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CONTROLLED RELEASE MEDICINAL TABLETS

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ABSTRACT OF THE DISCLOSURE

A tablet core containing a medicinal agent is coated with a film made up of a water-insoluble plastic and particles of a material which is chosen for its selective solubility or digestibility in gastro or intestinal fluids. The removal of the latter material by the intended gastro or intestinal fluids results in a membranous or dialytic film through which the medicinal agent slowly leaches out.

RELATED CASES

This is a continuation-in-part of U.S. patent application Ser. No. 586,623, filed Oct. 14, 1966, and U.S. patent application Ser. No. 597,861 filed Nov. 30, 1966 both now abandoned.

PRIOR ART

See related cases.

This invention relates to pharmaceutical compositions and particularly to tablet preparations which upon ingestion are capable of controlling the release of the contained medicine or drug over extended periods of time. This invention also involves a process for making these pharmaceutical tablets.

This controlled 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 blood 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 blood level. The controlled 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 moreof 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 blood level that undesirable side reactions will occur. The controlled 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 concentrations of the medicine. The tablet of the present invention prevents the build-up of such a troublesome concentration.

Tablets have been prepared in the past which will control 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 ingredients 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 lacked a uniform release time 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 controlled drug release must be physiologically acceptable. 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 a person's tissues.

In accordance with the invention, a tablet containing the drug is made in a conventional manner and to it is applied a coating composition which will form a membranous film through which the drug slowly will be leached out. This slow leaching action will occur because gastro-intestinal fluids can but slowly pass through the coating film to reach the drug in the tablet core and the drug which then becomes dissolved in the gastro-intestinal fluids can but slowly pass out through the coating film and into the stomach and/or intestines. As the film remains substantially intact throughout the time that all the drug is being leached out the escape of the drug is prolonged and the rate of drug administration remains about uniform.

The coating composition is made up of a plastic having a low water vapor permeability such as cellulose acetate, a film modifying agent hereinafter to be described, a solvent such as acetone and, if desired, a plasticizer and/or a coloring material. The plastic should be insoluble in gastro-intestinal fluids. Suitable plastics in addition to cellulose acetate are ethylcellulose, cellulose nitrate, low water soluble polyvinyl alcohols and the other plastic pharmaceutical coatings.

The film modifying agent mentioned above should be a material which is chosen so that it will be selectively but readily soluble or digestible in either the stomach fluids or in the intestinal fluids so that when it is partially or fully removed from the coating film the plastic which remains is of a membranous or dialytic nature. If it is intended that the medicament be released in the stomach, the film modifying agent must be one that will be removed by the acid conditions of the stomach. On the other hand, if it is intended that the medicament be released in the intestines (i.e. the tablet is to pass through the stomach substantially intact). The film modifying agent must be one that will be removed by the alkaline conditions of the intestines.

For removal in the stomach, suitable film modifying agents are calcium carbonate, calcium phosphates (mono, di, tri), magnesium citrate, magnesium oxide, sodium bicarbonate, potassium bicarbonate, tetraethanolamine, lactose, polyvinyl pyrrolidone and solid polyethylene glycols; they are hereinafter referred to as Table 1 agents. Satisfactory results have been obtained when from about 0.1 to about 30 parts by weight of the plastic substance has been combined with one part by weight of modifying agent. Most satisfactory results have been obtained when from 1 part to 3 parts by weight of the plastic substances have been combined with one part of the modifying agent.

For removal in the intestines, suitable film modifying agents are benzoic acid, propionic acid, sorbic acid, salicyclic acid and cellulose acetate phthalate; they are hereinafter referred to as Table 2 agents. These agents are used in the same relative amounts set forth above for the other film modifying agents.

In addition to acetone, conventional solvents, such as methanol, ethanol and chloroform may be used. The plasticizer may be the conventional ones such as diethyl phthalate, caster oil, propyelne glycol or glycerol, added

to the film forming composition to make it less fragile if this is desired.

The film forming composition is applied as a coating to the tablet cores, the amount and coating thickness being dependent upon the desired rate of release of the medicinal agent of the tablet. In practice, it has been found that satisfactory results may be obtained when an average pharmaceutical tablet is coated with from about 5 to about 100 mg. of the novel composition of this invention, although the amounts of the composition involved may be varied in accordance with the medicament employed and the amount of control of release desired by the practitioner hereof.

To apply this coating composition, conventional tablet coating practices are used. This may use a tumbling barrel into which the coating composition is sprayed or it may use the fluidized column technique in which the coating composition is sprayed upwardly through the bed.

Heretofore, it has been the practice to apply an enteric-type coating to pharmaceutical tablets to insure nonlesion inducing passage through the stomach. This enteric-type coating resists disintegration by stomach fluids but is fully disintegrated or dissolved by the intestinal fluids on entering and going through the intestine. The present invention obviates the necessity for any such enteric-type coating upon either the stomach or the intestine dissolving film modifying agent membrane of this invention. This is because this novel film resists disintegration by stomach fluids and prevents or delays release of the medicinal agent in the stomach according to the selected intent. It allows slow release of the medicinal agent from the tablet into either the stomach or the intestines depending on the chosen intent, and does not permit a rapid release.

This is because, as stated above, the continuous dialytic film of this invention serves as a membrane to selectively let gastro or intestinal fluids through to reach the tablet core to dissolve the medicinal agent contained therein and to let the dissolved medicinal agent slowly leach outward through this continuous dialytic film and into the gastro or intestinal tract. The dialytic film not only restricts the access of the gastro-intestinal fluids to the medicinal agent of the matrix core, but it moreover serves to position or space the medicinal agent itself away from the gastro-intestinal mucosa so that a large concentration thereof is not permitted to reach a compartively small area of the gastro-intestinal mucosa.

In the practice of this invention, it is possible to provide a final overcoating to improve the appearance, taste or stability of the tablet. This may contain sugar, or a film former in combination with dyes or pigments, or even other medicaments. This latter medicament may for example, be one which is to be administered with the drug in the tablet core but which should not be in contact with each other in the complete tablet. This may be because of the incompatibility of the two or because it is desired that the medicine in the outer coating be released rapidly and that the drug in the core be released slowly.

The following examples are illustrative of compositions of the present invention and are not to be construed as limiting. Examples 1 to 11 inclusive described tablets having coatings which will become a membranous film in the stomach. Examples 12 to 21 inclusive describe tablets having coatings which will become membranous in the intestines after passing intact through the stomach.

EXAMPLE 1

Ingredients for the tablet core:	Per tablet, mg.
Potassium chloride (granular)	572
Glyoxalated gelatin	572
Stearic acid	6

The amounts of potassium chloride and glyoxalated gelatin set forth above are intimately mixed. A portion is removed and mixed with the stearic acid. This is then

passed through a number 12 sieve and added to the remaining potassium chloride glyoxalated gelatin mixture. The resultant mixture is then slugged, and the slugs are crushed and fed through a Fitzmill fitted with a 2A screen, and the resulting granules are compressed to form tablets having the desired weight of potassium chloride.

Ingredients for the membranous coating:	Percent
Nitrocellulose	3.0
Calcium carbonate	1.0
Castor oil	1.0
Propylene glycol	1.0
Acetone to 100.0%.	

The nitrocellulose is first wetted with a small amount of acetone, and the mixture agitated until all of the nitrocellulose is dispersed. The calcium carbonate is dispersed in some of the acetone, and the caster oil and propylene glycol in the remaining acetone. To the nitrocellulose dispersion the calcium carbonate, castor oil and propylene glycol dispersion is added with stirring. By passing the product through an homogenizer or mill, the incidence of nozzle clogging in the subsequent spraying operation is reduced significantly.

The film coating is applied to the tablet cores by a continuous spraying operation well known to skilled workers in the art. Eight (8) milligrams of dry coating are applied to each matrix tablet.

EXAMPLE 2

Other examples of the invention involve the substitution for the potassium chloride in Example 1 of other drugs which require a prolonged administration. Potassium chloride is one example of an irritating drug which should slowly be released and other examples such as aspirin are apparent. An example of a drug which should be released over a prolonged period to maintain a blood level for an extended period is an antihistamine such as neoantergan. Other drugs, such as hypotensive, tranquilizers, etc., are obvious.

Furthermore, instead of the tablet forming materials named in Example 1, the core tablets may be made of other conventional materials and be shaped by known methods.

EXAMPLE 3

Following the procedure set forth in Example 1 but substituting an equivalent amount of ethyl cellulose or cellulose acetate for the nitro cellulose, equivalent results are obtained.

EXAMPLE 4

Tablets containing 572 mg. potassium chloride are prepared as described in Example 1.

A film forming composition of the formula:

Nitrocellulose	4.0%
Polyethylene glycol 400	1.2%
Acetone q.s., 100.0%.	

is prepared in accordance with the general procedures set forth in Example 1, with the substitution of the different interchanged ingredients hereof. The resultant film coat is applied to the tablets by a continuous spraying operation as in Example 1. Five (5) milligrams of dry coating are applied to each matrix tablet.

EXAMPLE 5

Tablets containing 572 mg. potassium chloride are prepared as described in Example 1.

A coating solution of the formula:

	Percent
Nitrocellulose	3.0
Castor oil	1.0
Propylene glycol	1.0
Lactose	1.0
Acetone q.s., 100.0%.	

is prepared according to the method described in Example 1. This solution is applied to the tablets by a continuous spraying operation. Fifteen (15) milligrams of coating are applied to each matrix tablet.

EXAMPLE 6

Tablets containing 572 mg. potassium chloride are prepared as described in Example 1.

A coating composition of the formula:

	Percent
Nitrocellulose	3.0
Castor oil	1.0
Propylene glycol	1.0
Magnesium oxide	1.0
Acetone q.s., 100.0%.	

is prepared according to the method described in Example 5, except that magnesium oxide is substituted for lactose. This solution is applied to the tablets by a continuous spraying operation. Twenty milligrams of coating are applied to each matrix tablet.

EXAMPLE 7

Tablets containing 572 mg. potassium chloride are prepared as described in Example 1.

A coating solution of the formula:

	Percent
Nitrocellulose	1.5
Castor oil	0.5
Propylene glycol	0.5
Magnesium oxide	0.5
Acetone q.s., 100.0%.	

is prepared according to the method described in Example 5. This solution is applied to the tablets by a continuous spraying operation. Twenty (20) milligrams of coating are applied to each tablet core.

EXAMPLE 8

Ingredients for the tablet core:	Per tablet, mg.
Potassium chloride (granular)	572
Stearic acid	3

The mixture is mixed, granulated and tableted as in conventional practices and the tablet core is coated as in any of the preceding examples.

EXAMPLE 9

Other examples of the invention involve substitution of one or more of the Table 1 agents mentioned above, for the calcium carbonate or magnesium oxide in the above examples.

EXAMPLE 10

To any one of the preceding coated tablets is added as an overcoating, a conventional sugar coating with or without a dye or a pigment. A representative overcoating is the following:

Place the tablets which have been undercoated in a coating pan and apply 2 charges of a gelatin-acacia solution and dust with kaolin. Then apply 7 charges of 17 lb. cut syrup and then apply 14 charges of white syrup which contains titanium dioxide. Over this is applied 12 charges of 17 lb. cut syrup. The tablets are trayed up and air dried, after which they are glazed with pharmaceutical glaze trayed up and again air dried.

EXAMPLE 11

The overcoating of Example 10 is applied but additionally includes a medicament. For example, with potassium chloride in the internal matrix core, the overcoating could contain hydrochlorothiazide in the amount of 25 mg. or 50 mg. per tablet. The hydrochlorothiazide is mixed and milled with cut syrup and it is applied onto the tablets which have been undercoated, just prior to the charges containing the titanium dioxide.

The titanium dioxide can be replaced with or be supplemented with any other pigment or dye which is pharmaceutically acceptable.

The tablets prepared in accordance with the teachings of Example 1 were tested for effectiveness in simulated gastric fluid and simulated intestinal baths and the results obtained are tabulated below in Table I.

TABLE I

	Test fluid [1]	Percent drug released time, hrs. 1	2	3	5½
Wt. of coating, mg.:					
8	A	75.0			
8	B	100.0			
12	A	5.0			
12	B			60.0	100.0

[1] A=Simulated gastric fluid; B=Simulated intestinal fluid.

Tablets prepared according to Example 4 tested in the same manner gave the following data:

TABLE II

	Test fluid [1]	Percent drug released time, hrs. 1	2	3	4
Wt. of coating, mg.:					
5	A	25.0			
5	B	90.0			

[1] A=Simulated gastric fluid; B=Simulated intestinal fluid.

The following Examples 12 to 21 inclusive illustrate tablets having coatings which will pass intact through the stomach and become a membranous film in the intestines.

EXAMPLE 12

Ingredients for the tablet core:	Per tablet, mg.
Potassium chloride (granular)	572
Glyoxalated gelatin	572
Stearic acid	6

The amounts of potassium chloride and glyoxalated gelatin set forth above are intimately mixed. A portion is removed and mixed with the stearic acid. This is then passed through a number 12 sieve and added to the remaining potassium chloride glyoxalated gelatin mixture. The resultant mixture is then slugged, and the slugs are crushed and fed through a Fitzmill fitted with a 2A screen, and the resulting granules are compressed to form tablets having the desired weight of potassium chloride.

Ingredients for the membranous coating	Percent	Amount per tablet, mg.
Cellulose acetate	2.0	6.67
Cellulose acetate phthalate	2.0	6.67
Diethyl phthalate	0.8	2.67
Acetone to	100.0	

The cellulose acetate is first wetted with a small amount of acetone, and the mixture agitated until all of the cellulose acetate is dispersed. The cellulose acetate phthalate is dispersed in some of the acetone, and the diethyl phthalate in the remaining acetone. To the cellulose acetate dispersion the diethyl phthalate solution and the cellulose acetate phthalate solution are added with stirring. By passing the product through a homogenizer or mill, the incidence of nozzle clogging in the subsequent spraying operation is reduced significantly.

The film coating is applied to the tablet cores by a continuous spraying operation well known to skilled workers in the art. Twenty seven (27) milligrams of dry coating are applied to each matrix tablet.

EXAMPLE 13

Other examples of the invention involve the substitution for the potassium chloride in Example 12 of other drugs which require a prolonged administration. Potassium chloride is one example of an irritating drug which

should slowly be released and other examples such as aspirin are apparent. An example of a drug which should be released over a prolonged period to maintain a blood level for an extended period is an antihistamine such as neoantergan. Other durgs, such as hypotensive, tranquilizers, etc. are obvious.

Furthermore, instead of the tablet forming materials named in Example 12, the core tablets may be made of other conventional materials and be shaped by known methods.

EXAMPLE 14

Following the procedure set forth in Example 12 but substituting an equivalent amount of ethyl cellulose for the cellulose acetate, equivalent results are obtained.

EXAMPLE 15

Tablets containing 572 mg. potassium chloride are prepared as described in Example 12.

A film forming composition of the formula:

	Percent
Nitrocellulose	1.5
Castor oil	0.5
Propylene glycol	0.5
Benzoic acid	0.5
Acetone q.s., 100.0%.	

is prepared in accordance with the general procedures set forth in Example 12, with the substitution of the different interchanged ingredients hereof. The resultant film coat is applied to the tablets by a continuous spraying operation as in Example 12. Thirty-three milligrams of dry coating are applied to each matrix tablet.

EXAMPLE 16

Tablets containing 572 mg. potassium chloride are prepared as described in Example 12.

A coating solution of the formula:

	Percent
Nitrocellulose	3.0
Castor oil	1.0
Propylene glycol	1.0
Benzoic acid	1.0
Acetone q.s., 100.0%.	

is prepared according to the method described in Example 12. This solution is applied to the tablets by a continuous spraying operation. Twenty-seven (27) milligrams of coating are applied to each matrix tablet.

EXAMPLE 17

Tablets containing 572 mg. potassium chloride are prepared as described in Example 12.

A coating composition of the formula:

	Percent
Nitrocellulose	3.0
Castor oil	1.0
Propylene glycol	1.0
Cellulose acetate phthalate	1.0
Acetone q.s., 100.0%.	

is prepared according to the method described in Example 16, except that cellulose acetate phthalate is substituted for benzoic acid. This solution is applied to the tablets by a continuous spraying operation. Twenty milligrams of coating are applied to each matrix tablet.

EXAMPLE 18

Tablets containing 572 mg. potassium chloride are prepared as described in Example 12.

A coating solution of the formula:

	Percent
Nitrocellulose	1.5
Castor oil	0.5
Propylene glycol	0.5
Cellulose acetate phthalate	0.5
Acetone q.s., 100.0%.	

is prepared according to the method described in Example 16. This solution is applied to the tablets by a continuous spraying operation. Twenty milligrams of coating are applied to each tablet core.

EXAMPLE 19

Ingredients for the tablet core:	Per tablet, mg.
Potassium chloride (granular)	572
Stearic acid	3

This mixture is mixed, granulated and tableted as in conventional practices and the tablet core is coated as in any of the preceding examples.

EXAMPLE 20

Other examples of the invention involve substitution of one or more of the Table 2 agents mentioned above, for the benzoic acid or cellulose acetate phthalate in the above examples.

EXAMPLE 21

To any one of the preceding coated tablets of Examples 12 to 20 is added as an overcoating, a conventional sugar coating, with or without a dye or a pigment. A representative overcoating is the following:

Place the tablets which have been undercoated in a coating pan and apply 2 charges of a gelatin-acacia solution and dust with kaolin. Then apply 7 charges of 17 lb. cut syrup and then apply 14 charges of white syrup which contains titanium dioxide. Over this is applied 12 charges of 17 lb. cut syrup. The tablets are trayed up and air dried, after which they are glazed with pharmaceutical glaze, trayed up and again air dried.

EXAMPLE 22

The overcoating of Example 21 is applied but it additionally includes a medicament. For example, with potassium chloride in the internal matrix core, the overcoating could contain hydrochlorothiazide in the amount of 25 mg. or 50 mg. per tablet. The hydrochlorothiazide is mixed and milled with cut syrup and it is applied onto the tablets which have been undercoated, just prior to the charges containing the titanium dioxide.

The titanium dioxide can be replaced with or be supplemented with any other pigment or dye which is pharmaceutically acceptable.

The tablets prepared in accordance with the teachings of Example 12 were tested for effectiveness in simulated gastric fluid and simulated intestinal baths and the results obtained are tabulated below in Table III.

TABLE III

	Test fluid [1]	Percent drug released time, hrs. 1	2	3	4
Wt. of coating, mg.:					
27	A	0.0	0.0	0.0	------
27	B	0.5	8.8	27.8	45.0
33	A	0.0	0.0	0.0	------
33	B	0.0	0.0	4.4	23.4

[1] A=Simulated gastric fluid; B=Simulated intestinal fluid.

Tablets prepared according to Example 19 tested in the same manner gave the following data:

TABLE IV

	Test fluid [1]	Percent drug released time, hrs. 1	2	3	4
Wt. of coating, mg.:					
16	A	0.5	1.0	------	
16	B	0.0	2.0	9.3	26.4

[1] A=Simulated gastric fluid; B=Simulated intestinal fluid.

What is claimed is:

1. A pharmaceutical tablet consisting of

(a) an internal matrix core comprising potassium chloride or other irritating active medicament which is soluble in gastro-intestinal fluids and which is known to be capable of producing lesions of the gastro-in-

testinal mucosa in passing through the stomach and intestines, particularly when a large concentration thereof is permitted to reach a comparatively small area of the gastro-intestinal mucosa; and

(b) a coating on said core which comprises an intimate mixture of from 0.1 to 30 parts by weight of a plastic substance and one part by weight of a film modifying agent,

(i) said plastic substance being one of low water vapor permeability and which remains substantially intact in gastro-intestinal fluids and which is selected from the group consisting of cellulose acetate, ethylcellulose, cellulose nitrate and low water soluble polyvinyl alcohols,

(ii) said film modifying agent being one that will be readily soluble in the stomach fluids and being selected from the group consisting of magnesium oxide, magnesium citrate, sodium bicarbonate, potassium bicarbonate, tetraethanolamine and lactose in the case of coatings to form a membranous film in the stomach,

and one that will be readily soluble in the intestinal fluids and being selected from the group consisting of propionic acid and sorbic acid in the case of coatings to pass intact through the stomach and form a membranous film in the intestines.

2. A tablet according to claim 1 in which said coating is 1 to 3 parts by weight of said plastic substance and 1 part film modifying agent.

3. A tablet according to claim 1 in which hydrochlorothiazide is incorporated in the coating and potassium chloride is in the internal matrix core.

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