DESCRIPTION

PHARMACEUTICAL COMPOSITION COMPRISING MEDROXYPROGESTERONE ACETATE

This invention relates to formulations of 6α-methyl, 17α-hydroxy-progesterone acetate (medroxyprogesterone acetate or MAP).

MAP was independently synthesized in 1958 by two different research groups. It is a synthetic steroid derived from progesterone and exerts, by oral and intramuscular routes, a progestinic activity.

MAP is also used, at higher doses and by the same administration routes, in cancer treatment. In this therapeutic application however, the oral treatment requires very high doses due to the poor bioavailability of the active drug substance. This characteristic is related to the poor wettability and dissolution characteristics (in aqueous or biological media) of MAP. It is these properties which control and limit the overall absorption of MAP into the body when administered orally.

The wettability and dissolution properties of an active drug substance greatly influence its bioavailability; in many cases very active drugs present a poor absorption profile due to their unfavourable dissolution characteristics. Usually the reduction of the particle size of the drug and the addition of wetting agents have been applied to overcome these problems but

very frequently they prove to be not effective enough. Therefore much effort has been devoted to develop new formulations or new techniques to get better results. Considerable attention has recently been gained by two new research lines based on the preparation of "solid dispersions" and of "inclusion compounds".

In the former approach the drug is molecularly dispersed in the carrier, usually a water-soluble polymer (S. Riegelman, W.L, Chiou 987,588 4/1976 Canada), while in the latter the drug forms molecular complexes with water-soluble cyclodextrins (J. Szejtli, "Cyclodextrins and their inclusion compounds", Akademia Viado, Budapest 1982).

This invention relates to systems in which MAP is loaded in/on any swellable, water-insoluble polymer (or combination thereof) e.g. cross-linked polyvinyl-pyrrolidone, hereinafter referred to as cross-linked PVP, (National Formulary XV, Supplement 3, p. 368), cross-linked sodium carboxymethyl-cellulose (National Formulary XV, Supplement 3, p. 367), cross-linked dextran etc, by using three different preparation techniques.

The resulting forms of MAP in/on swellable water-insoluble polymers greatly enhance dissolution and wettability properties of MAP in aqueous or biological media due to one or both of the following factors:

1) reduction of the dissolution energy of MAP brought about by its complete or partial amorphization or

by the transition of its original crystalline state into a higher energy state (lower melting point);

2) increase of the wettability of MAP by dispersing its molecules in/on the network of a highly hydrophilic and swellable polymer.

The present invention accordingly provides a process for loading a water-swellable water-insoluble polymer with crystalline methylhydroxyprogesterone acetate (MAP), which process comprises:

(a) preparing and grinding a dry mixture of a said polymer and the MAP; and/or

(b) preparing a mixture of a said polymer which is stable and does not melt under the heating to which the mixture is subjected in step (ii) and the MAP, and (ii) heating the mixture up to the melting temperature of MAP; and/or

(c) swelling a said polymer with a MAP solution capable thereof and drying the resulting swollen polymer/MAP system; such that a degree of amorphization of the MAP is achieved or the crystalline MAP is transformed into another more energetic form.

The basic advantages of the systems consisting in drugs loaded in/on hydrophilic, swellable, water-insoluble polymers over "solid dispersions" and "inclusion compounds" are:

1. Higher increase of the drug wettability due

to the high hydrophilicity and swelling capacity in water of the hydrophilic, swellable, water-insoluble polymers.

2. More rapid disintegration in water of the system and faster dispersion of the drug particles. Some of the hydrophilic, swellable, water-insoluble polymers which may be used in the present process are in fact already used and marketed as disintegrants for oral solid dosage forms.

3. Avoidance of the viscous layer around the drug which can be related with the use of water-soluble polymers and can hinder the drug diffusion and slow down the dissolution process.

Systems, prepared according to the invention, consist of MAP and any hydrophilic, swellable, water-insoluble polymer or two or more thereof (non-limiting examples of such polymers are: cross-linked PVP, cross-linked sodium carboxymethylcellulose, cross-linked starch, cross-linked dextran, etc.)

having the following common characteristics:

1. High swelling ability in water (from 0.1 ml to 100 ml of water volume uptake per gram of dry polymer). This characteristic brings about a high swelling and an effective disintegration (in water or in biological fluids) of the system with a powerful dispersion of its constituents and an immediate release of MAP molecules.
2. Fast rate of water swelling (e.g. cross-linked PVP achieves maximum swelling in less than five minutes). This property allows that the aforementioned effects of swelling, disintegration, dispersion and dissolution of the MAP molecules are accomplished in a very short period of time.
3. Water insolubility. This property rules out possible negative effects able to slow down the MAP dissolution process (e.g. building up of a viscous layer around MAP) and brings about the formation of a finely dispersed homogeneous suspension which assures a rapid gastric emptying to the absorption site.

Three methods can be applied to prepare the systems comprising MAP and any of the insoluble swellable polymers aforementioned: 1) grinding of a mixture of MAP and the polymer; 2) heating up to the melting temperature of MAP of a mixture of the drug and the polymer; 3) swelling of the polymer with a solution of MAP and subsequent drying. The details of the three methods are given below.

1. Cogrinding of mixture of MAP and the polymer

A dry mixture of MAP and any of the swellable insoluble polymers aforementioned is placed in a rotating ball mill, in a vibrational ball mill, in an automatic mortar mill or any other suitable crushing apparatus and ground as long as complete amorphization of the crystalline MAP is achieved. The completeness of the amorphization process can be checked by the absence in the Differential Scanning Calorimetry thermogram of the resulting drug-polymer system of the transition peak relative to the solid/liquid endothermic transition of the crystalline MAP (i.e., enthalpy of melting practically null). The grinding of the MAP swellable polymer mixture can be also stopped any time a degree of amorphization (0-100%) of MAP (measured by the reduction of the enthalpy of melting of the crystalline MAP) sufficient to sensibly increase the MAP dissolution rate is achieved. Alternatively, the grinding of the MAP-swellable polymer mixture can be stopped any time the original crystalline form of MAP has been transformed into another, more energetic form: this transformation is indicated by the shifting of the original endothermic peak to lower temperatures. This new, higher energy form of MAP presents higher dissolution rate and bioavailability.

Weight ratios between MAP and the swellable water-in-

soluble polymer in the mixture to be ground can vary from 1 : 0.1 to 1 : 100 w/w MAP:polymer, preferably from 1 : 1 to 1 : 100 w/w MAP:polymer. For each total amount of mixture the correct time of grinding necessary for the desired degree of amorphization or the formation of a higher energy form of MAP must be checked, therefore for each MAP-polymer system the most practical combination of weight ratio and time of grinding can be identified. Examples of drug: swellable insoluble polymer weight ratios and grinding times will be given later.

The resulting ground mixture of MAP and the swellable polymer can then be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to guarantee further homogeneity.

The resulting powdered ground system of MAP and swellable polymer can be subsequently used to prepare any desired solid dosage form (e.g. capsules, tablets, etc.) with or without the addition of any of the common excipients used in pharmaceutical formulations.

2. Heating up to melting temperature of MAP of a mixture of the drug and the polymer.

A dry mixture of crystalline MAP and any of the swellable insoluble polymers aforementioned (chosen among those with good thermal stability at the melting point of MAP) is placed in a container inside a thermoregulated high vacuum oven; after evacuation, a nitrogen flow is established over the MAP-polymer mixture and temperature raised to a value sufficient to bring about the melting of MAP. Alternatively, the mixture of MAP and the polymer is placed in the glass flask of a

rotating evaporator; after evacuation, a flow of nitrogen is established over the MAP-polymer mixture and the glass flask placed in an oil bath at a temperature sufficient to bring about the melting of MAP. Any other heating apparatus (hot plate, muffle, tube oven, etc.) can be usefully applied, as long as the temperature can be carefully checked and held constant.

The MAP-polymer mixture is heated as long as the desired degree of amorphization (0-100%) of crystalline MAP is achieved, which can be checked by Differential Scanning Calorimetry.

Weight ratios of MAP and the polymer in the mixture to be heated can vary from 1 : 0.1 to 1 : 100 w/w MAP:polymer, preferably from 1 : 1 to 1 : 100 w/w MAP:polymer. For each MAP:polymer weight ratio composition and for each total amount of mixture, the time of heating necessary to achieve the desired degree of amorphization must be checked. Examples of MAP:polymer weight ratio compositions, of heating temperature and time will be given later.

The resulting heated mixture of MAP and swellable polymer can then be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to guarantee further homogeneity. The resulting powdered MAP-polymer mixture can be used to prepare any desired solid dosage form (e.g. tablet, capsule, etc.) with or without the addition of any of the common excipients used in pharmaceutical formulations.

3. Swelling of the polymer with a solution of MAP and subsequent drying.

A solution of MAP of desired concentration (in any of the common solvents for MAP, e.g. methylenechloride, chloroform, acetone, etc.) is prepared and subsequently poured over a predetermined amount of any or combination thereof of the water-insoluble swellable polymers aforementioned; the resulting swollen powder is subsequently dried with any convenient apparatus. The volume of MAP solution which can be loaded on the chosen weight of polymer should be of any value up to the maximum swelling volume of the polymer in that particular solvent. The process of swelling can be carried out with any suitable apparatus. For example, one can add the correct volume of MAP solution to the chosen quantity of swellable insoluble polymer in a mortar, mix thoroughly and subsequently dry the resulting swollen powder in a

vacuum oven; or one can place the desired quantity of swellable insoluble polymer in the glass flask of a rotating evaporater, add the correct volume of MAP solution and heat the resulting swollen polymer until it becomes dry.

Weight ratios between MAP and the polymer which can be obtained by the swelling method can vary from 1 : 0.1 to 1 : 100 w/w MAP:polymer, preferably from 1 : 1 to 1 : 100 w/w MAP:polymer. For each given solvent-polymer system the maximum amount of MAP which can be loaded in the polymer is limited by the solubility of MAP in that solvent and by the swelling volume of the polymer in that solvent. In any case, for each solvent-polymer system, by varying the quantity of MAP loaded, one can achieve a degree of amorphization (0-100%) of MAP sufficient to sensibly increase the dissolution rate or the transformation into a higher energy form. Examples of MAP: polymer weight ratio composition, of MAP solution volumes and of polymer weight will be given later on.

The MAP-polymer mixture resulting from the swelling and drying process can then be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to guarantee further homogeneity. The resulting powdered MAP-polymer mixture can be used to prepare any desired solid dosage form (e.g. tablet, capsules, etc.) with or without the addition of any of the common excipients used in pharmaceutical formulations.

The amount of the MAP/polymer system of the invention which is administered to a subject will depend upon a variety of factors including the condition to be treated and the age and condition of the patient.

The following non-limiting examples illustrate some methods of making the preparations of the present invention.

EXAMPLE 1

2 gram of crystalline MAP and 6 gram of cross-linked PVP were mixed with a suitable mixer, subsequently placed in an automatic mortar mill and ground for 3 hours. The resulting MAP/cross-linked PVP system was then sieved to 260 µm range and subsequently mixed with a suitable mixer. This powdered MAP/cross-linked PVP system could then be incorporated in any desired solid dosage form.

EXAMPLE 2

The MAP/cross-linked PVP system described in Example 1 has been employed to prepare tablets having the following unitary composition:

- MAP/cross-linked PVP ground system	200 mg
- Cross-linked PVP	40 mg

in which pure cross-linked PVP is added only as a disintegrating agent.

The aforementioned ingredients were thoroughly mixed with a suitable mixer and subsequently compressed to tablets with a 13 mm flat punch compaction machine.

EXAMPLE 3

The MAP/cross-linked PVP powdered system described in Example 1 has been employed to prepare capsules having unitary composition as follows:

- MAP/cross-linked PVP ground system	200.0 mg
- Cross-linked PVP	40.0 mg
- Magnesium stearate	2.5 mg

EXAMPLE 4

0.7 gram of crystalline MAP and 3.5 gram of cross-linked sodium carboxymethylcellulose were mixed with a suitable mixer, subsequently placed in an automatic mortar mill and ground for 3 hours. The resulting MAP/cross-linked sodium carboxymethylcellulose powdered system was then sieved to 260 μm and subsequently mixed with a suitable mixer. This powdered MAP/cross-linked sodium carboxymethylcellulose system could then be incorporated in any desired solid dosage form.

EXAMPLE 5

0.2 gram of crystalline MAP and 1.0 gram of cross-linked PVP were mixed with a suitable mixer, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 215°C for 45 minutes, under a nitrogen flow.

The resulting MAP/cross-linked PVP system was then sieved to 260 μm and mixed with a suitable mixer. This powdered system could then be incorporated in any desired solid dosage form.

EXAMPLE 6

The MAP/cross-linked PVP system described in Example 5 has been employed to prepare tablets having the following unitary composition:

- MAP/cross-linked PVP heated system	300 mg
- Cross-linked PVP	60 mg

in which pure cross-linked PVP is added only as a disintegrating agent. The aforementioned ingredients were thoroughly mixed with a suitable mixer and subsequently compressed to tablets with a 13 mm flat punch compaction machine.

EXAMPLE 7

5 gram of crystalline MAP were dissolved in 100 ml methylenechloride; 20 ml of this solution were poured over 5 gram of cross-linked PVP, under gentle mixing in a mortar. The resulting swollen MAP/cross-linked PVP system was then dried in a vacuum oven, at 60°C, for 2 hours. The resulting dried powder was then sieved to 260 μm and subsequently mixed with a suitable mixer. This powdered system could then be incorporated in any desired solid dosage form.

EXAMPLE 8

The MAP/cross-linked PVP system described in Example 7 has been employed to prepare, by means of a 13 mm flat punch compaction machine, tablets having the following unitary composition:

- MAP/cross-linked PVP (swelling system)	300 mg

EXAMPLE 9

The MAP/cross-linked PVP powdered system described in Example 7 has been employed to prepare tablets having the following composition:

- MAP/cross-linked PVP (swelling system)	600 mg
- Microcrystalline cellulose PH-101	150 mg
- Magnesium stearate	6 mg

"IN VITRO" CHARACTERISTICS OF MAP-SWELLABLE POLYMER SYSTEMS

1. Differential Scanning Calorimetry Data

The D.S.C. (T.A. 3000, Mettler) data relative to the preparations by grinding described in Examples 1 and 4 are shown in Table I.

By comparing these data with the D.S.C. analysis of the pure MAP and of the micronized pure MAP, it is possible to observe that in the case of the ground mixture (1:3 w/w) of MAP and cross-linked PVP at three hours of grinding there is a 60% reduction of the original heat of fusion and the shifting of the original melting point (205.6°C) to a lower value (196°C). In the case of the ground mixture (1:5 w/w) of MAP and cross-linked sodium carboxymethylcellulose, after 3 hours of grinding there is a 50% degree of amorphization.

D.S.C. data of the MAP/swellable polymer system (Example 5) made by heating are also shown in Table I: there is a practically complete amorphization of MAP.

In the case of the MAP system prepared by swelling the cross-linked PVP with a solution of MAP in methylene-chloride (Example 8) there is no reduction of heat of fusion, but a lowering of the original melting point.

2. Solubility Data

The solubility (saturation concentration) of the MAP/

swellable polymer systems was measured by placing an excess amount of the powdered systems, equivalent to 50 mg of MAP, in flasks containing 50 ml of pH 5.5 buffer solution, at 37°C; the flasks were placed in a shaking thermostated apparatus and aliquots of sample solutions were taken by filtering through a Millipore (Registered Trade Mark) membrane; concentration of MAP in the filtered aliquot was determined both by spectrophotometry (SP8-100, Pye Unicam (Registered Trade Mark)), after dilution with methanol, and by HPLC(column: Spherisorb (Registered Trade Mark) S3ODS2, Phase Sep.; mobile phase: acetonitrile/water 70/30 v/v; flow rate: 1 ml/min; U.V. detection, λ = 242 nm), after dilution with acetonitrile.

As shown in Table II, a relevant increase of the MAP solubility values is achieved, also at very short times, by loading MAP into a swellable insoluble polymer by any of the three proposed techniques. It is particularly interesting to observe that at five minutes MAP concentrations dissolved from the polymeric systems are even 10-100 times higher than from crystalline MAP.

3. "Continuous Flow" Dissolution Data

"Continuous Flow" dissolution of tablets of the MAP/swellable polymer systems was measured by placing the tablets in a thermostated beaker, containing 150 ml

of pH 5.5 phosphate buffer solution at 37°C, magnetically stirred. The sample solution was continuously pumped (via a perystaltic pump, Watson-Marlow, England), through a Sartorius membrane, to a spectrophotometer cell (SP-8-100,Pye Unicam), and then pumped back into the dissolution beaker; concentrations of MAP were also checked by HPLC. The dissolution rates registered in "sink" conditions, i.e. up to MAP concentrations not higher than 20% of MAP solubility, are reported in Table III ("Sartorius" is a Registered Trade Mark). The dissolution rates of the MAP/swellable polymer systems are very much higher than that of the commercial tablet and of the mixture of ground crystalline MAP and ground cross-linked PVP. These results stress the relevance of MAP loading on/in swellable polymers induced by any of the three preparation methods (grinding, heating, solvent swelling) described by this invention.

BIOAVAILABILITY OF MAP/SWELLABLE POLYMERS SYSTEMS

The bioavailability of MAP from the MAP/swellable polymers systems covered by this patent and prepared by the procedures described in the previous paragraphs has been checked and compared with that of MAP from a commercial formulation and from a physical mixture consisting of MAP and cross-linked PVP.

To this aim the above mentioned formulations have been administered (oral route, cross-over design) to 6 beagle dogs (male and female, 9-13 kg weight) not fed for 17 hours before and for 4 hours after treatment. At predetermined times after administration, 4 ml blood samples were taken, transferred into heparinized tubes and centrifuged (3,000 r.p.m., 10 min.). The separated plasma was stored frozen (-20°C) until analysis.

The MAP plasma levels were determined by a specific, accurate and precise method which consists of: extraction of MAP with n-hexane, clean-up of the extract (partition with acetonitrile), high performance liquid chromatographic separation (column: Lichrosorb RP 18 Merck, mobile phase = methanol: water (75:25 v/v), flow rate 1 ml/min) and UV (242 nm) detection ("Lichrosorb" is a Registered Trade Mark).

In a first study, dogs were treated (oral route, cross-over design) with 250 mg of MAP in a commercial formulation and with cross-linked PVP loaded with MAP (50 mg) by the co-grinding, solvent swelling and heating methods respectively.

The data obtained and reported in Table IV show that MAP plasma levels after administration of the MAP/cross-linked PVP are comparable with or even higher than those produced by commercial tablets at a dose five times higher. Also the AUC values (7 hours) confirm the highly enhanced

bioavailability of MAP from the MAP/cross-linked PVP systems prepared by different procedures compared to that of MAP from a commercial formulation.

In a second study, dogs were treated (oral route, cross-over design) with tablets prepared using a physical mixture (1:3 w/w) of MAP (50 mg) and cross-linked PVP separately ground (3 hours) and with tablets prepared using a system consisting of MAP loaded (by cogrinding for 3 hours of 1:3 w/w mixture) in/on cross-linked PVP.

The data obtained and reported in Table V show that oral treatment with MAP/cross-linked PVP system brings about a remarkable increase of plasma levels and AUC (7 hours) compared with those after oral administration of the physical mixture of MAP and cross-linked PVP.

From these findings and from the <u>in vitro</u> studies previously reported, it is possible to conclude that the MAP/swellable polymer systems covered by the present patent possess the property to increase the dissolution characteristics of MAP and to enhance its bioavailability.

TABLE 1

Differential Scanning Calorimetry Data of Various MAP/Swellable Polymer Systems.

MAP preparation	Melting Point ° C	Heat of Fusion J/g	% Residual of Original Heat of Fusion
Pure crystalline MAP	205-206	88.003	100 %
Micronized pure MAP (3 hours of grinding)	205.3	82.798	94.1 %
MAP/cross-linked PVP 1:3 system (grinding method) Example 1	195.9	33.1	37.7 %
MAP/Sodium Carboxy-methylcellulose-cross-linked 1:5 system (grinding method) Example 4	204.4	44.6	50.6 %
MAP/cross-linked PVP 1:5 system (heating method) Example 5	-	~0	~0 %
MAP/cross-linked PVP 1:5 system (solvent swelling method) Example 7	195.2	85.4	97.1 %

TABLE II

Solubility Data (mcg/ml) of Various MAP/Swellable Polymer Systems(ph 5.5 phosphate buffer solution, at 37°C).

MAP preparation	Time			
	5 min	15 min	1 hr	6 hrs
Pure crystalline MAP	<0.04	0.32	0.68	1.00
MAP/cross-linked PVP 1:3 system (grinding method) Example 1	2.26	3.08	2.90	5.28
MAP/cross-linked PVP 1:5 system (heating method) Example 5	3.83	6.10	4.76	3.28
MAP/cross-linked PVP 1:5 system (solvent swelling method) Example 7	1.00	1.61	1.69	2.04

TABLE III

Dissolution Rate in "Sink" Conditions of Various MAP/ Swellable Polymer Systems (continuous flow method, pH 5.5 phosphate buffer, at 37°C).

MAP preparation	Dissolution Rate mg/min
Commercial Tablet[a] (containing 250 mg crystalline MAP)	0.144
1:3 w/w Physical Mixture[b] of ground crystalline MAP and ground cross-linked PVP (3 hrs of grinding)	0.041
1:3 w/w MAP/cross-linked PVP System[b], prepared by grinding for 3 hrs (preparation of Example 2)	0.428
1:5 w/w MAP/cross-linked PVP System[b], prepared by heating (preparation of Example 6)	0.500
1:5 w/w MAP/cross-linked PVP System[b], prepared by solvent swelling (preparation of Example 8)	0.530

[a] The commercial tablet unitary composition was: 250 mg of crystalline MAP; 121.25 mg of lactose, 60.00 mg of Corn Starch, 22.50 mg of linear polyvinylpyrrolidone, 31.25 mg of Sodium carboxymethyl starch, 5 mg of magnesium stearate

[b] System containing 50 mg of MAP.

TABLE IV

Plasma MAP Concentrations (ng/ml) Determined by HPLC Method from Bioavailability Studies in Fasted Beagle Dogs (Mean values and standard errors relative to six dogs).

Time (hrs)	Preparation			
	Commercial[a] Tablet 1 x 250 mg	MAP/cross-linked PVP[b] 1:5 w/w System (heating method) 1 x 50 mg	MAP/cross-linked PVP[c] 1:5 w/w System (solvent swelling method) 1 x 50 mg	MAP/cross-linked PVP[d] 1:3 w/w System (cogrinding method) 1 x 50 mg
1	12.94 (2.80)	19.16 (6.35)	23.48 (5.50)	94.65 (39.56)
2	20.33 (7.49)	14.00 (2.52)	41.38 (13.62)	69.21 (19.93)
4	26.73 (18.48)	10.72 (1.95)	16.06 (4.87)	34.96 (15.45)
7	9.51 (2.94)	8.74 (3.74)	8.52 (2.51)	11.63 (2.73)
AUC[e] (0-7 hrs) mcg x hr/ml	124.5 (48.1)	80.07 (9.42)	138.50 (32.30)	303.31 (83.52)

[a] Commercial tablet unitary composition was as follows: 250 mg of crystalline MAP; 121.25 mg of lactose; 60.00 mg of corn starch; 22.50 mg of linear polyvinyl-pyrrolidone; 31.25 mg of sodium carboxymethyl starch; 5 mg of magnesium stearate.

[b] Tablets were prepared as shown in Example 6.

[c] Tablets were prepared as shown in Example 8.

[d] Tablets were prepared as shown in Example 2.

[e] Area under the plasma MAP concentration-time curve.

TABLE V

Plasma MAP Concentrations (ng/ml) Determined by HPLC Method from Bioavailability Studies in Fasted Beagle Dogs. (Mean values and standard errors).

Time (hours)	Preparation	
	Control Tablet[a] (Physical Mixture 1:3 w/w ground MAP ground cross-linked PVP) Mean of five dogs 2 x 50 mg	MAP cross-linked PVP[b] 1:3 w/w (by cogrinding) Mean of six dogs 2 x 50 mg
1	9.71 (3.91)	86.67 (41.81)
2	13.24 (6.62)	95.99 (29.41)
4	31.19 (14.30)	79.58 (44.58)
7	11.01 (2.80)	25.41 (9.10)
AUC[c] (0-7 hrs) mcg x hr/ml	123.57 (35.45)	467.7 (150.11)

[a] Control tablets unitary composition was as follows: 200 mg of physical mixture 1:3 w/w of MAP and cross-linked PVP ground separately for 3 hours, 40 mg of cross-linked PVP alone as disintegrant. Each dog was given two tablets containing each 50 mg of MAP.

[b] Tablets of MAP cross-linked PVP system were prepared as shown in Example 2. Each dog was given two tablets containing each 50 mg of MAP.

[c] Area under the plasma MAP concentration - time curve.

* C L M S *

CLAIMS

1. A process for loading a water-swellable water-insoluble polymer with crystalline methyl-hydroxyprogesterone acetate (MAP), which process comprises:

(a) preparing and grinding a dry mixture of a said polymer and the MAP; and/or

(b) preparing a mixture of a said polymer which is stable and does not melt under the heating to which the mixture is subjected in step (ii) and the MAP, and (ii) heating the mixture up to the melting temperature of MAP; and/or

(c) swelling a said polymer with a MAP solution capable thereof and drying the resulting swollen polymer/MAP system; such that a degree of amorphization of the MAP is achieved or the crystalline MAP is transformed into another more energetic form.

2. A process according to claim 1 wherein the weight ratio of MAP:swellable polymer is from 1:0.1 to 1:100 w/w.

3. A process according to claim 1 or 2 wherein two or more water-insoluble polymers capable of swelling in water are employed.

4. A process according to any one of the preceding claims wherein the swellable water-insoluble polymer is cross-linked polyvinylpyrrolidone.

5. A process according to any one of the preceding claims wherein the swellable water-insoluble polymer is cross-linked sodium carboxymethylcellulose.

6. A water-swellable water-insoluble polymer loaded with MAP by a process as claimed in any one of the preceding claims.

7. A pharmaceutical composition comprising a water-swellable water-insoluble polymer loaded with MAP as claimed in claim 6.

8. A pharmaceutical composition according to claim 7 further comprising a pharmaceutically acceptable excipient.

9. A process for loading a water-swellable water-insoluble polymer with MAP, said process being substantially as hereinbefore described in any one of Examples 1, 4, 5 and 7.

10. A water-insoluble water-swellable polymer loaded with MAP substantially as hereinbefore described in any one of Examples 1, 4, 5 and 7.

11. A pharmaceutical composition substantially as hereinbefore described in any one of Examples 2, 3, 6, 8 and 9.