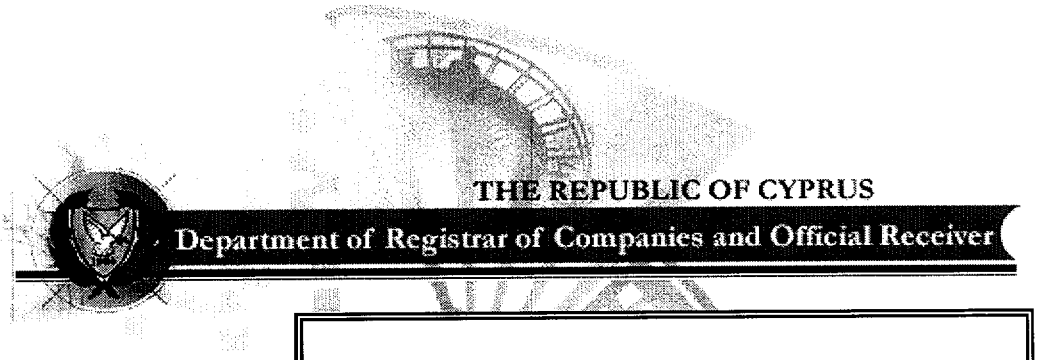


**ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ**

**THE PATENT OFFICE OF CYPRUS**

**ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ** **CY1589**
**PUBLICATION NUMBER**

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ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
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GB 1355537 US 3682930
British National Formulary, No. 6 (1983) page 110

(58) Field of search
A5B
Selected US specifications from IPC sub-class A61K

# (54) Ketotifen compositions

(57) Ketotifen pharmaceutical compositions are adapted for once-a-day oral administration e.g. based on a fat matrix.

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FIG. 1

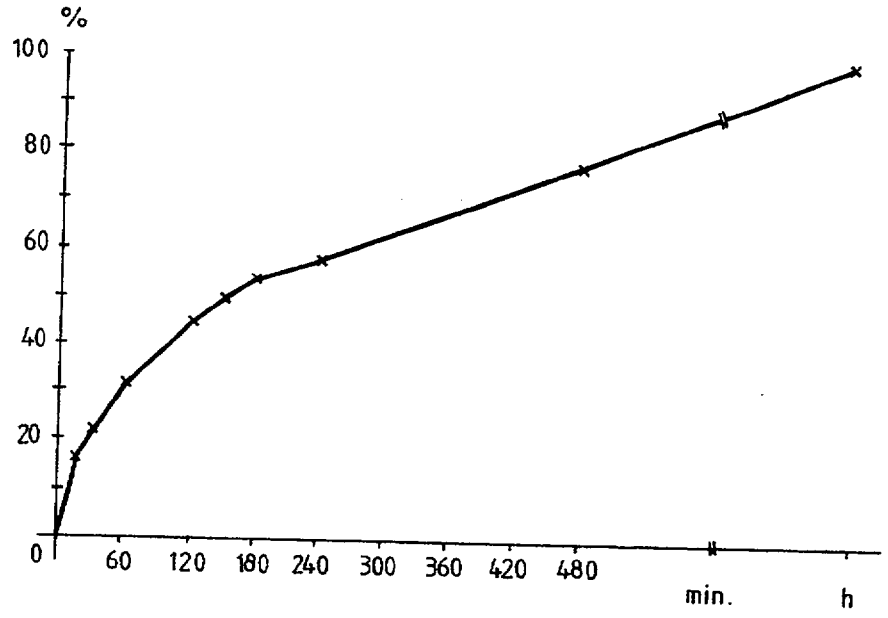


FIG. 2

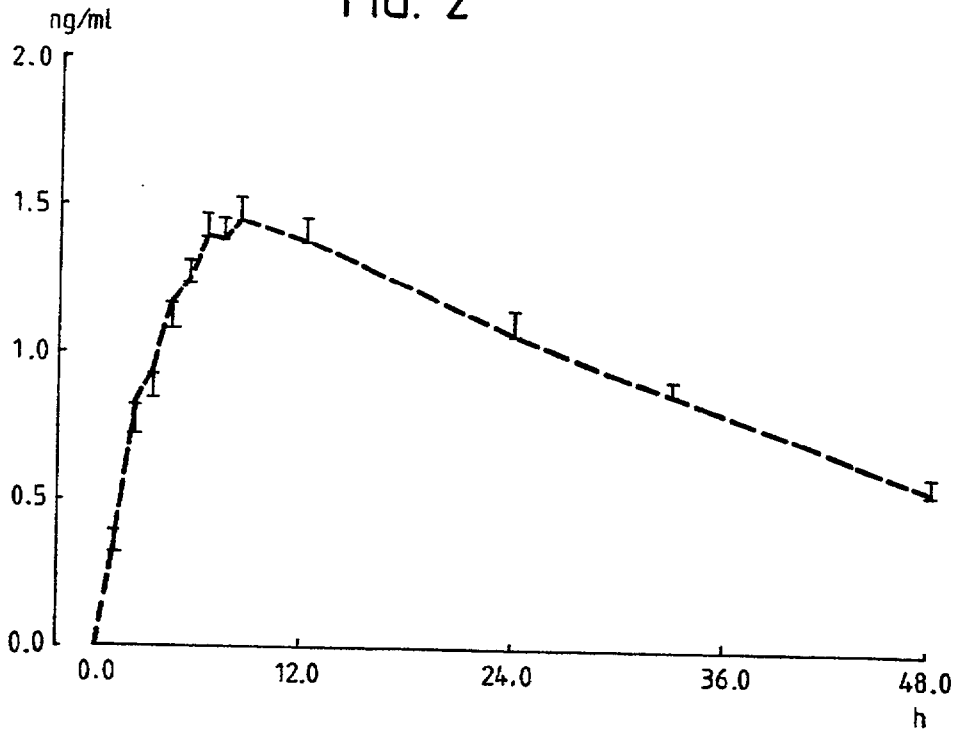

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FIG. 3

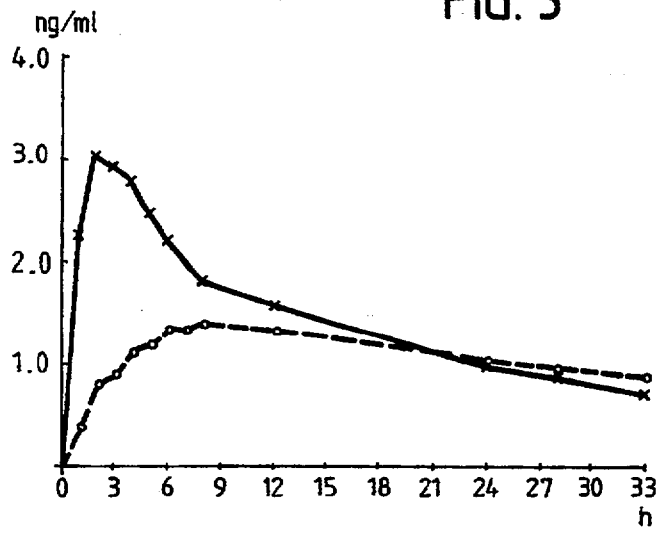


FIG. 4

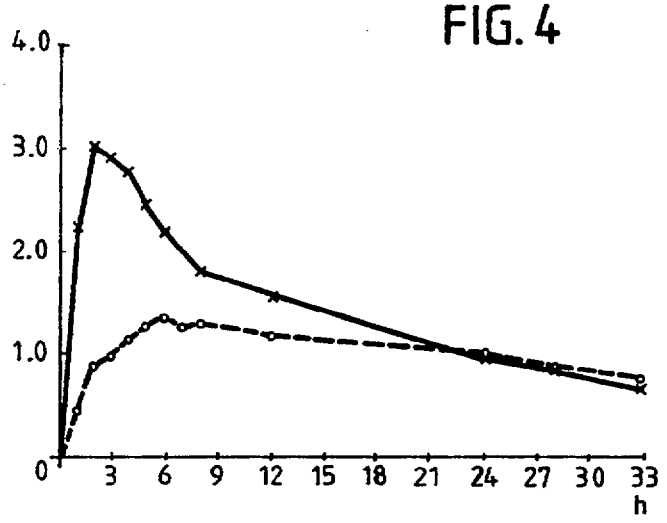


FIG. 5

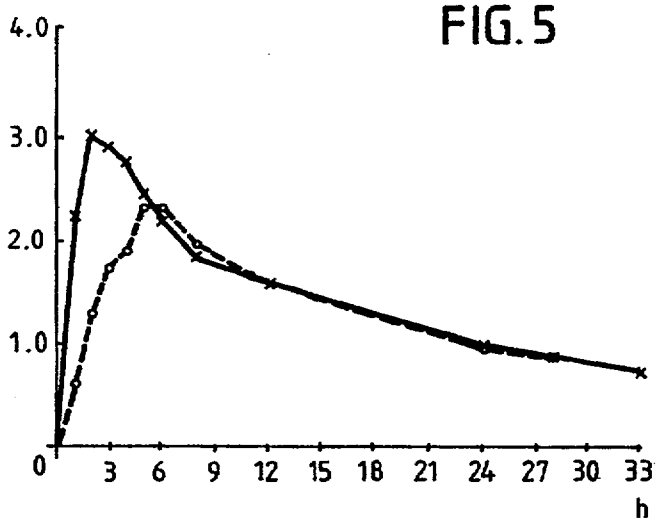

FIG. 6

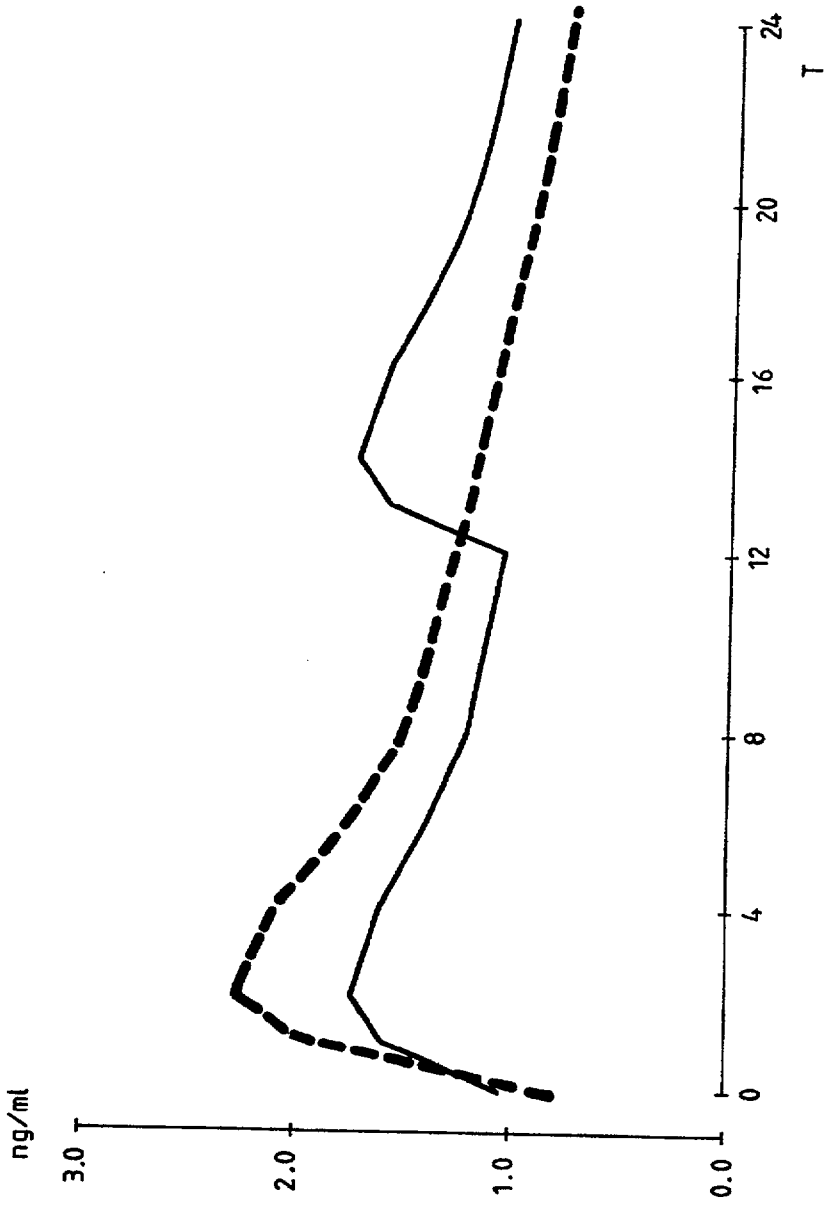

FIG. 7

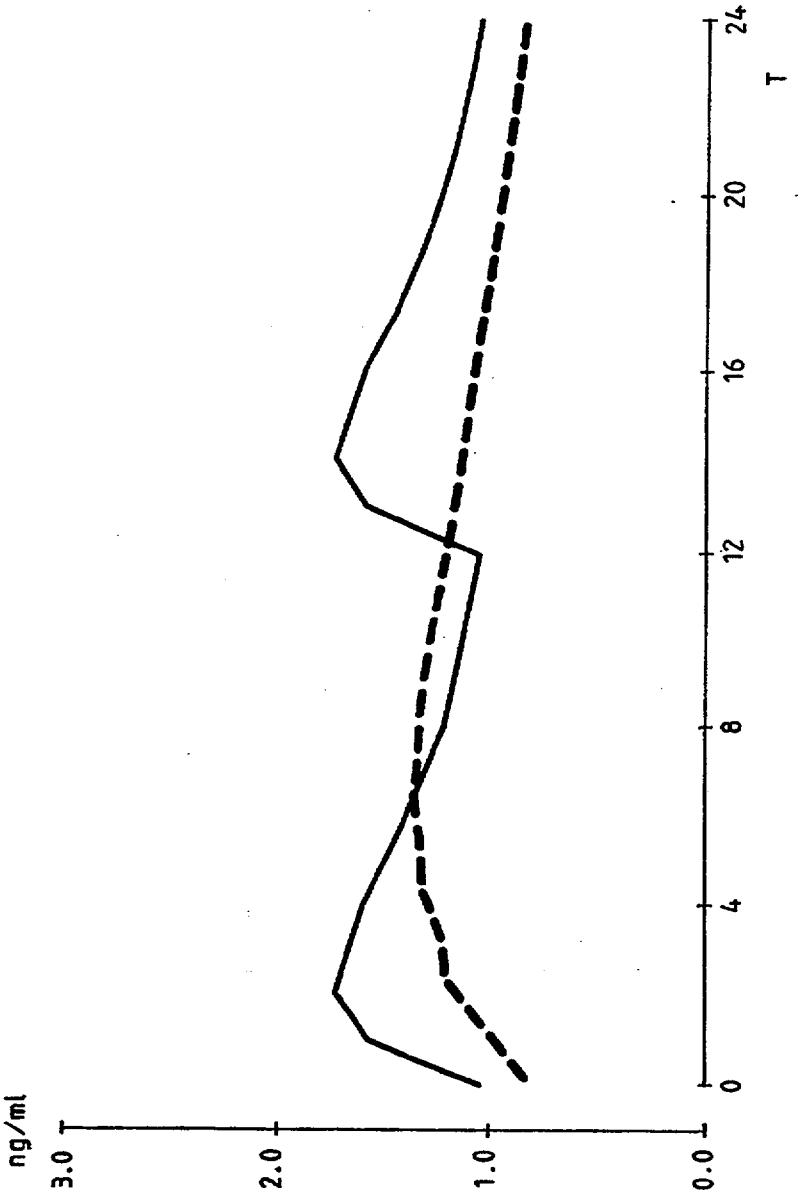

FIG. 8

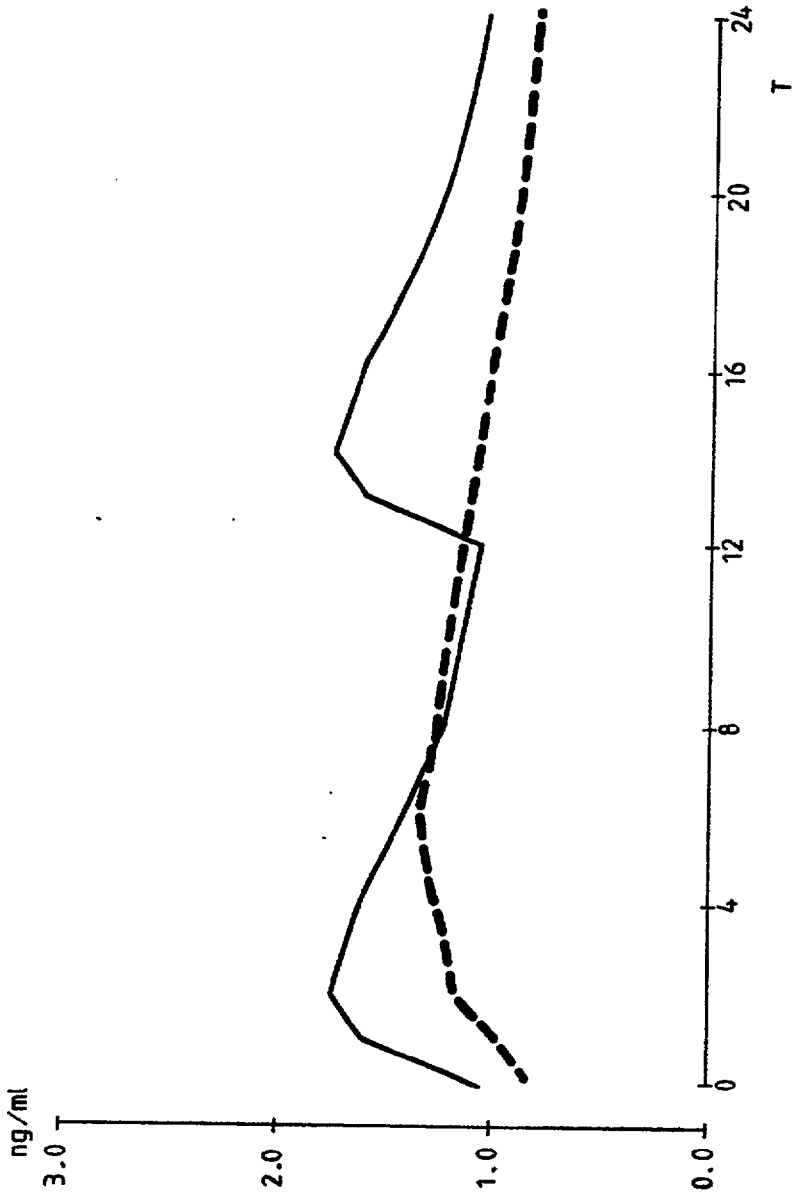

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FIG. 9

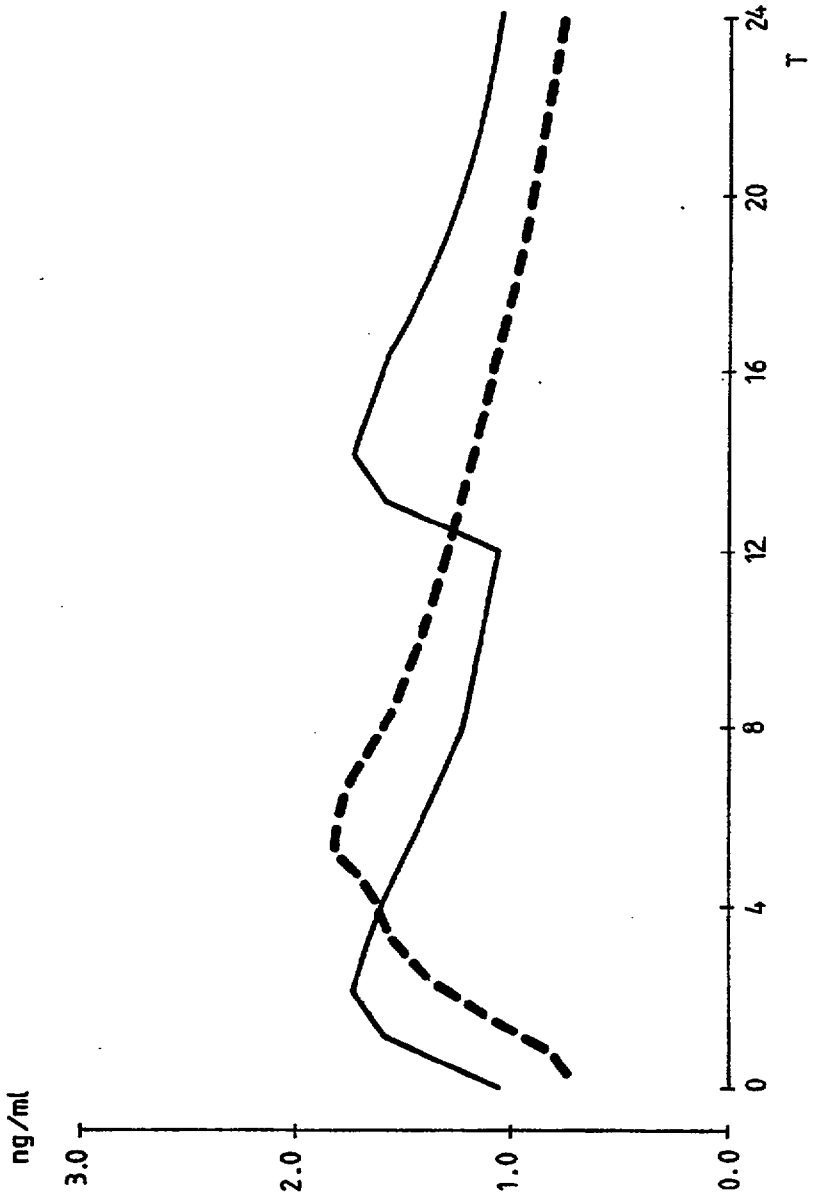

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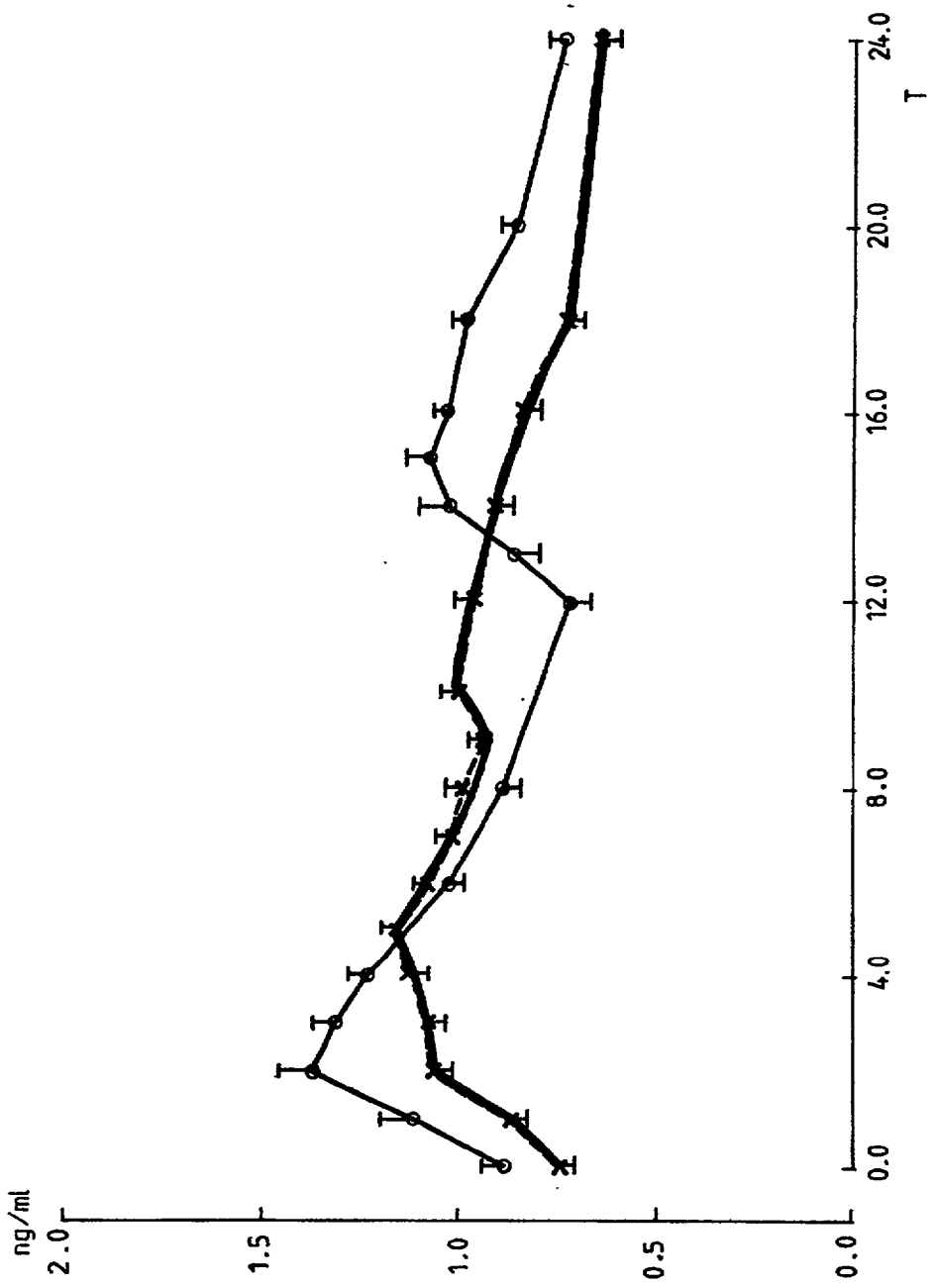
FIG. 10



SPECIFICATION

**Pharmaceutical compositions**

This invention relates to pharmaceutical compositions, particularly containing as an active agent 4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-10(9H)-one, also known as ketotifen, and especially those which are sustained release or retard formulations.

Ketotifen is described in German Patent 2,111,071. It has anti-anaphylactic and anti-histamine properties and is useful, e.g. for the prophylaxis of asthma and treatment of allergies. Ketotifen is generally administered twice-a-day. Adults usually take a unit dose of 1 mg.

Little has been published in the patent and academic literature on formulations of ketotifen which would provide a satisfactory therapeutic effect on once-a-day administration of a unit dosage formulation.

After extensive research into the biopharmaceutical and physical properties of ketotifen and extensive testing of ketotifen retard compositions we have now provided a commercially acceptable once-a-day oral pharmaceutical composition containing ketotifen.

The pharmaceutical compositions of the invention provide for the first time a once-a-day administration of ketotifen. These pharmaceutical compositions are especially indicated for use in asthma prophylaxis. Asthma attacks occur unexpectedly and not infrequently in the very early morning.

Pharmaceutical compositions of the present invention provide an effective level of ketotifen over long periods, and will provide protection against such attacks.

The pharmaceutical compositions of the invention provide a sustained and high absorption of ketotifen. The fluctuations in the plasma levels of ketotifen observed on steady state administration of the pharmaceutical compositions are unexpectedly small. Administration of the pharmaceutical compositions of the invention are associated with unexpectedly few side effects.

The present invention provides an oral ketotifen pharmaceutical composition adapted for once-a-day administration. It is a unit dosage form and preferably contains 2 milligrams of ketotifen. The pharmaceutical composition is preferably in a matrix form.

The bioavailability of the pharmaceutical compositions of the invention may be measured in conventional manner, e.g. by specific radioimmunoassays to measure the drug concentration in blood plasma.

One radioimmunoassay may be made by conjugating the desmethyl derivative of ketotifen via a Mannich reaction to the free amine groups of bovine serum albumin as protein and polyclonal antibodies are developed from the conjugate in sheep. The typical titre of the resultant antiserum is 1:8000. A radioimmunoassay is developed using ketotifen labelled in the 6 position with tritium. Labelled and unlabelled compound are allowed to compete for the available binding sites on the antibody. At equilibrium free and bound ligand are separated using a dextran coated active charcoal. Total radioactivity of the soluble portion may be measured by liquid scintillation counting.

In another aspect the present invention provides a once-a-day oral pharmaceutical composition comprising ketotifen and on administration providing a mean residence time of ketotifen in plasma of from 24 to 28 hours.

Preferably 2 mg ketotifen is administered. Preferably the mean residence time is from 25 to 27 hours.

The mean residence time (MRT) of an active agent in blood plasma is one recognized method for determining the slowing down of absorption of an active agent, as indicated by for example a delayed onset of the rise of active agent concentration in the blood plasma and/or a decrease in the rate at which the active agent concentration decreases after the peak active agent concentration has been reached.

$$\text{MRT is } \frac{{}_0\int^{\infty} C(t).t.dt}{{}_0\int^{\infty} C(t).dt.}$$

wherein C(t) is the concentration of active agent in plasma at a time t on the basis of single dose administration trials.

The desired plasma concentrations are preferably analysed with regard to the maximum and minimum active agent concentration (Cmax and Cmin) in steady state bioavailability studies. (either actual—see Example 7 or simulated—see Example 6) relative to corresponding values for reference forms.

In another aspect the present invention provides a once-a-day oral pharmacuetical composition comprising ketotifen which on administration in the steady state provides a $\frac{\text{Cmax}}{\text{Cmin}}$ ratio of from 1.2 to 2.4, for example to 2.3.

Preferably the Cmax/Cmin ratio is from 1.4 to 2.0.

The plasma concentrations may be compared to conventional forms of ketotifen to be administered twice-a-day, e.g. tablets and/or capsules. These are administered in steady state bioavailability trials every 12 hours using half the daily ketotifen dose.

The Cmax and Cmin values may be compared for the pharmaceutical compositions tested. Preferably the relative Cmax is from 0.5 to 1.3, especially 0.7 to 1.1. Preferably the relative Cmin is from 0.6 to 1.3, e.g. to 1:1.

If desired the relative bioavailability compared to a conventional form may be determined in the form of a quotient, e.g.

$$\frac{\text{AUC per mg dose (retard composition)}}{\text{AUC per mg dose (reference form)}}$$

wherein AUC is the Area under the curve extrapolated to infinity, e.g. by measuring from 0 to 33 hours and then extrapolating further (see example 5) in the case of a single dose or from 0 to 24 hours in the case of a steady state trial.

Preferably the relative bioavailability is from 70 to 125 per cent, especially 80 to 105 per cent.

We have also found that preferred oral pharmaceutical compositions containing ketotifen may be characterised by their in-vitro release data.

In yet a further aspect there is provided an oral pharmaceutical composition comprising ketotifen having the following in vitro ketotifen release rates, according to the rotating basket method at 120 rmp at 37°C in 500 ml 0.1 N HCl changed to pH 6.8 after 120 minutes:—

5 to 20 per cent after 15 minutes
10 to 25 per cent after 35 minutes
15 to 40 per cent after 60 minutes
25 to 60 per cent after 120 minutes, e.g. 35-50%
35 to 70 per cent after 180 minutes
40 to 75 per cent after 240 minutes
45 to 80 per cent after 300 minutes

In another aspect there is provided an oral pharmaceutical composition comprising ketotifen having the following in vitro ketotifen release rates, according to the rotating paddle method at 50 rpm at 37°C in 500 ml distilled water:—

10 to 30 per cent after 120 minutes
20 to 50 per cent after 240 minutes
30 to 60 per cent after 360 minutes
40 to 75 per cent after 480 minutes
55 to 90 per cent after 720 minutes
70 to 95 per cent after 960 minutes
80 to 100 per cent after 1440 minutes.

In a further aspect their is provided an oral pharmaceutical composition comprising ketotifen having the following in vitro ketotifen release rates according to the rotating paddle method at 120 rpm at 37°C in 500 ml 0.1 N HCl changed to pH 6.8 after 120 minutes:—

10 to 20 per cent after 15 minutes
15 to 25 per cent after 30 minutes
25 to 35 per cent after 60 minutes
35 to 50 per cent after 120 minutes
40 to 55 per cent after 150 minutes
45 to 60 per cent after 180 minutes

The first 2 sets of the above mentioned 3 sets of release rate characteristics are the preferred characteristics.

The in vitro release data may be effected according to conventional methods, e.g. those disclosed in the US pharmacopeia XX for the rotating paddle/rotating basket methods. HPLC or ultra-violet spectroscopy may be used to measure the ketotifen released.

The pharmaceutical compositions of the invention may be made up from conventional pharmaceutical excipients, of which at least one excipient acts to retard the release and/or resorption of the ketotifen.

A wide range of pharmaceutical excipients may be employed. Naturally the combination of specific pharmaceutical excipients and the relative amounts present may have to be determined by routine experimentation.

The ketotifen is preferably present in acid addition salt form, especially the hydrogen fumarate. If desired the free base may be used.

In yet a further preferred aspect the invention provides an oral pharmaceutical composition containing ketotifen in a lipophilic material.

In another aspect the present invention provides a process for the production of an oral once-a-day pharmaceutical composition containing ketotifen which comprises mixing, and, if desired, granulating ketotifen with a lipophilic material, preferably a fat, and working up into a unit dosage formulation, preferably a tablet composition.

The pharmaceutical compositions may be formulated in conventional manner, e.g. as used to provide sustained release formulations. Granulating and film coating techniques used in the art may be employed.

Preferably the lipophilic material is a fat. Fats which are preferred include cetyl palmitate, and especially glyceryl fatty acid esters such as glyceryl palmitates or stearates.

The fat is preferably a glyceryl palmitato-stearate, preferably ditripalmito stearate. Preferably it contains about 40 per cent full tri - ester palmito - stearic - triglycerides, 45 per cent partial (di)ester palmito - stearic diglycerides, 14 per cent partial monoester stearic monoglyceride and about 1% glycerol. Such a product is commercially available under the tradename Precirol, e.g. Precirol Ato5, from Gattefosse, France.

Preferably the fat is in a matrix. Especially preferred are compositions containing a high amount of fat, e.g. with a ratio of ketotifen to fat from about 1:10 to about 1:30, e.g. 1:20 to 1:25.

The composition may be in unit dosage form. It may conveniently be encapsulated. Preferably it is in a composition suitable for tabletting. For this preferably the ketotifen and fat is in the form of a granulate. Conveniently this granulate contains a diluent, filler or bulking agent, which may regulate the release rate, such as lactose, starch, e.g. corn starch, microcrystalline cellulose etc. If desired iron oxide may be present.

The fat granulate is preferably mixed with a placebo granulate containing agents which aid tabletting. The placebo granulate may also contain an agent which helps provide bulk for the tablet, improves flow of the particles in the tabletting machine and may be used to vary slightly the release characteristics of the ketotifen. Preferably the placebo granulate contains a filler such as lactose. Alternatives include calcium phosphate and sulphate. Preferably a disintegrant such as starch, especially corn starch, is present. Preferably a binding agent such as polyvinylpyrrolidone is present.

The placebo granulate preferably has another binding agent to slow down disintegration of the structure. Examples include cellulose derivatives such as hydroxypropylmethylcellulose or especially ethylcellulose.

The ethylcellulose preferably comprises 2.4 to 2.5 hydroxyl groups per glucose moiety. The ethylcellulose preferably has a viscosity between 4 and 22, preferably 7, cps in a 5 per cent solution.

The tablets may be made in conventional manner. The fat granulate may be made by mixing the components, sieving them, granulating at a slightly elevated temperature, e.g. about 50°C, cooling to about 20 to 40°C, and sieving or grinding the mass. The placebo granulate may for example be made in analogous manner to that described in DOS

2,426,811. The placebo granulate is for example made by mixing the components, sieving, granulating with e.g. ethanol, drying and sieving. The fat and placebo granulates may then be mixed.

To aid the tabletting process the fat granulate and any placebo granulates are preferably coated with an outer lubricant phase. If desired one of the granulates may be coated with at least part of or some of the components of an outer phase before mixing with the other granulate. Further coating to provide the complete outer phase may then be provided. A preferred example of lubricant is magnesium stearate. A glidant may be present. A preferred example of glidant is colloidal silica. The preferred form of silica is amorphous. It is commercially available as Aerosil. If desired hyroxypropylmethylcellulose may be present.

In one preferred embodiment the present invention provides:—

a) a fat granulate comprising ketotifen, lactose and glyceryl palmito-stearate,

b) a lactose placebo granulate also comprising starch and polyvinylpyrrolidone and optionally ethyl cellulose,

c) an outer phase comprising magnesium stearate and optionally silica.

Typical weight ratios of fat granulate to placebo granulate are from about 1:0.1 to about 1:1, e.g. 1:0.5 to 0.7. Typical weight ratios of ketotifen to total lactose are from about 1:6 to about 1:40, e.g. 1:20 to 1:40. The outer phase may be from about 0.1 to about 25, e.g. 0.5 to 2, per cent of the total weight.

Tabletting may be effected in conventional manner for the compression of high fat content mixtures. Preferred crushing strengths (hardness coefficients) are from about 15 to 50 N, conveniently 20 to 40 N.

Typical tablets weigh about 100-200 mg and have a film coating of about 2 mg.

Conveniently the tablets may be coated to improve their appearance, e.g. with a non-enteric coating. This may be for example a cellulose ether, e.g. hydroxypropylmethylcellulose. Other excipients such as silica, titanium oxide, talc, polyethyleneglycol or iron oxide may be present. Such films preferably have no significant effect on the retardation.

The pharmaceutical compositions of the invention may be used in the same indications and in the same manner as the known tablets. The efficacy may be determined in standard clinical trials, e.g. by decreasing the number of asthma attacks. Conveniently the pharmaceutical composition of the invention are given in the mornings or evenings, with a dose of 2 mg of ketotifen. Clinical trials show the excellent acceptance of the pharmaceutical compositions, few side effects such as sedation, and good efficacy on once-a-day administration. Furthermore, there seem to be no evidence of significant dose dumping or food interaction from pharmacokinetic trials.

All values herein, e.g. to MRT, refer except where otherwise stated to mean values.

The following examples illustrate the invention:—

Glyceryl ditripalmitostearate is conveniently brand Precirol preferably Precirol Ato5 (from Gattefosse, France). Silica is conveniently brand Aerosil 200 (from Degussa, Germany).

Polyvinylpyrrolidone is conveniently brand Plasdone K-29-32. Ethylcellulose is conveniently brand Ethylcellulose N7 cps (Hercules, USA).

Hydroxypropylmethylcellulose is conveniently brand Methocel E 5 cps. in the film layer and in the outer phase conveniently brand Methocel K 15M.

Further details of the composition of these components may be obtained from Fiedler H.P., Lexikon der Hilfsstoffe, 2nd Edition, Edito Cantor, Aulendorf, W. Germany.

*EXAMPLE 1:* Tablets comprising

a) a fat granulate
of 2.75* mg ketotifen hydrogen fumarate
23.50 mg lactose
2.50 mg corn starch
0.05 mg iron oxide (red or yellow)
41.20 mg glyceryl ditripalmitostearate

b) a placebo granulate
of 35.54 mg lactose
1.33 mg corn starch
2.33 mg polyivinylpyrrolidone
0.40 mg ethylcellulose

c) an outer phase
of 0.20 mg silica
0.20 mg magnesium stearate

* corresponding to 2 mg ketotifen in base form, crushing strength 15.40 N, thickness 2.5 mm, diameter 7 mm.

Further examples hereinafter refer to the above composition. If desired the 41.20 mg glyceryl ditripalmitostearate may be replaced by 30 mg glyceryl ditripalmitostearate.

*EXAMPLE 2:* Tablets comprising

a) a fat granulate
of 2.75 mg ketotifen hydrogen fumarate
26.0 mg microcrystalline cellulose
0.05 mg iron oxide (red or yellow)
41.20 mg glyceryl ditripalmitostearate

b) a placebo granulate
of 12.45 mg lactose
0.45 mg corn starch
1.00 mg polyivinylpyrrolidone
0.70 mg ethylcellulose and

c) an outer phase
of 0.20 mg silica
0.20 mg magnesium stearate

Weight 110 mg, crushing strength 30-40 N, thickness 2.5 mm. diameter 7 mm.

*EXAMPLE 3:* Tablets comprising

a) a fat granulate
of 2.75 mg ketotifen hydrogen fumarate
31.5 mg microcrystalline cellulose
0.05 mg iron oxide (red or yellow)
35.7 mg glyceryl ditripalmitostearate

b) a placebo granulate
of 57.0 mg lactose
7.0 mg corn starch
5.5 mg polyivinylpyrrolidone and

c) an outer phase
of 0.5 mg magnesium stearate.

Weight 140 mg, crushing strength 40-50 N, thickness 2.8 mm, diameter 7 mm.

The tablets of examples 1 to 3 may be coated in conventional manner with a film comprising:—

| | Parts by weight |
|---|---|
| Hydroxypropyl methylcellulose | 0.250 |
| Titanium dioxide | 0.0475 |
| Talc | 0.025 |
| Iron oxide | 0.006 |

*EXAMPLE 4: In vitro and in vivo release*

The in vitro release rate of ketotifen from a tablet of Example 1 may be determined according to the rotating paddle method (USP XX) at 120 rpm in 500 ml HC1 0.1N at 37°C.

After 120 minutes the pH is changed to 6 by the addition of a buffer.

The release rates may be:—

10 to 20 percent after 15 minutes
15 to 25 per cent after 30 minutes
25 to 35 per cent after 60 minutes
35 to 50 per cent after 120 minutes
40 to 55 per cent after 150 minutes
45 to 60 per cent after 180 minutes

According to the rotating basket method effected under the same conditions with pH change to 6.8 the example 1 had release rates of for example:—

16 per cent after 15 minutes
22 per cent after 30 minutes
32 per cent after 60 minutes
46 per cent after 120 minutes
55 per cent after 180 minutes
59 per cent after 240 minutes
64 per cent after 300 minutes
79 per cent after 480 minutes

a representative release rate is given in the accompanying figure 1.

The in vivo release from two tablets corresponding to 5.50 mg ketotifen hydrogen fumarate administered to 8 healthy patients (4 females and 4 males) who had taken two pharmaceutical compositions according to the invention 10 minutes before breakfast was determined.

The drug level in plasma is followed over 48 hours by taking 12 samples of blood.

The levels give an average profile according to figure 2. The kinetic profile is similar to that given in Example 5.

*EXAMPLE 5: Determination of relative Bioavailability*

Unfilmed retard tablets of examples 1, 2 and 3 were compared with a non-retarded reference capsule of the following composition:—

| | |
|---|---|
| Ketotifen hydrogen fumarate | 1.38 mg* |
| Silica | 0.30 mg |
| Magnesium stearate | 1.40 mg |
| Corn starch | 56.00 mg |
| Mannitol | 80.92 mg |
| | 140.00 mg |

* corresponding to 1 mg free base

In a first study the tablets of example 3 are compared with the reference capsule in 9 healthy volunteers and the plasma profile of both forms measured at regular intervals.

In a second study the tablets of examples 1 and 2 are tested in 8 healthy subjects under similar conditions to that in the first study. The plasma profile is determined.

The plasma profiles of the reference capsules and the tablets of examples 1 and 2 are followed for 33 hours and for the tablets of example 3 for 28 hours.

For the retard forms a single dose of 2 tablets (=4 mg ketotifen base) and for the reference forms of 2 capsules (=2 mg ketotifen base) were administered. The plasma concentration of the reference was doubled for the comparison.

The doubled value of the references are shown in figure 3 with the plasma profile of the tablets of example 1, in figure 4 with the plasma profile of tablets of example 2 and in Figure 5 with the plasma profile of tablets of example 3. (Plasma profiles are in nanograms/ml versus the time T in hours after administration).

Results:—

Fig. 3 (tablets of example 1)
Relative bioavailability = 85.5%
Fig. 4 (tablets of example 2)
Relative bioavailability = 85%
Fig. 5 (tablets of example 3)
Relative bioavailability = 90.1%

The relative bioavailability of the pharmaceutical compositions of the invention is preferably between 70 and 125%, especially between 80 and 105%, more especially up to 88%.

For the calculation of the relative bioavailability the curves are extrapolated to infinity.

*EXAMPLE 6:*

*Determination of the average mean-residence time and relative Cmax and Cmin and Cmax*

$$\frac{\quad}{Cmin}$$

These parameters are obtained from single dose trials and the results simulated to steady state trials over 24 hours using the retarded Example 1 form.

In this trial the plasma curve of a retarded single daily dose of 2.75 mg ketotifen hydrogen fumarate (=2 mg base) is determined over 2 hours, and compared with the plasma curve of one unit dose of a non-retarded reference form and measured over 12 hours. (In Figures 7, 8 and 9, the dotted plasma curve is compared with the reference curve from 0 to 12 hours which in the figures is simulated for the second time interval from 12 to 24 hours).

In figure 6 as a comparison (dotted line) a non-retarded table of 2.75 mg ketotifen hydrogen fumarate (= 2 mg base) after a single dose is measured for 24 hours and compared with the plasma curve of a unit dose of non-retarded reference form after two single administrations at time zero and at the time 12 hours respectively.

From the profiles shown in figures 6, 7, 8 and 9 the following results are obtained:—

| | Fig. 6 Ref. Form 1mg Base =1 caps. 2xpro day | Fig. 6 Ref. Form 2mg Base = 2 caps. 1xpro day | Fig. 6 Ex. 1 2mg Base =1 Tabl. 1x pro d. | Fig. 7 Ex. 2 2mg Base =1 Tabl. 1x pro d. | Fig. 8 Ex. 3 2mg Base =1 Tabl 1x pro d. | Fig. 9 |
|---|---|---|---|---|---|---|
| Mean residence time | | 22.4 | | 26 | 26 | |
| C max Retard form / C max Reference f. | 1 | | 1.31 | 0.78 | 0.77 | 1.05 |
| C min Retard form / C min Reference f. | 1 | | 0.77 | 0.80 | 0.79 | 0.73 |
| C max / C min | 1.7 | | 2.8 | 1.6 | 1.6 | 2.4 |

In general the mean residence time in plasma is from 24 to 29, and especially 25 to 28, hours for a pharmaceutical composition of the invention.

The relative Cmax after a single daily oral administration is especially 0.5 to 1.3, e.g. 0.7 to 1.1, the relative Cmin especially 0.6 to 1.3, e.g. 0.6 to 1.1 and Cmax / Cmin especially 1.2 to 2.3, e.g. 1.4 to 2.0, based on the non-retarded form, and over a 12 hour interval for half daily dose.

*EXAMPLE 7:*

Analogous to Example 6 a full steady state trial with 12 healthy subjects with the retarded tablets of example 1 (given in the morning), and the reference form described in example 5, given in the morning and 12 hours later, was effected. The results are shown in figure 10.

The difference to the trial in example 6 resides in the fact that the profile of the retard forumlation (thick line) is derived from the seventh day onwards and no extrapolation is made. The second curve is derived from the reference forms.

In this steady state trial the relative bioavailability of the pharmaceutical composition of the invention was 93% (based on the AUC from 0 to 24 hours). The relative ratios of the $C_{max}$ was 83% based on day 7, $C_{min}$ based on day 7) 84% and the ratio of $C_{max}$ to $_{min}$ was 1.63 for the composition of the invention compared to 1.65 for the reference.

*EXAMPLE 8: Tablet production*

| Ingredient | Weight (mg) |
|---|---|
| *Fat granulate* | |
| Ketotifen hydrogen fumarate | 2.75 |
| Lactose (200 mesh) | 23.55 |
| Corn starch | 2.5 |
| Glyceryl ditripalmitostearate | 41.2 |
| *Pacebo granulate* | |
| Lactose (200 mesh) | 35.6 |
| Corn starch | 1.3 |
| Polyvinylpyrrolidone | 2.3 |
| Ethylcellulose | 0.4 |
| *Outer phase* | |
| Silica | 0.2 |
| Magnesium stearate | 0.2 |
| *Film coating* | |
| Hydroxypropyl methylcellulose | 1.25 |
| Polyethylene glycol 6000 | 0.125 |
| Titanium oxide | 0.356 |
| Talc | 0.125 |
| Silica | 0.125 |
| Iron oxide yellow | 0.0188 |

Total weight (112 mg; Core 110 mg, Film coating 2 mg).

*Fat granulate*

The fat granulate is made in 2 batches. The preparation of one batch is as follows:—

2.75 kg of ketotifen hydrogen fumarate is mixed with 8.55 kg lactose for 5 minutes. The mass is sieved (vibration sieve; mesh width 500; hole size 250 microns).

Separately 15 kg lactose and 2.5 kg corn starch are sieved and mixed (vibration sieve; hole size 1600 microns, wire diameter 630 microns). Glyceryl ditripalmitostearate is sieved (mesh width 1600, hole size 630 microns) and 41.2 kg thereof is mixed with two previously sieved masses, forming ketotifen fat granulate over ca. 30 minutes to ca. 50°C. The fat granluate is cooled to about 20 to 30°C. The mass is broken up using a sieve (hole size 1.5 mm). Total weight (two batches) 140 kg.

*Placebo granulate*

71.2 kg lactose, 2.6 kg corn starch, 4.6 kg polyvinylpyrrolidone and 0.8 kg ethyl cellulose N7 are sieved (vibration sieve mesh width 1600; hole size 630 microns) and mixed for about 2 minutes. 8 kg 94% ethanol are added and the mass granulated. The mass is dried at room temperature of 50°C (granulate temperature 36°C). The mass is broken up as for the fat granulate to produce the placebo granulate. Total weight 79.2 kg.

*Tabletting composition*

0.4 kg silica are mixed with 4 kg of the fat granulate and sieved (mesh width 1000; hole size 400 microns) and the sieved mass is mixed with the rest of the fat granulate. 3 kg of the placebo granulate and 0.4 kg of magnesium stearate are mixed and sieved (mesh width 1000, hole size 400 microns). This mass is mixed with the rest of the placebo granulates, and then with the silica/fat granulate mass. 220 kg mass is sufficient for 2 million tablets.

Tabletting is effected e.g. on a Fette 1000 Perfekta machine to provide tablets of 110 mg weight, 2.8 mm thickness under a pressure of 3-6 kN.

*Film coating*

A solution of 4.5 kg hydroxypropyl methylcellulose, 0.4 kg polyethylene glycol and 67.5 kg demineralized water is made up 0.18 kg 25% ammonia are added. 8.1 kg demineralized water is added. 1.2825 kg titanium dioxide, 0.45 kg talc, 0.45 kg silica and 0.0675 iron oxide yellow are mixed, ground, mixed with 7.02 kg water, and added to the solution to provide a film suspension (98 kg). The tablets are coated with the solution at ca. 35°C in a coating pan (Accela-Cota 48 inches).

*In vitro release rates*

Release rates measured by the rotating paddle method at 50 rpm at 37°C in 500 ml distilled water for 6 tablets:—

| Time (minutes) | Per cent released | SEM |
|---|---|---|
| 120 | 16.0 | 2.7 |
| 240 | 34.5 | 2.4 |
| 360 | 47.3 | 2.9 |
| 480 | 56.3 | 4.8 |
| 600 | 63.5 | 3.7 |
| 720 | 70.9 | 3.1 |
| 960 | 80.5 | 4.8 |
| 1200 | 89.5 | 3.9 |
| 1440 | 92.1 | 3.2 |

Release rates measured by the rotating basket method at 120 rpm at 37°C in 500 ml 0.1 N HCl with a pH change to 6.8 after 2 hours:—

| Time (minutes) | Per cent released |
|---|---|
| 60 | 23 |
| 120 | 34 |
| 150 | 34 |
| 180 | 37 |
| 240 | 41 |
| 300 | 46 |

CLAIMS

1. An oral ketotifen pharmaceutical composition adapted for once-a-day administration.

2. A composition according to claim 1 comprising 2 mg of ketotifen.

3. a once-a-day oral pharmaceutical composition comprising ketotifen and on administration providing a mean residence time of ketotifen in plasma of from 24 to 28 hours.

4. A once-a-day oral pharmaceutical composition comprising ketotifen which on administration in the steady state provides a

$$\frac{\text{Cmax}}{\text{Cmin}}$$

ratio of from 1.2 to 2.4.

5. A pharmaceutical composition according to claim 4 which on administration compared to a conventional form administered twice-a-day has a relative Cmax of from 0.5 to 1.3 and a relative Cmin of 0.6 to 1.3.

6. An oral pharmaceutical composition comprising ketotifen having the following in vitro ketotifen release rates according to the rotating paddle-method at 120 rpm at 37°C in 500 ml 0.1 N HCl changed to pH 6.8 after 120 minutes.

10 to 20 per cent after 15 minutes
15 to 25 per cent after 30 minutes
25 to 35 per cent after 60 minutes
35 to 50 per cent after 120 minutes
40 to 55 per cent after 150 minutes
45 to 60 per cent after 180 minutes

7. An oral pharmaceutical composition comprising ketotifen having the following in vitro ketotifen release rates, according to the rotating paddle method at 50 rpm at 37°C in 500 ml distilled water:—

10 to 30 per cent after 120 minutes
20 to 50 per cent after 240 minutes
30 to 60 per cent after 360 minutes
40 to 75 per cent after 480 minutes
55 to 90 per cent after 720 minutes
70 to 95 per cent after 960 minutes
80 to 100 per cent after 1440 minutes

8. An oral pharmaceutical composition comprising ketotifen having the following in vitro ketotifen release rates, according to the rotating basket method at 120 rpm at 37°C in 500 ml 0.1 N HCl changed to pH 6.8 after 120 minutes:—

5 to 20 per cent after 15 minutes
10 to 25 per cent after 30 minutes
15 to 40 per cent after 60 minutes
25 to 60 per cent after 120 minutes
35 to 70 per cent after 180 minutes
40 to 75 per cent after 240 minutes
45 to 80 per cent after 300 minutes

9. A pharmaceutical composition according to any one of claims 1 to 8 having, compared to a conventional form administered twice-a-day, a relative steady state bioavailability of from 70 to 125 per cent.

10. A once-a-day oral pharmaceutical composition containing ketotifen in a lipophilic material.

11. A pharmaceutical composition according to claim 10 having on administration compared to a conventional form administered twice-a-day a relative steady state bioavailability of from 70 to 125 per cent.

12. A pharmaceutical composition according to claim 10 or 11 wherein the lipophilic material is a fat.

13. A pharmaceutical composition according to claim 12 wherein the fat is glyceryl palmitostearate.

14. A pharmaceutical composition according to claim 12 wherein the fat is in the form of a mixture.

15. A pharmaceutical composition according to any one of claims 1 to 14 wherein the composition is a tablet composition.

16. A pharmaceutical composition according to any one of claims 12 to 14 wherein the ratio of ketotifen to fat is from 1:10 to 1:30.

17. A pharmaceutical composition according to any one of claims 12 to 16 wherein the ketotifen is in a fat granulate.

18. A pharmaceutical composition according to any one of claims 1 to 17 wherein the ketotifen is in admixture with a placebo granulate.

19. A pharmaceutical composition according to claims 17 or 18 wherein the ketotifen is coated with an outer lubricant phase.

20. A pharmaceutical composition comprising a fat granulate containing ketotifen and glyceryl palmitostearate, a lactose placebo granulate also containing starch and polyvinylpyrrolidone and an outer phase containing magnesium stearate.

21. A pharmaceutial composition according to any preceding claim in the form of a tablet having a non-enteric coating.

22. An oral ketotifen pharmaceutical composition substantially as hereinbefore described with reference to any one of the examples.

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