be made of relatively small size. Furthermore, the total elapsed drug release time can be varied and established by the practice of this invention.

Another important consideration is that the material which causes the prolonged drug release must be physiologically accpetable. It must have no or a negligible toxic

effect upon the person. It must be completely eliminated so that even during prolonged use it does not accumulate in the person's tissues.

In accordance with the invention, the drug is mixed with a suitable wax or wax-like substance which will melt at a temperature at which the drug will not decompose or be otherwise adversely affected. This wax or wax-like substance is hereinafter called the wax additive and preferred ones are cetyl alcohol, castor wax, glycerol monostearate, stearyl alcohol, stearic acid, beeswax and solid polyethylene glycols. Lubricants and/or flow conditioners which are conventional in the tablet art may or may not be added with further intermixing. The mixture is then compressed to form tablets containing the desired weight of the drug.

The tablets are coated with a suitable film forming material, such as methylcellulose, which is not affected either by the molten wax or by the elevated temperature at which the wax melts. This coating material should not become tacky during the subsequent heating procedure so as to thereby prevent agglomeration of the tablets. The coated tablets are placed for a predetermined period in a drying oven set at a temperature higher than the melting point of the wax additive. This heating causes the wax additive to soften or melt and the coating serves to preserve the shape of the tablet and to prevent agglomeration of tablets. After cooling to room temperature the tablets exhibit the desired sustained release effect.

The mechanism involved in producing the sustained release property is that the drug particles are coated during the melting operation with a continuous film of the wax-additive. When the compressed, coated tablets are exposed to an elevated temperature, the additive melts and flows between the drug particles. This step in the process serves the additional function of driving off residual solvents from the film coat. Upon cooling to room tempearture, the wax additive solidifies to form a continuous structure in which drug particles are imbedded. Upon ingestion, the wax additive is slowly dissolved or disintegrated, resulting in the availability of the drug at a controlled rate.

The wax-additives which may be employed in the practice of this invention should have melting points above body temperature and should be slowly soluble or disintegratable by digestion in gastro-intestinal fluids. Among them are those derived from both natural and synthetic sources, including such organic compounds as hardened fats and oils, for example, animal, mineral or vegetable fats or oils, such as animal fats and hardened vegetable oils, including hydrogenated fats and oils; higher fatty alcohols and acids such as octyl, decyl, lauryl, myristyl, cetyl or stearyl.

The coating which is applied directly to the wax-additive core, in addition to the methylcellulose mentioned above, may be ethylcellulose, cellulose acetate, cellulose acetate phthalate or a substituted alkyl cellulose such as hydroxypropyl methylcellulose. Other conventional coatings may be used if it is known that it will not melt or become sticky during the heating step which melts the waxy core. Sufficient coating should be applied so that it will serve to retain the shape and also prevent agglomeration of the tablets during the time that the core is molten, and for this purpose the film should be from .03 to 0.1 mm. thick.

The heating temperature should be slightly above the predetermined melting temperature of the wax additive and it should be sustained for a period that will assure the melting of the entire wax additive. This will generally require a minimum of about 30 minutes although the tablets may be heated for as long as an overnight period.

The amount of weight of the wax additive should be from 5% to 95% and preferably from 10% to 20% of

the weight of the drug. Amounts higher than 25% generally will be used when a mixture of additives is required for special release effects such as a release spread over an entire day or more. The release time of the drug will be dependent upon the particular selected wax additive and the particle size of the drug.

The process of this invention is an economical one as it utilizes conventional equipment, materials and techniques. No special labor skills are required. The time consuming slugging step which is often required in the production of matrix-type tablets, is eliminated.

These coated, cooled tablets can be swallowed in the form in which they come from the heating step and consequently they may be sold as the final end use product. However, their appearance, taste and ability to stand shipment and shelf age, may make it desirable to further coat them. This overcoating may be a conventional sugar or plastic coating which is applied in a tumbling pan or by a spray using known materials, the spray being directed upon the tumbling tablets in a pan or upwardly into a fluidized column of tablets. These are known techniques and form no part of this invention as the feature of this concept is the core of such a coated tablet.

A medicament may be added to the coating next to the wax core if the medicament will withstand the heating step. This may be utilized if this medicament is chemically incompatible with the medicament in the core, or if it is desired that the medicament in the coating be quickly released. For example, the coating may contain a diuretic such as hydrochlorothiazide so as to quickly get it into the person's system and the core may contain potassium chloride so that it will be released slowly. The overcoating may, as well, contain a medicament, for the same reasons.

The invention is illustrated by the following examples:

EXAMPLE 1

Ingredients per core tablet:

	Mg.
Potassium chloride (granular)	1,000
Cetyl alcohol	150

Procedure.—The ingredients are thoroughly intermixed and compressed to form tablets containing the desired weight (1,000 mg.) of potassium chloride.

A coating solution of the following composition is prepared:

	Percent
Hydroxypropylmethylcellulose	2.0
Alcohol	50.0
Chloroform to	100.0

The film coating is applied to the tablets by a continuous spraying operation well known to those in the industry. Thirty milligrams of coating are applied to each tablet. The tablets are then placed in an oven (110° C.) for 30 minutes. The finished product is obtained by cooling the tablets to room temperature. The dissolution time of the resulting tablet in water (75 ml.) was as follows:

Time in minutes:	Percent dissolved
30	12
60	24
90	38
120	51
150	57
180	65
210	70
240	75

EXAMPLE 2

Instead of the cetyl alcohol in Example 1, a like amount of castor wax is used.

EXAMPLE 3

Ingredients per core tablet:

	Mg.
Potassium	1,000
Castor wax	150
Stearic acid	5

The procedure described in Example 1 is followed.

EXAMPLE 4

Ingredient per core tablet:

	Mg.
Amitriptyline	50
Cetyl alcohol	900
Polyethylene glycol 4000	50

The procedure of Example 1 is followed, and the dissolution rate of the resulting tablet in water (750 ml.) is as follows:

Time (hours):	Percent dissolved
1	31.8
2	44.6
3	52.0
4	58.5
5	63.2
6	69.0
7	72.5
8	76.0
9	79.5
10	82.5
11	85.5
12	88.0
13	90.1

EXAMPLE 5

Any one of the preceding examples is carried out but 5 mg. of anhydrous colloidal silica is added per tablet.

Other examples are apparent from the above specific, illustrative ones. Any one of the wax-additives mentioned above may be substituted for those in the above examples and they may be added within the 5 to 95% range which has been mentioned. The medicament may be substances other than potassium chloride, such as is represented by the following:

EXAMPLE 6

Ingredients per core tablet:

	Mg.
Chlorothiazide	500
Cetyl alcohol	75

The procedure of Example 1 is carried out. Also, other examples are evident, considering that for the hydroxypropylmethylcellulose coating may be substituted other known coating agents which will perform the same function of retaining the shape of te tablet and preventing their sticking together during the heating step.

We claim:

1. The method of making a medicine tablet which will prolong the release of the contained medicine which comprises mixing together medicine particles and a wax additive which is solid at room temperature but which melts at a temperature at which the medicine will not be affected adversely and which is slowly dissolved in or is slowly disintegrated by gastric fluids, compressing the mixture into tablet form to make a tablet core, coating the core with a material which will retain its shape at the temperature at which the wax additive melts, heating the coated core to at least the melting temperature of the wax additive for a period to assure the melting of the wax additive, and cooling the tablet to room temperature.

2. The process according to claim 1 in which the wax additive is selected from the group consisting of hardened organic animal oils, vegetable and mineral fats and oils,

higher fatty alcohols, higher fatty acids, beeswax, glycerol monostearate and solid polyethylene glycols.

3. The process according to claim 1 in which the coating material is selected from the group consisting of methylcellulose, ethylcellulose and a substituted alkylcellulose.

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