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(57) Abstract

Three pharmaceutical compositions are described: slow-release transdermal patches, sublingual/chewable tablets, and sprays based on apocodeine (APC) and/or its derivatives, for the treatment of male impotence and for the stimulation of male and female libido.

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PHARMACEUTICAL COMPOSITIONS COMPRISING APOCODEINE AND/OR ITS DERIVATIVES

Disorders associated with reduced sexual potency and a fall in sexual desire are the most common problems for which adults currently resort to alternative medical practices rather than conventional medicine, one reason being that a confident diagnosis cannot be met with an adequate pharmacological remedy.

Besides bringing together diverse activity, the drugs currently commercially available show the greatest and most significant differences with regard to the side effects, the duration of action and the ease of use.

These differences are the most important factor to take into consideration when choosing a drug, since they determine both the safety and the patient compliance.

In addition, the safety of use and the compliance make the difference all the more perceptible in drugs for which indications are given which improve the quality of life and which are not "lifesaving" drugs.

Important considerations regarding the choice of drug for the treatment of male sexual impotence and for the stimulation of male and female libido concern the side effects liable to be induced and the safety of use in a self-administration regime.

The current limitations in the treatment of impotence and in the stimulation of desire are due to the fact that effective drugs exist, but they can only be used with extreme caution on account of the numerous and extremely serious side effects which can be induced, and equally effective drugs exist which, although not exhibiting side effects, require highly sophisticated production technology, as a result of

which the marketed product is penalized by a high cost, thus restricting its use.

The present invention, which relates to the use of apocodeine (APC) and/or its derivatives for the preparation of various medicinal forms (patches, tablets, sprays), overcomes the current limitations of the treatment in use for treating the pathologies under consideration, since, in the forms and doses proposed, APC is effective, is free of side effects and requires only simple and cost-effective technology for its preparation.

Transdermal patch

Description in support of a patent application entitled:

Pharmaceutical compositions (transdermal patches, chewable/sublingual tablets, sprays) comprising apocodeine (APC) and/or its derivatives, for the treatment of male impotence and for the stimulation of male and female libido.

The molecule APC and its derivatives are stable with respect to air and light.

In the abovementioned therapeutic indications, APC is a powerful drug which can be administered transdermally.

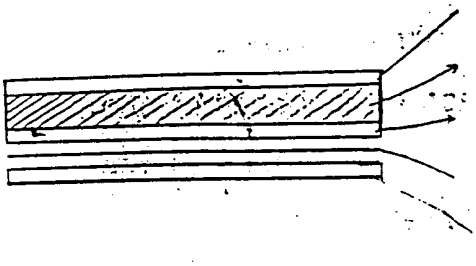
The active principle (APC) is rapidly absorbed, becomes effective rapidly (latency time 8'-18') and is equally rapidly eliminated (half-life 30').

Thus, in order to ensure that the patient has the required pharmacological cover with effective, sufficient and constant levels in the blood, it will be necessary to make the individual take the drug at the physiological dose via the transdermal route for the time required to satisfy the expectations.

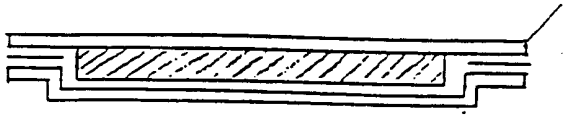
For transdermal administration, it will be sufficient to apply a slow-release patch (TDDS = transdermal drug delivery system), referred to hereinbelow as a TDDS patch, based on APC in order to provide pharmacological cover for about 8 hours.

Three basic types of TDDS patch can be prepared, as represented schematically in the drawings below:

TYPE I DESCRIPTION



TYPE II



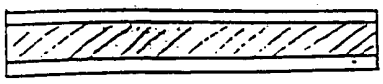
impermeable support film (backing)

ring of adhesive

matrix

release strip

TYPE III



impermeable support film (backing)

adhesive matrix

protective release strip

A subject of the present invention is thus a pharmaceutical composition comprising, in pharmaceutically acceptable and effective doses, APC and/or its derivatives.

A further subject of the invention is a transdermal patch comprising, as active principle, APC and/or its derivatives, this patch having a type I, type II or type III structure, and its shape and size being suitably sized in relation to the site of application and the desired dosage.

A further subject of the invention is the use of APC and/or its derivatives, for the preparation of a transdermal patch for the treatment of male impotence and for the stimulation of male and female libido.

Three basic types of transdermal patch (TDDS patch) can be prepared:

TYPE I: is a device comprising an impermeable support film on which is a matrix or reservoir in which the active substance is dissolved and/or dispersed. The matrix, on the side opposite the support, is coated with a membrane which is permeable to the active substance and regulates its cross-flow. A contact adhesive is layered on the free side of the permeable membrane (adhesive layer), protected by a release strip. The device is used as follows: the release strip is pulled off and the device is positioned over the desired part of the patient's body and applied with light pressure.

TYPE II: This device comprises an impermeable support film on which is a matrix or reservoir in which the active substance is dissolved or dispersed. It lacks the membrane which is permeable to the active substance, which modulates the cross-flow, as a result of which the matrix is free on one side and comes into direct contact with the epidermis. The adhesive is located around the edge of the device, as a kind of adhesive ring. The assembly is protected on the free side by a single removable release strip, as in type I.

The device is used as follows: the release strip is pulled off and the device is positioned over the desired part of the patient's body and applied with light pressure.

TYPE III: This is also known as a "drug in an adhesive matrix" assembly. In this device, the pharmacological dose is housed directly, in dissolved or dispersed form, in the adhesive, which thus also acts as a reservoir matrix and is layered on an impermeable support film. The adhesive matrix is protected on one side by the support (backing), and on the other side by the release strip. The device is used as follows: the release strip is pulled off and the device is positioned over the desired part of the patient's body and applied with light pressure.

The differences between the structures and shape (rectangular or anatomical) of the three types of patch are specifically designed to compensate for:

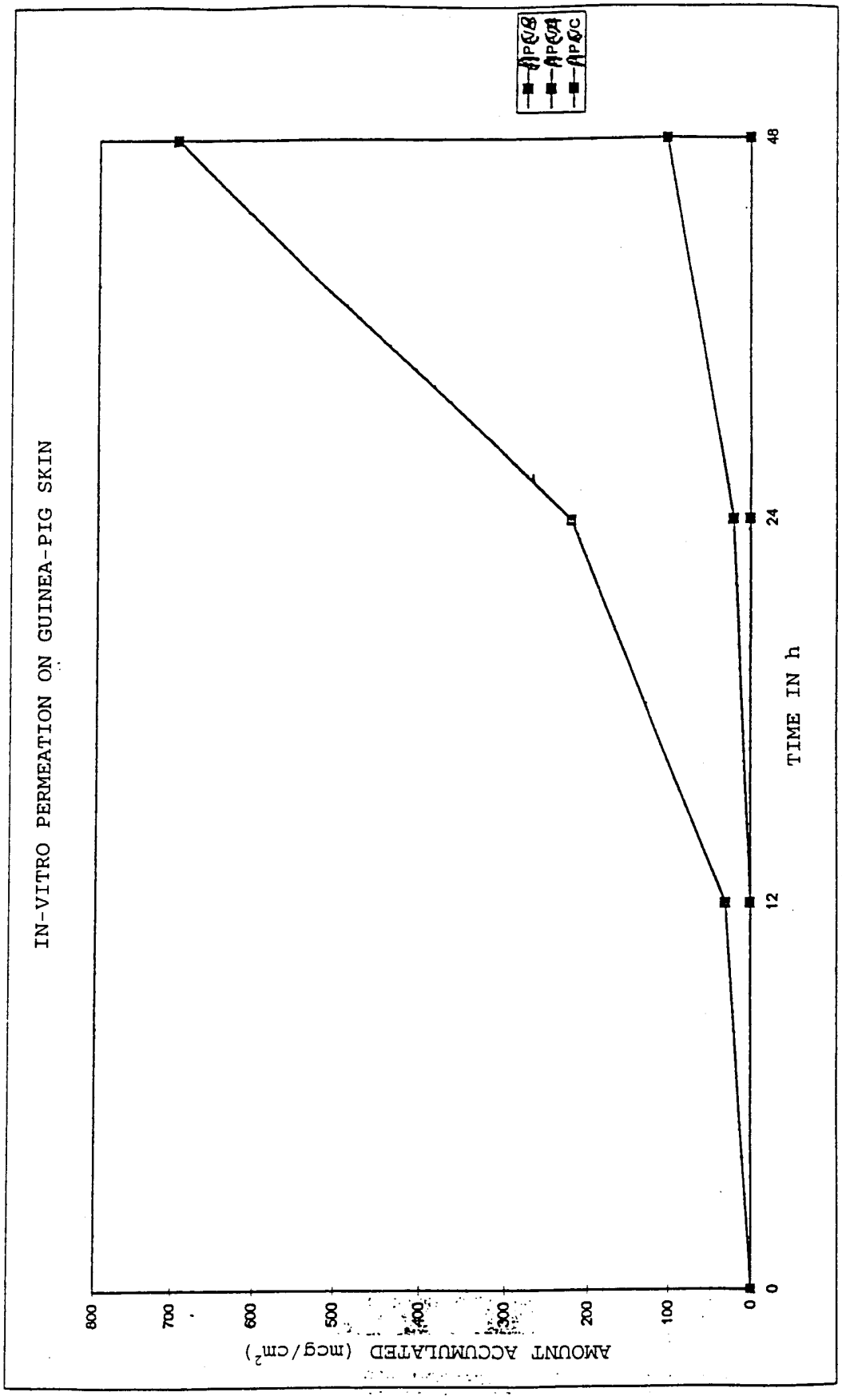
- the interactions which may exist between the active principle, the adhesive (different types of adhesive can be used at the same time), the support material and other materials, such as excipients, stabilizers, etc.
- the improved stability on the preselected site of application
- the dosage (greater surface area = greater dosage)

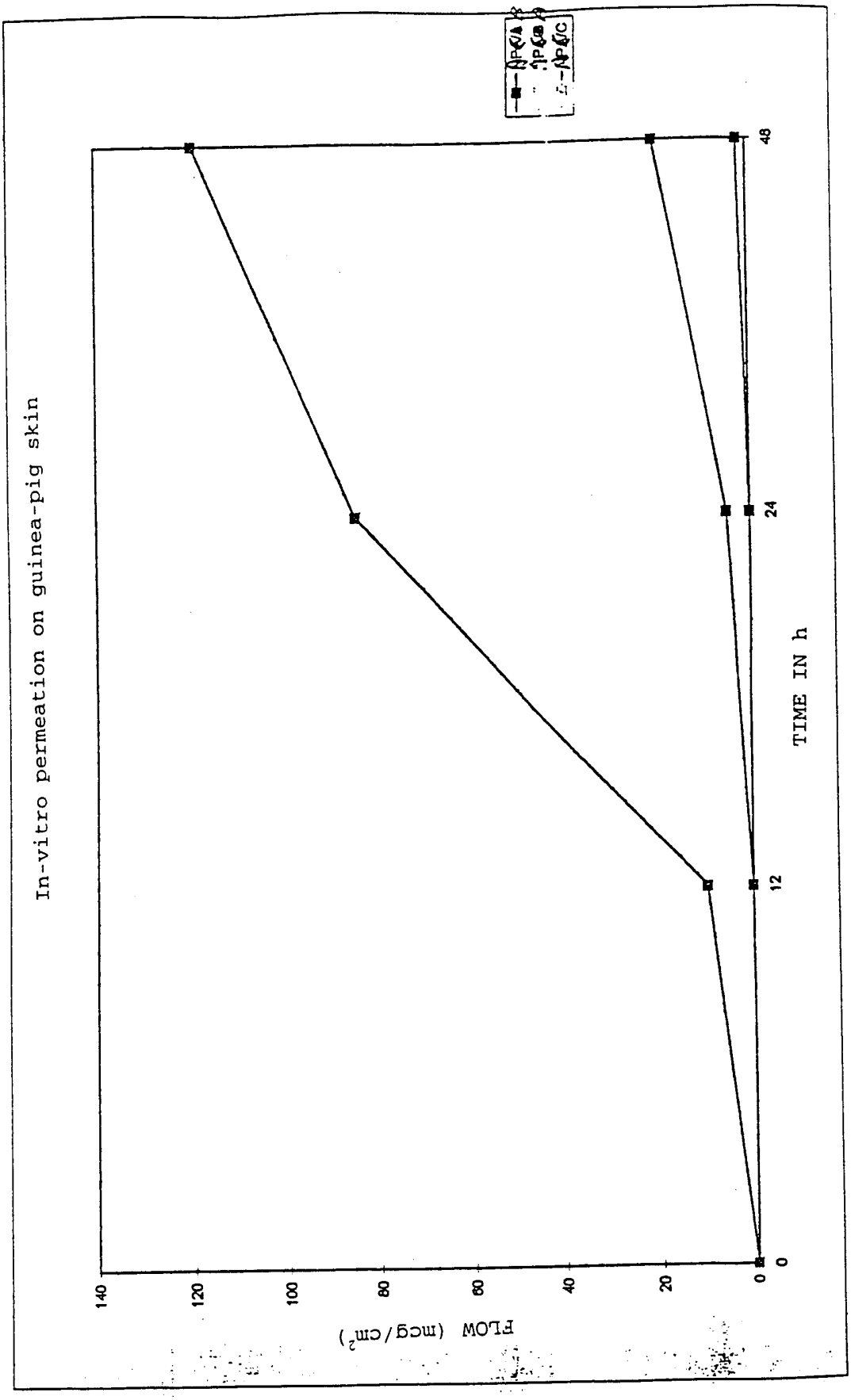
In the present invention, in consideration of the physicochemical properties of APC and/or its derivatives, the preferred patch is the type III patch, and more preferably the type III patch with acrylic adhesives, in rectangular shape when it is desired to

achieve constantly high doses for long periods, or in anatomical shape when a targeted rapid result is desired (e.g. treatment of sexual impotency).

The present invention will now be illustrated by means of its illustrative, non-limiting examples, in which reference will be made to the following figures, using analytical results obtained with a 40 cm^2 standard rectangular type III patch.

- Fig. 1 is a graph of the accumulation of APC over time.
- Fig. 2 is a graph of the flow of APC over time;
- Fig. 3 is the approximate curve representing the levels in human plasma at the times indicated, relative to the APC active principles.


IN-VITRO PERMEATION ON GUINEA-PIG SKIN
AMOUNT ACCUMULATED (mcg/cm²)
TIME IN h
0
100
200
300
400
500
600
700
800
0
12
24
48
APGB
APGA
APGC


In-vitro permeation on guinea-pig skin
FLOW (mcg/cm²)
140
120
100
80
60
40
20
0
0
12
24
48
TIME IN h

Method for manufacturing the type III transdermal patch

1. The active principle APC or a derivative thereof is incorporated simultaneously with the other components (stabilizer, permeation activators, etc.) into the hot adhesive solution and is homogenized by stirring until the liquid adhesive matrix or reservoir is formed;

2. the liquid adhesive matrix is cooled and acquires a "thready" consistency,

3. the process of lamination of the adhesive matrix on the support is carried out using a laminating machine linked continuously to a drying machine, according to the following phases:

A. the blade of a knife is mounted across the entire width of the conveyor belt of the laminating machine on which the release strip is solidly positioned;

B. the "thready" adhesive matrix is poured in front of the blade which, as the conveyor belt advances, distributes a uniform layer (lamination) of adhesive matrix over the release strip;

C. the thickness of the layer is determined mainly by the distance between the edge of the knife blade and the release strip passing underneath it;

D. the release strip, loaded with the adhesive matrix, rotates inside the drying machine, in which the adhesive matrix is solidified by evaporation of the solvent, obtained by gradually increasing the

"ventilation" temperature as reported in scheme I below.

Scheme I

Drying phase	Time (in minutes)	T°C	Vent. (rpm)
1	15	40°	700
2	20	55°	1000
3	25	70°	1200

The process described allows the removal of the solvent, thus avoiding its occlusion by the rapid formation of a surface crust.

4. Once the adhesive matrix has dried, the support film (backing) is affixed.

This phase, known as "lamination" concludes the process.

The process is described in the literature (9B,10B,11B) and produces a TDDS patch in which the adhesive matrix is protected, on the one hand, by the "backing" and, on the other hand, by the removable release strip.

It is very important to use an adhesive which is inert and permeable with respect to APC and its derivatives, whose adhesive properties (cohesion, adhesion and interlacing) are not adversely affected by this active principle and/or by excipients, or by any other material added.

Composition of the type III TDDS patch

Adhesive matrix: formulation

- active principle: APC or its derivatives;
- antioxidant: sodium metadisulphite, EDTA disodium salt;
- solubilizing agent: a glycol;
- permeation activator: fatty acids;
- acrylic resin to improve the cohesive force: cationic copolymers based on dimethylaminoethyl methacrylate and methacrylic esters
- cellulose derivatives to improve the ethylcellulose force;
- surfactant: SDS (sodium dodecyl sulphate);
- pressure-contact adhesive: mixture of two adhesives, A and B, in which A is an acrylic contact adhesive of average molecular weight which is not self-bonding, with a high interlacing index, a dermal irritation index of 0.20, classified as "minimally irritant" and containing 100% ethyl acetate as solvent; and B is an acrylic adhesive of high molecular weight, which is self-bonding, with a moderate interlacing index, a dermal irritation index of 0, classified as "non-irritant" and containing a mixture of ethyl acetate, isopropanol, hexane and toluene as solvent.

Release strip

The release strip is a polyester film laminated with silicone on one side (the side facing the adhesive matrix). The thickness is approximately 125 µm.

Backing

The backing is a laminated, clear, occlusive polyester film with a heat-welding layer. The total thickness is approximately 51 µm.

Amount of active principle

The amount of APC or its derivatives, referred to as APC, is 5% by weight of the adhesive matrix and corresponds to 5 mg/cm^2 in the TDDS patch. Most of the drug is dispersed in the matrix and acts as a reservoir, while the drug which is available for release and permeation is the dissolved drug.

Application efficacy of the transdermal patch based on APC and/or its derivatives

Various batches of patches of different formulation containing APC and/or its derivatives were prepared for this purpose.

Using the technique of in-vitro cell permeation, recommended by the US FDA (1B, 2B,3B), the following results were obtained, for example, with three different formulations given below, in which the pharmacologically active molecule was used as APC active principle:

APC/A batch, with addition of permeation inducers:

1) APC	2.00%
2) Sodium metabisulphite	0.20%
3) Solubilizing agent	4.00%
4) Acrylic resin	29.00%
5) Fatty acid 1	3.20%
6) Fatty acid 2	1.60%
7) Pressure-sensitive adhesive	60.0%

APC/B batch with addition of permeation inducers, 4.5% active principle dispersed in the matrix (reservoir), 0.5% active principle dissolved in the matrix.

1) APC/B	4.99%
2) Sodium metabisulphite	0.50%
3) EDTA	0.025%
4) Solubilizing agent	9.96%
5) Fatty acid 1	7.96%
6) Fatty acid 2	3.97%
7) Acrylic resin	1.99%
8) Cellulose derivative	0.25%
9) Surfactant	19.90%
10) Pressure-sensitive adhesive	50.455%

APC/C batch, with addition of permeation inducers, 0.5% active principle in the matrix (all of the drug is dissolved):

1) APC/C	0.50%
2) Sodium metabisulphite	0.50%
3) EDTA	0.025%
4) Solubilizing agent	9.96%
5) Fatty acid 1	7.96%
6) Fatty acid 2	3.97%
7) Acrylic resin	1.99%
8) Cellulose derivative	0.25%
9) Surfactant	19.90%
10) Pressure-sensitive adhesive	50.945%

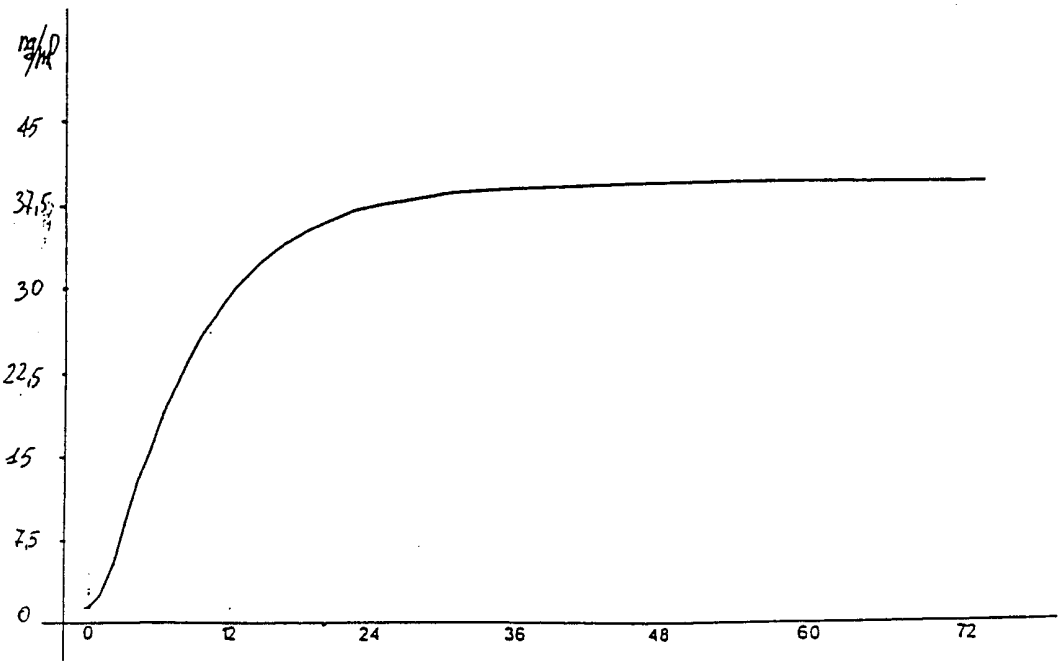
Experimental results

The study of in-vitro permeation with guinea-pig skin, carried out in accordance with the procedures mentioned, gave a permeation rate equal to the values reported in Fig. 1 (total amount) and in Fig. 2 (flow) at the various times.

The in-vitro permeation data reported above were analysed by means of one of the most adequate pharmacokinetic models for the transdermal administration of drugs (10B,11B), obtained with a 40 cm^2 (5×8 cm) patch and the following constants:

molecular weight	331.8
water/alcohol coefficient of distribution:	0.05
half-life	45'
distribution volume	132 litres

The approximate curve representing the levels in human plasma at the times indicated, in the case of application of a single NPA/B batch patch, is illustrated in Fig. 3.



It may be concluded that the skin permeability of APC is sufficient per se and can be increased or decreased by means of various permeation activators such as fatty acids or alcohols.

All of the in-vitro permeation studies were carried out on models using guinea-pig skin, which we know has comparable permeability to that of human skin

and which gives more reproducible results than the latter.

The chemical stability of APC in the formulation of the patch is achieved by adding an antioxidant (sodium metabisulphite) and is demonstrated by means of a 15-day accelerated stability test at 40°C and 75% RH (relative humidity).

The surfactant (SDS) is added to dissolve most of the APC, since only the dissolved APC is available for release and permeation.

The patches also demonstrated good physico-chemical properties, which can be optimized by those skilled in the art for the purposes of adhesion at the site of application and tolerability by the individual undergoing the treatment, without modifying the rate of permeation of the active principle.

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Chewable/sublingual tablets

Description in support of a patent application entitled:

Pharmaceutical compositions (transdermal patches, chewable/sublingual tablets, sprays) comprising apocodeine and/or its derivatives for the treatment of male impotence and for the stimulation of male and female libido.

In the abovementioned therapeutic indications, APC is a powerful drug which can be administered orally.

The active principle (APC) is rapidly absorbed, becomes effective rapidly (latency time 8'-18') and is equally rapidly eliminated (half-life 30').

Thus, in order to ensure that the patient has the required pharmacological cover with effective, sufficient levels in the blood, it will be necessary to make the individual take the drug orally in the form of a chewable/sublingual tablet at a dosage of 150 mg/tablet.

Product: 150 mg APC tablet

Description: yellow tablets, 2-3 mm thick and 8 mm in diameter

Composition:	active principle APC	150 mg
Excipients:	corn starch	8 mg
	tribasic citrate	43 mg
	magnesium stearate	2 mg

total 200 mg

Manufacturing process:

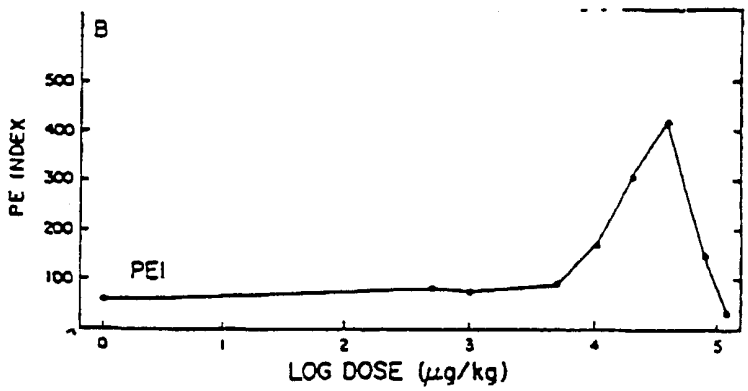
dry mixing, precompression and compression with a rotating tabletting machine

Primary packaging: blisters

in vivo experimental study:

When APC is administered via the intragastric route at doses 100 times greater than those via the i.p. route, there is an increase in P.E., without any stereotypicity being detected.

Graph



(B) the dose/effect ratio for induction of the penile erection (PE) activity by means of oral apocodeine (APC) in rats.

The rats received apocodeine solution or saline solution. The animals were counted in accordance with a double-blind experimental plan. The penile erections

were recorded continuously. The penile erection index (PEI) was obtained by multiplying the percentage of rats affected by the average number of penile erections per rat.

Table 2. penile erection (PE) induced by oral apocodeine (APC) in rats

APC $mg.kg^{-1}$	% rats affected PE	PE per rat	PEI
Saline	40(35)	1.5 ± 0.1	60
0.5	70(10)	1.2 ± 0.1	84
1	50(10)	1.6 ± 0.3	80
5	60(5)	1.6 ± 0.3	96
10	80(5)	2.2 ± 0.4	176
20	100(10)	3.1 ± 0.4 AS	310
40	100(5)	4.2 ± 0.8 AS	420
80	60(5)	2.6 ± 0.8S	156
120	20(5)	1 ± 1	40

The number of animals is given in parentheses

The effective dose is between 10 and 40 mg/kg, the optimum being 20 mg/kg.

Assuming that the theoretical human dosage level is 1/10 of the dosage level for rats,

the dosage we are proposing will be:

$$\left(\frac{20}{10} \times 70\right) \text{ about } 140 \text{ mg/ dose} = 150 \text{ mg/tablet}$$

SPRAY

In support of a patent application entitled:

Pharmaceutical compositions (transdermal patches, chewable/sublingual tablets, sprays) comprising apocodeine and/or its derivatives for the treatment of male impotence and for the stimulation of male and female libido.

In the abovementioned therapeutic indications, APC is a powerful drug which can be administered orally in the form of a spray.

The active principle (APC) is rapidly absorbed, becomes effective rapidly (latency time 8'-18') and is equally rapidly eliminated (half-life 30').

Thus, in order to ensure that the patient has the required pharmacological cover with effective, sufficient levels in the blood, it will be necessary to make the individual take the drug orally in the form of a spray at a dosage level of 150 mg/dose.

Product: APC single-dose spray

Description:

single-dose bottle with distribution cap (deliverable volume 1 ml).

% composition

A.P.:	APC and/or its derivatives	15%
	Menthol	0.84%
	Thymol	0.40%
	Tannic acid	1.68%

Alcohol	45.00%
Purified water	37.08%
total	100

The abovementioned formulation is given by way of non-limiting illustration.

Manufacturing process:

The suspension is prepared at the time of use and is distributed under aseptic conditions into the containers of the distributing machine which automatically closes the bottles by clamping the metering tap onto the neck of the container.

Claims

1. Pharmaceutical composition comprising APC and/or its derivatives in pharmaceutically acceptable and effective doses.

2. Pharmaceutical composition according to Claim 1, in which the said APC derivatives are organic derivatives or salts.

3. Pharmaceutical composition according to Claim 1, in which the said salt is its hydrochloride salt.

4. Transdermal patch comprising APC and/or its derivatives as active principle.

5. Transdermal patch according to Claim 4, in which the APC derivatives are organic derivatives or salts.

6. Transdermal patch according to Claim 5, in which the said salt is its hydrochloride salt.

7. Use of APC and/or its derivatives for the preparation of a transdermal patch for the treatment of male impotence and for the stimulation of male and female libido.

8. Chewable/sublingual tablets comprising APC and/or its derivatives as active principle.

9. Chewable/sublingual tablets according to Claim 8, in which the APC derivatives are organic derivatives or salts.

10. Chewable tablets according to Claim 9, in which the said salt is its hydrochloride salt.

11. Use of APC and/or its derivatives for the preparation of a tablet for the treatment of male impotence and for the stimulation of male and female libido.

12. Spray comprising APC and/or its derivatives as active principle.

13. Spray according to Claim 12, in which the APC derivatives are organic derivatives or salts.

14. Spray according to Claim 13, in which the said salt is its hydrochloride.

15. Use of APC and/or its derivatives for the preparation of a spray for the treatment of male impotence and for the stimulation of male and female libido.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/IE 00/00065

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/70 A61K9/12 A61P15/10 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SMITH, ROBERT V. ET AL: "Conversion of apocodeine to apomorphine and norapomorphine in rats" J. PHARM. SCI. (1974), 63(1), 161-2 , XP002150206 the whole document ---	1-3
X	BARALDI, M. ET AL: "Apocodeine -induced stereotypies and penile erection in rats" NEUROPHARMACOLOGY (1979), 18(2), 165-9 , XP000952177 page 165 -page 166 ---	1-3
X	US 4 806 341 A (CHIEN YIE W ET AL) 21 February 1989 (1989-02-21) claim 24 --- -/--	1,2,4,5, 7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2000	03/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/IE 00/00065

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 257 887 A (HOUSTON BIOTECHNOLOGY) 2 March 1988 (1988-03-02) claim 12 ---	1,2,12, 13
X	WO 97 33566 A (ALZA CORP) 18 September 1997 (1997-09-18) claim 10 -----	1,2,8,9, 11

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3

   Pharmaceutical composition comprising apocodeine

2. Claims: 4-7

   Transdermal patch comprising apocodeine

3. Claims: 8-11

   Chewable/sublingual tablet comprising apocodeine

4. Claims: 12-15

   Spray composition comprising apocodeine

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,4,5,7,8,9,11,12,13, and 15

Present claims 1,2,4,5,7,8,9,11,12,13, and 15 relate to compounds defined by the expression "APC and/or its derivatives" or "organic derivatives" which, except for APC and its salts, are not defined in the present application and are unclear. It is indeed impossible to know what kind of compound can ba a "derivative" or an "organic derivative" of APC. Consequently, a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear , namely the compound APC (apocodeine) and its salts.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interr nal Application No
PCT/IE 00/00065

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