COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

I
We EUROCELTIQUE S.A.
Of 122, Boulevard de la Petrusse,
Luxembourg.

596249

hereby apply for the grant of a Standard Patent for an invention entitled:

"SPHEROIDS"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

Number	Convention Country	Date
8628728	UNITED KINGDOM	2nd December 1986

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 14.2.90

LODGED AT SUB-OFFICE
- 2 DEC 1987
Melbourne

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 2nd day of December 19 87

To: THE COMMISSIONER OF PATENTS

H. d. Rimington
(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

P/0213/AU/N

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention entitled: Spheroids

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

I ~~We~~ Fritz Scharer Of Mundi-Inter S.A., Schutzenmattstr. 52, 4051 - Basel, SWITZERLAND

Mr F. Scharer, Authorised to sign on behalf of Euroceltique S.A. under a Power of Attorney.

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)

1(b) relates to application made by company; insert name of applicant company.

do solemnly and sincerely declare as follows :–

1. (a) ~~I am / We are the applicant(s) for the patent~~

or (b) I am authorized by Euroceltique S.A., 122, Boulevard de la Petrusse, LUXEMBOURG.

the applicant..... for the patent to make this declaration on ~~my~~ its behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply

2(a) relates to application made by inventor(s)

2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

2. (a) ~~I am / We are the actual inventor(s) of the invention~~

or (b) Stewart Thomas LESLIE, 4 Babraham Road, CAMBRIDGE. CB2 2RA

Sandra Therese Antoinette MALKOWSKA, 14, Abrahams Close, Landbeach, CAMBRIDGE.

Joanne MARCHANT, 11 Gainsborough Drive, Burleigh Hill, St. Ives, CAMBRIDGE.

Philip John NEALE, 28 London Road, Harston, CAMBRIDGE. CB2 5QH

All of the United Kingdom.

~~I am~~ / are the actual inventor.....s..... of the invention and the facts upon which the applicant..... ~~is~~ / are entitled to make the application are as follows :–

State manner in which applicant(s) derive title from inventor(s)

by virtue of the employment of the inventors and an agreement between the inventors' employer and Euroceltique S.A. dated 1st January 1984, the applicant would if a patent were granted on an application made by the said inventors be entitled to have the patent assigned to it.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ~~was~~ / were made

in Great Britain on the 2nd December 1986

by Euroceltique S.A.

in ..... on the .....

by .....

in ..... on the .....

by .....

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~ / were the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Basle this 20th day of October 1987

Signature of declarant(s) (no attestation required)

Mr F. Scharer, Authorised to sign on behalf of Euroceltique S.A. under a Power of Attorney.

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-81997/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 596249

(54) Title
FILM COATED SPHEROIDS OF 3-ALKYL-XANTHINES

International Patent Classification(s)
(51)[4] **A61K 031/52 A61K 009/36 A61K 009/52**

(21) Application No. : **81997/87** (22) Application Date : **02.12.87**

(30) Priority Data

(31) Number (32) Date (33) Country
8628728 02.12.86 GB UNITED KINGDOM

(43) Publication Date : **02.06.88**

(44) Publication Date of Accepted Application : **26.04.90**

(71) Applicant(s)
EUROCELTIQUE S.A.

(72) Inventor(s)
SANDRA THERESE ANTOINETTE MALKOWSKA; STEWART THOMAS LESLIE; JOANNE MARCHANT; PHILIP JOHN NEALE

(74) Attorney or Agent
DAVIES & COLLISON, MELBOURNE

(56) Prior Art Documents
AU 81823/87 A61K 9/20, 31/52, 31/71

(57) Claim

1. A controlled release pharmaceutical composition comprising a plurality of film coated spheroids, the film coated spheroids comprising a 3-alkylxanthine, a non-water soluble spheronising agent and between 4% and 9% (by weight) water, wherein the in-vitro dissolution rate of the 3-alkylxanthine from the film coated spheroids, when measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH 6.5) at 37°C is between 7.5% and 25.0% (by wt) release after 1 hour, between 22.5% and 45.0% (by wt) release after 2 hours, between 40.0% and 60.0% (by wt) release after 3 hours, between 50.0% and 75.0% (by wt) release after 4 hours, between 70.0% and 92.5% (by wt) release after 6 hours, and between 80.0% and 100.0% (by wt) release after 8 hours.

5. A composition according to claim 4 wherein the 3-alkylxanthine comprises acepifylline, bamifylline, bufylline, diprophylline, etamiphylline, etofylline, proxyphylline or theophylline.

15. A process for the preparation of a controlled release pharmaceutical composition according to claim 1. comprising

(a) granulating a mixture comprising a 3-alkylxanthine, a non-water soluble spheronising agent and water,

(b) extruding the granulated mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed,

(d) drying the spheroids, and

(e) coating the spheroids with a film coat that permits release of the 3-alkylxanthine at a controlled rate in an aqueous medium, to give film coated spheroids, wherein the spheroids are dried in step (d) above to such an extent that the film coated spheroids contain between 4% and 9% (by weight) water and the in-vitro dissolution rate of the 3-alkylxanthine from the film coated spheroids, when measured by the USP Paddle Method at 100rpm on 900ml aqueous buffer (pH 6.5) at 37°C is
betweem 7.5% and 25.0% (by wt) release after 1 hour,
between 22.5% and 45.0% (by wt) release after 2 hours,
between 40.0% and 60.0% (by wt) release after 3 hours,
between 50.0% and 75.0% (by wt) release after 4 hours,
between 70.0% and 92.5% (by wt) release after 6 hours, and
between 80.0% and 100% (by wt) release after 8 hours.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

CLASS INT. CLASS

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published: 596249

Priority:

Related Art:

NAME OF APPLICANT: EUROCELTIQUE S.A.

ADDRESS OF APPLICANT: 122, Boulevard de la Petrusse, Luxembourg.

NAME(S) OF INVENTOR(S) Steward Thomas LESLIE
Sandra Therese Antoinette MALKOWSKA
Joanne MARCHANT
Philip John NEALE

ADDRESS FOR SERVICE: **DAVIES & COLLISON**, Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"SPHEROIDS"

The following statement is a full description of this invention, including the best method of performing it known to us :-

1A

SPHEROIDS

The present invention relates to a controlled release pharmaceutical composition containing a 3-alkylxanthine.

It is one object of the present invention to provide a 3-alkylxanthine containing controlled release pharmaceutical composition having a narrow range of in-vitro dissolution rates over a wide pH range (pH 1.6 to 7.2). Other objects and advantages of the present composition will become apparent from the following detailed description thereof.

According to the present invention, there is provided a controlled release pharmaceutical composition comprising a plurality of film coated spheroids, the film coated spheroids comprising a 3-alkylxanthine, a non-water soluble spheronising agent and between 4% and 9% (by weight) water, wherein the in-vitro dissolution rate of the 3-alkylxanthine from the film coated spheroids, when measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH 6.5) at 37°C is
between 7.5% and 25.0% (by wt) release after 1 hour,
between 22.5% and 45.0% (by wt) release after 2 hours,
between 40.0% and 60% (by wt) release after 3 hours,
between 50.0% and 75.0% (by wt) release after 4 hours,
between 70.0% and 92.5% (by wt) release after 6 hours, and
between 80.0% and 100% (by wt) release after 8 hours.

In the present specification "per cent (by weight) water" refers to the water content of the spheroids as measured using a Karl Fischer titration method.

Preferably the water content of the film coated spheroids is between 4% and 8% (by weight), and the in vitro dissolution

rate of the 3-alkylxanthine is between 8.0% and 22.5% (by wt) release after 1 hour, between 25% and 42.5% (by wt) release after 2 hours, between 42.5% and 60% (by wt) release after 3 hours, between 52.5% and 72.5% (by wt) release after 4 hours, between 72.5% and 92.5% (by wt) release after 6 hours and between 82.5% and 100% (by wt) release after 8 hours.

Most preferably, the water content is between 4% and 7% (by weight) and the in vitro dissolution rate is between 8.0% and 20% (by wt) release after 1 hour, between 25% and 40% (by wt) release after 2 hours, between 42.5% and 57.5% (by wt) release after 3 hours, between 55% and 70% (by wt) release after 4 hours, between 75.0% and 90.0% (by wt) release after 6 hours, and between 82.5% and 100% (by wt) release after 8 hours.

The term "spheroid" is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5mm and 2.5mm, especially between 0.5mm and 2mm.

The present inventors have surprisingly found that the water content of the present film coated spheroids has a dramatic effect on the in-vitro release rate of the active ingredient. When the water content of the film coated spheroids is below 4% (by wt), the release rate is too fast. When the water content of the film coated spheroids is above 9%, the release rate is too slow. For example, when two groups of film coated spheroids having identical formulations except for their water contents which were, respectively, 0.82% (by wt) and 10.26% (by wt), were subjected to in-vitro dissolution, it was found that the "0.82" formulation released, in-vitro, 60.2% (by wt) theophylline after 1 hour, 91.9% (by wt) after 2 hours, 95.7% (by wt) after 3 hours and 96.0% (by wt) after 4 hours, whilst the "10.26" formulation released, in-vitro, 7.1% (by wt)

theophylline after 1 hour, 22.5% (by wt) after 2 hours, 38.1% (by wt) after 3 hours and 51.8% (by wt) after 4 hours.

It is a particular advantage of the present composition that the in-vitro dissolution rate is substantially independent of pH over a wide range (pH 1.6 to 7.2)

The present film coated spheroids contain a 3-alkylxanthine. The phrase "3-alkylxanthine" in the present specification incorporates

i) Any xanthine substituted at the 3 nitrogen by an alkyl group, and

ii) Any salt or derivative of such a 3-alkyl substituted xanthine.

Thus, the 3-alkylxanthine may be, for example, enprofylline or theobromine. Preferably, however, the 3-alkylxanthine is a 1,3-dimethylxanthine, such as acepifylline, bamifylline, bufylline, diprophylline, etamiphylline, etofylline, proxyphylline or theophylline. Of these 1,3-dimethyl xanthines, theophylline (anhydrous or hydrate) or a salt or derivative of theophylline, such as aminophylline, choline theophyllinate, theophylline monoethanolamine, theophylline sodium glycinate or theophylline calcium salicylate is particularly preferred. Theophylline (anhydrous or hydrate) is the most preferred.

Preferred doses of the 3-alkylxanthines in a unit dose of the present composition are as follows:

Acepifylline	125 - 1000mg
Aminophylline	50 - 450mg

Bamifylline HCl	150 - 600mg
Bufylline	30 - 120mg
Choline Theophyllinate	50 - 400mg
Diprophylline	50 - 400mg
Enprofylline	50 - 600mg
Etamiphylline camsylate	50 - 600mg
Etofylline	100 - 600mg
Proxyphylline	100 - 600mg
Theobromine	50 - 600mg
Theophylline	50 - 400mg
Theophylline Monoethanolamine	50 - 400mg
Theophylline Na Glycinate	50 - 600mg

The concentration of 3-alkylxanthine in the present film coated spheroids will depend, amongst other factors, on the amount of xanthine to be administered and the total weight of film coated spheroids to be administered. In the case of theophylline, the film coated spheroids preferably contain between 40% and 75% (by wt), especially between 45% and 70% (by wt), of the active ingredient.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporaration). According to one preferred embodiment of the present composition, the film coated spheroids contain between 20% and 50% (by wt), especially between 25% and 45% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the 3-alkylxanthine, spheronising agent and water, the present spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl celluloses, such as hydroxy propyl cellulose, are preferred.

The present spheroids are film coated with a material that permits release of the 3-alkylxanthine at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the spheroids' other ingredients, the in-vitro release rate outlined above (between 7.5% and 25.0% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit (Trade Mark).

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water

soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

A unit dose of the present pharmaceutical composition may consist of, for example, a capsule, sachet or cachet containing a predetermined quantity of film coated spheroids. In the case of a capsule or cachet, the dosage form may be administered directly via the oral route. In the case of a capsule, sachet or cachet, the film coated spheroids may be sprinkled onto food which is then taken as part of a meal.

The present controlled release pharmaceutical composition may be prepared, in a second aspect of the present invention, by

(a) granulating a mixture comprising a 3-alkylxanthine, a non-water soluble spheronising agent and water,

(b) extruding the granulated mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed,

(d) drying the spheroids, and

(e) coating the spheroids with a film coat that permits release of the 3-alkylxanthine at a controlled rate in an aqueous medium, to give film coated spheroids, wherein the spheroids are dried in step (d) above to such an extent that the film coated spheroids contain between 4% and 9% (by weight) water and the in-vitro dissolution rate of the 3-alkylxanthine from the film coated

spheroids, when measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH 6.5) at 37°C is between 7.5% and 25.0% (by wt) release after 1 hour, between 22.5% and 45.0% (by wt) release after 2 hours, between 40.0% and 60.0% (by wt) release after 3 hours, between 50.0% and 75.0% (by wt) release after 4 hours, between 70.0% and 92.5% (by wt) release after 6 hours, and between 80.0% and 100% (by wt) release after 8 hours.

Preferably, after drying, in step (d) above, the spheroids are sieved to give spheroids having a predetermined particle size range.

The present composition and process will now be described by way of Example only.

Determination of Water Content by the Karl Fischer Method

1. A Karl Fischer Autotitration unit (Baird and Tatlock) was set up according to the manufacturer's instructions.

2. A sample volume of Karl Fischer reagent (Fisons) was standardised.

3. A predetermined quantity of spheroids was ground to a fine powder in a mortar and pestle.

4. Approximately 0.5g of the powdered spheroids were weighed into the sample vessel.

5. The Karl Fischer reagent was neutralised in the reaction vessel and then the sample was added. The mixture was stirred for 3 minutes.

6. The sample vessel was reweighed in order to determine the weight of sample used.

7. A Karl Fischer titration was then carried out in the reaction vessel, the amount of titrant added being noted. The test was carried out in duplicate.

Example 1

Spheroid Formation

Anhydrous theophylline (BP, 60.61 parts by wt), microcrystalline cellulose (Avicel PH 101, Trade Mark, 37.39 parts by wt) and hydroxypropyl cellulose (Klucel GF, Trade Mark, 2.0 parts by wt) were dry mixed. Water (550 parts by weight) was added to the mixture until a densely granulated mass was obtained. The granulated mass was passed through a 1mm cylinder on an extruder to give a uniform, free flowing extrudate. The extrudate was then spheronised.

The wet spheroids were dried until they had a water content (as measured by the Karl Fischer method) of 6.49 wt% (of the total spheroid weight). Finally, the spheroids were sieved to give a particle size range between 1.0 and 1.4mm.

Film Coating

A film coat containing the following ingredients, in a solvent system consisting of methanol (60% v/v) in dichloromethane was employed,

	% w/v
Ethyl cellulose NF (N10 , Trade Mark)	3.5
Hydroxypropylmethyl cellulose EP (Methocel E15, Trade Mark)	1.5
Propylene glycol BP	0.5
Opaspray K-1-7000B (Trade Mark)	3.0

The dried spheroids were film coated with the above formulation. The dried film coat corresponded to about 6.7% (w/w) of the total, film coated spheroid weight. The film coated spheroids had a water content (by Karl Fischer) of 6.2 wt% (of the total, film coated spheroids weight).

Example 2

The procedure of Example 1 was followed except that the spheroids were dried until they had a water content of 6.8 wt% (of the total spheroid weight). The film coated spheroids had a water content of 5.6 wt% (of the total, film coated spheroid weight).

Example 3

The procedure of Example 1 was followed except that the spheroids were dried until they had a water content of 7.3 wt% (of the total spheroid weight). The film coated spheroids had a water content of 6.4 wt% (of the total, film coated spheroid weight).

Example 4

The procedure of Example 1 was followed except that the spheroids were dried until they had a water content of 6.7 wt% (of the total spheroid weight). The film coated spheroids had

a water content of 5.8 wt% (of the total, film coated spheroid weight).

Example 5

The procedure of Example 1 was followed except that the spheroids were dried until they had a water content of 6.9 wt% (of the total spheroid weight). The film coated spheroids had a water content of 5.95 wt% (of the total, film coated spheroid weight).

Comparative Example

The procedure of Example 1 was followed except that the spheroids were dried until they had a water content of 12.0 wt% (of the total spheroid weight). The film coated spheroids had a water content of 10.3 wt% (of the total, film coated spheroid weight).

Comparative Example

The procedure of Example 1 was followed except that the spheroids were dried until they had a water content of 0.5 wt% (of the total spheroid weight). The film coated spheroids had a water content of 0.8 wt% (of the total, film coated spheoid weight).

Example 6

Spheroid Formation

Anhydrous theophylline (BP, 50 parts by wt), microcrystalline cellulose (Avicel PH101, Trade Mark, 46 parts by wt) and hydroxyethylcellulose (Natrosol 250L, 4 parts by wt) were dry

mixed. Water (600 parts by wt) was added to the mixture until a densely granulated mass was obtained. The granulated mass was passed through a 1mm cylinder on an extruder to give a uniform, free flowing extrudate. The extrudate was then spheronised.

The wet spheroids were dried. Finally the spheroids were sieved to give a particle size range between 1.0 and 1.4mm.

Film Coating

A film coat containing the following ingredients, in a solvent system consisting of methanol (60% v/v) in dichloromethane was employed,

	% w/v
Ethyl cellulose NF (N10, Trade Mark)	3.5
Hydroxypropylmethyl cellulose EP (Methocel E15, Trade Mark)	1.5
Propylene Glycol BP	0.5
Opaspray K-1-7000B (Trade Mark)	3.0

The dried spheroids were film coated with the above formulation. The dried film coat corresponded to about 17% (w/w) of the total, film coated spheroid weight. The film coated spheroids had a water content (by Karl Fischer) of 4.4 wt% (of the total, film coated spheroids weight)).

Dissolution Methods

A. Materials

1. Dissolution Apparatus

USP Paddle Dissolution apparatus fitted with a peristaltic pump and a UV spectrophotometer. The spectrophotometer had 1mm pathlength flow cells.

2. Reagents

Theophylline anhydrous (BP of known purity)
Sodium Hydroxide (AR)
Potassium dihydrogen orthophosphate (AR)
Distilled, deionised water

3. pH 6.5 USP Buffer

Potassium dihydrogen orthophosphate (6.805g) and sodium hydroxide (0.56g) was dissolved in distilled water (1 litre) for each litre of buffer required.

The pH of the solution was adjusted, if necessary, to pH 6.5. Prior to use, the buffer solution was purged with helium for at least 30 minutes.

Methods

Medium:	USP Buffer, pH 6.5, deaerated
Volume:	900ml
Temperature:	37°C $\pm$ 0.5°C
Paddle Speed:	100rpm
Sampling Time:	1 hour intervals
Sampling Period:	until at least 90 wt% theophylline released
Pump Speed:	15ml/minute
Detection:	UV absorbance at 244nm
Pathlength:	1mm

TABLE 1

Dissolution Results (mean of 5 samples)
(% Theophylline Released)

Example	Water Content of Film Coated Spheroids (wt%)	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	10h
1	6.2	13.9	33.7	50.2	64.0	75.1	83.7	90.2	95.5	100
2	5.6	13.5	34.1	51.1	64.8	75.8	84.1	90.7	95.4	100
3	6.4	17.3	36.2	52.6	65.4	75.6	84.3	89.9	94.5	99.4
4	5.8	13.9	33.7	50.2	63.5	74.5	83.0	89.7	94.4	99.4
5	5.95	12.0	30.0	45.3	57.9	68.5	76.6	83.0	87.9	92.6
6	4.4	10.4	30.6	47.9	62.0	73.1	82.5	90.2	94.7	100.4
Comparative	10.3	7.1	22.5	38.1	51.8	64.0	73.8	82.0	88.1	95.6
Comparative	0.8	60.2	91.9	95.7	96.0	-	-	-	-	-

CB1AAC

Film coated spheroids prepared according to the methods of Examples 1 to 6 and the Comparative Examples were subjected to the above in-vitro dissolution test. The results obtained are set out in Table 1.

B. The dissolution method was as described in method A except that the buffer was pH 1.6 USP Buffer.

pH 1.6 USP Buffer

Potassium chloride (3.7275g) and hydrochloric acid (1M, 32.4ml) was dissolved in distilled water for each litre of buffer required. The pH of the solution was adjusted, if necessary, to pH 1.6. Prior to use, the buffer solution was purged with helium for at least 30 minutes.

Film coated spheroids prepared according to Example 5 were subjected to the in-vitro dissolution test (pH 1.6). The results (mean of 5 experiments) obtained are set out in Table 2.

TABLE 2

Dissolution of Film coated Spheroids (Water Content 5.95 wt%) in USP Buffer, pH 1.6

Time(hr)	% Theophylline Released (by wt)
1.0	13.8
2.0	34.5
3.0	51.7
4.0	65.3
5.0	75.9
6.0	83.8

7.0	89.6
8.0	93.0
10.0	95.8

CLINICAL STUDIES

A. A 12 volunteer study was carried out to compare the steady state pharmacokinetics of

i) Theophylline spheroids (200mg theophylline) prepared as described in Example 5, and

ii) A sustained release theophylline tablet (UNIPHYLLIN CONTINUS tablet containing 200mg theophylline).

Method

12 Healthy male volunteers were studied on two separate occasions. During each study period of 6 days, the subjects received either a UNIPHYLLIN CONTINUS tablet containing 200mg of theophylline b.d. or theophylline spheroids (Example 5, 200mg of theophylline) b.d. for 5 days, with a single dose of either tablet or spheroids being administered on the morning of day 6.

Blood samples were collected over 24 hours following this last dose and the plasma obtained was analysed for theophylline.

Plasma theophylline concentrations are given in Table 3.

TABLE 3

Plasma Theophylline Concentration (mcg ml^{-1})

Time(hr)	UNIPHYLLIN CONTINUS TABLETS	THEOPHYLLINE SPHEROIDS
0	4.0	3.4
4	4.1	4.1
5	4.3	4.6
6	4.2	4.2
7	4.3	4.0
8	4.1	3.9
10	3.7	4.2
12	3.5	3.0
24	1.2	0.9

Theophylline spheroids (Example 5) were found, on the basis of this study, to be bioequivalent to the UNIPHYLLIN CONTINUS tablet.

B. A 6 volunteer, single dose, crossover study was carried out to compare the pharmacokinetic properties of

i. Theophylline spheroids (200mg theophylline) prepared as described in Example 6, and

ii. A sustained release theophylline tablet (UNIPHYLLIN CONTINUS tablet containing 400mg theophylline).

Results are given in Table 4.

TABLE 4

Plasma Theophylline Concentration (mcg ml^{-1})

Time(hr)	UNIPHYLLIN CONTINUS TABLETS	THEOPHYLLINE SPHEROIDS
0	0	0.1
1	1.3	0.6
2	2.7	1.8
3	3.8	2.2
4	4.5	3.2
6	5.2	4.0
8	5.4	4.6
10	5.5	2.9
12	5.0	2.3
24	1.4	0.9

This study showed that the theophylline spheroid formulation had the same bioavailability as a UNIPHYLLIN CONTINUS tablet.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A controlled release pharmaceutical composition comprising a plurality of film coated spheroids, the film coated spheroids comprising a 3-alkylxanthine, a non-water soluble spheronising agent and between 4% and 9% (by weight) water, wherein the in-vitro dissolution rate of the 3-alkylxanthine from the film coated spheroids, when measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH 6.5) at 37°C is
between 7.5% and 25.0% (by wt) release after 1 hour,
between 22.5% and 45.0% (by wt) release after 2 hours,
between 40.0% and 60.0% (by wt) release after 3 hours,
between 50.0% and 75.0% (by wt) release after 4 hours,
between 70.0% and 92.5% (by wt) release after 6 hours, and
between 80.0% and 100.0% (by wt) release after 8 hours.

2. A composition according to claim 1 wherein the film coated spheroids contain between 4% and 8% (by weight) water and the in vitro dissolution rate of the 3-alkylxanthine is
between 8.0% and 22.5% (by wt) release after 1 hour,
between 25% and 42.5% (by wt) release after 2 hours,
between 42.5% and 60% (by wt) release after 3 hours,
between 52.5% and 72.5% (by wt) release after 4 hours,
between 72.5% and 92.5% (by wt) release after 6 hours,
and
between 82.5% and 100% (by wt) release after 8 hours.

3. A composition according to claim 2 wherein the film coated spheroids contain between 4% and 7% (by weight) water and the in vitro dissolution rate of the 3-alkylxanthine is
between 8% and 20% (by wt) release after 1 hour,
between 25% and 40% (by wt) release after 2 hours,
between 42.5% and 57.5% (by wt) release after 3 hours,

between 55% and 70% (by wt) release after 4 hours, between 75% and 90% (by wt) release after 6 hours, and between 82.5% and 100% (by wt) release after 8 hours.

4. A composition according to any one of claims 1 to 3 wherein the 3-alkylxanthine comprises a 1,3-dimethylxanthine, or a salt or derivative of a 1,3-dimethylxanthine.

5. A composition according to claim 4 wherein the 3-alkylxanthine comprises acepifylline, bamifylline, bufylline, diprophylline, etamiphylline, etofylline, proxyphylline or theophylline.

6. A composition according to claim 4 wherein the 3-alkylxanthine comprises theophylline, aminophylline, choline theophyllinate, theophylline monoethanolamine, theophylline sodium glycinate or theophylline calcium salicylate.

7. A composition according to either claim 5 or claim 6 wherein the 3-alkylxanthine comprises theophylline.

8. A composition according to claim 7 wherein the film coated spheroids comprise between 40% and 75% (by weight) theophylline.

9. A composition according to claim 8 wherein the film coated spheroids comprise between 45% and 70% (by weight) theophylline.

10. A composition according to any one of claims 1 to 9 wherein the spheronising agent comprises microcrystalline cellulose.

11. A composition according to any one of claims 1 to 10 wherein the film coated spheroids comprise between 20% and 50%, (by weight) of the spheronising agent.

12. A composition according to claim 11 wherein the film coated spheroids comprise between 25% and 45% (by weight) of the spheronising agent.

13. A composition according to any one of claims 1 to 12 wherein the film coat comprises ethyl cellulose and hydroxypropylmethyl cellulose.

14. A controlled release pharmaceutical composition according to claim 1 substantially as hereinbefore described with particular reference to any one of the Examples 1 to 6.

15. A process for the preparation of a controlled release pharmaceutical composition according to claim 1. comprising

(a) granulating a mixture comprising a 3-alkylxanthine, a non-water soluble spheronising agent and water,

(b) extruding the granulated mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed,

(d) drying the spheroids, and

(e) coating the spheroids with a film coat that permits release of the 3-alkylxanthine at a controlled rate in an aqueous medium, to give film coated spheroids,

wherein the spheroids are dried in step (d) above to such an extent that the film coated spheroids contain between 4% and 9% (by weight) water and the in-vitro dissolution rate of the 3-alkylxanthine from the film coated spheroids, when measured by the USP Paddle Method at 100rpm on 900ml aqueous buffer (pH 6.5) at 37°C is

betweem 7.5% and 25.0% (by wt) release after 1 hour,
between 22.5% and 45.0% (by wt) release after 2 hours,
between 40.0% and 60.0% (by wt) release after 3 hours,
between 50.0% and 75.0% (by wt) release after 4 hours,
between 70.0% and 92.5% (by wt) release after 6 hours, and
between 80.0% and 100% (by wt) release after 8 hours.

16. A process according to claim 15 wherein, after the spheroids are dried and before the spheroids are film coated, the spheroids are sieved to give spheroids having a predetermined particle size range.

17. A process for the preparation of a controlled release pharmaceutical composition according to claim 15 substantially as hereinbefore described with particular reference to any one of the Examples 1 to 6.

~~18. The steps, features, compositions and compounds~~ referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any ~~two or more of said steps or features.~~

Dated this 2nd day of December 1987

EUROCELTIQUE S.A.,
By its Patent Attorneys,
DAVIES & COLLISON.