(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 015 635**
A1

EXHIBIT 65

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **80300094.2**

(22) Date of filing: **10.01.80**

(51) Int. Cl.³: **A 61 K 9/16**

(30) Priority: **09.03.79 US 19810**

(43) Date of publication of application: **17.09.80 Bulletin 80/19**

(84) Designated Contracting States: **DE GB NL SE**

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(54) **Nabilone granulation and process for preparing same.**

(57) A process is described for the preparation of a formulation comprising nabilone for oral administration to mammals which comprise dissolving nabilone and polyvinylpyrrolidone or polyethylene glycol in anhydrous ethanol and using the thus-formed viscous solution to granulate a pharmaceutically-acceptable ethanol-insoluble excipient by thoroughly mixing the solution with the excipient, and then drying the thus-formed granulation.

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TITLE MODIFIED
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0015635

NABILONE GRANULATION

This invention relates to a process for formulating a pharmaceutical ingredient and to the products of the process.

Nabilone[trans-dl-1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydrobenzo[b,d]pyran-9-one] is encompassed within a group of useful intermediates prepared by Farenholtz, et al., J. Am. Chem. Soc., 88, 2079 (1966), 89, 5934 (1967) for the preparation of Δ^9-THC (tetrahydrocannibinol) and its alkylated congeners having alkyl groups of from 1 to 10 carbon atoms at C-3. (Δ^9-THC is trans-dl-1-hydroxy-3-n-pentyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydrobenzo-[b,d]pyran). Archer, U.S. Patents No. 3,928,598, 3,953,603, 3,9446,673, and 3,987,188 disclosed that nabilone, in addition to being a "useful intermediary", had activity as an anti-depressant, anti-anxiety, analgesic and/or sedative drug, and Archer and Lemberger further extended its useful actions to that of anti-emetic and for the treatment of glaucoma, U.S. Patents No. 4,087,545 and 4,087,547. Nabilone is not well absorbed from the intestine upon oral administration. Thakker, et al., J. Pharm. Pharmac., 29, 783 (1977) describe some useful formulations for nabilone including a dispersion in polyvinylpyrrolidinone. Thakker, et al. mix nabilone with PVP in a ratio of 1:2-20 in a solvent such as ethanol and then remove the solvent by evaporation in vacuo. The product thus obtained is a glassy solid which must first be broken up and then reduced to a fine powder in order to disperse

it uniformly in other pharmaceutical excipients prior to filling into telescoping gelatin capsules.

An object of the invention is to provide a process for preparing a granulation formulation for nabilone which avoids the inconvenience and difficulties of the aforesaid Thakker et al solid dispersion.

Thus the invention comprises a process for formulating nabilone for oral administration to mammals which comprises dissolving nabilone and polyvinylpyrrolidone or polyethylene glycol in anhydrous ethanol and using the thus-formed viscous solution to granulate a pharmaceutically-acceptable ethanol-insoluble excipient by thoroughly mixing the solution with the excipient, and then drying the thus-formed granulation.

The granulating solution is used to granulate pharmaceutical excipients and carriers such as starch, lactose, cellulose and the like. After drying and grinding, the powdered granular material is suitable for blending with other materials to make a formulation suitable for filling into telescoping gelatin capsules as provided. In other words, the nabilone-PVP dispersion of Thakker et al. (loc. cit.) is formed in situ as a granulation for excipients which are insoluble in ethanol. The ratio of nabilone to PVP is preferably one part of nabilone to 2 to 20 parts of PVP.

A granulation thus prepared is shown to have excellent stability as regards nabilone, and dissolution data has shown that the granulation is equivalent to the Thakker et al. dispersion prepared as a glass in the rotary evaporator and then powdered. Equivalent bioavailability has been demonstrated in dogs for the granulation of this invention as compared with the Thakker et al. dispersion.

Other nabilone dispersions prepared by Thakker, et al., including one in polyethylene glycol,

can be prepared similarly in situ on the particular excipient using our novel process as described for the nabilone-PVP dispersion above and preferably at a ratio of one part of nabilone to 2 to 20 parts of polyethylene glycol, solution in ethanol being followed by granulation of an ethanol-insoluble excipient.

This invention is further illustrated by the following specific example.

Example 1

Five grams of nabilone were dissolved in 125 ml. of anhydrous ethanol .45 g. of polyvinylpyrrolidone (PVP) were dissolved therein. The resulting viscous solution was added to 450 g. of starch flowable powder in a Hobart mixer. A small amount of additional anhydrous ethanol was used to rinse the nabilone-PVP solution into the mixer. After thorough mixing, the granulation was wet screened through a no. 4 screen (a no. 6 screen can also be used). The screened granulation was air dried and then ground to the desired size in a ball mill.

A nabilone-PVP-starch granulation so prepared can be further blended with other excipients to give a final mixture having the desired nabilone concentration for loading into empty telescoping gelatin capsules.

Other ethanol insoluble excipients such as lactose, mannitol and dextrose can be used in place of flowable starch in preparing the above granulation.

CLAIMS

1. A process which formulates nabilone for oral administration to mammals which comprises dissolving nabilone and polyvinylpyrrolidone or polyethylene glycol in anhydrous ethanol and using the thus-formed viscous solution to granulate a pharmaceutically-acceptable ethanol-insoluble excipient by thoroughly mixing the solution with the excipient, and then drying the thus-formed granulation.

2. A process of claim 1 which comprises dissolving polyvinylpyrrolidone and nabilone in ethanol to form the granulating solution.

3. A process according to claim 2 in which the ratio of nabilone to polyvinylpyrrolidone is one part of nabilone to 2 to 20 parts of polyvinylpyrrolidone.

4. A process which formulates nabilone substantially as herein before described with particular reference to Example 1.

5. A formulation prepared by a process according to any of claims 1 to 4.

6. A formulation according to claim 5 for use as a pharmaceutical.

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EUROPEAN SEARCH REPORT

0015635
Application number
EP 80 30 0094

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	FR - A - 2 249 666 (THAKKAR) * Page 2, lines 4-35; page 3, line 15 - page 5, line 4; claims 1-5 * & GB - A - 1 487 638 --	1-6
	GB - A - 1 487 635 (THAKKAR) * Page 1, line 76 - page 2, line 13; page 2, lines 26-50 * --	1-6
D	J. PHARM. PHARMAC., no. 29, 17th August 1977, pages 783-784 London, G.B. A. THAKKAR: "Solid dispersion approach for overcoming bioavailability problems due to polymorphism of Mabilane...." * Whole document * --	1-6
	FR - A - 2 106 553 (SANDOZ) * Page 3, line 24 - page 4, line 15; examples 1-3; claims 1,5-12 * --	1-6
	AT - B - 329 556 (ELI-LILLY) * Page 2, lines 23-41 * --	1-6
D,A	US - A - 3 953 603 (ARCHER) * Column 2, line 50 - column 3, line 20; column 3, lines 55-56 * -- ./.	

CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)

A 61 K 9/16

TECHNICAL FIELDS SEARCHED (Int.Cl. 3)

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CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18-06-1980	GERMINARIO

EPO Form 1503.1 06.78

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D,A	US - A - 3 944 673 (ARCHER) * Column 2, line 51 - column 3, line 21; column 3, lines 57-58 *		
A	US - A - 3 864 492 (FAGER-WIDELBURG) * Column 1, lines 15-52; column 6, line 19 - column 7, line 9 *		TECHNICAL FIELDS SEARCHED (Int. Cl. 3)

ACTUAL PATENT URL LINK:
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PATENT CURRENT ASSIGNEE URL LINK:
https://patents.google.com/patent/EP0015635A1/en?oq=EP:+0015635A1

Abstract

A process is described .for the preparation of a formulation comprising nabilone for oral administration to mammals which comprise dissolving nabilone and polyvinylpyrrolidone or polyethylene glycol in anhydrous ethanol and using the thus-formed viscous solution to granulate a pharmaceutically-acceptable ethanol-insoluble excipient by thoroughly mixing the solution with the excipient, and then drying the thus-formed granulation.

Classifications

A61K9/1652 Polysaccharides, e.g. alginate, cellulose derivatives; Cyclodextrin

View 3 more classifications

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Other languages: German, French

Inventor: James William Conine

Current Assignee : Eli Lilly and Co

Worldwide applications

1979 · ~~US~~ 1980 · *NZ ZA* ~~CA DK CH FR BE IL~~ IT ~~JP GB EP IE~~ *LU* ~~AU~~

Application EP80300094A events

1979-03-09 • Priority to US06/019,810

1980-01-10 • Application filed by Eli Lilly and Co

1980-09-17 • Publication of EP0015635A1

1987-02-27 • Priority to US19810