PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 9/02, A61J 3/08	A1	WO 92/22283
		(43) International Publication Date: 23 December 1992 (23.12.92)

(21) International Application Number: PCT/DK92/00187

(22) International Filing Date: 16 June 1992 (16.06.92)

(30) Priority data:
1165/91 17 June 1991 (17.06.91) DK

(71) Applicant *(for all designated States except US):* FARMACEUTISK LABORATORIUM FERRING A/S [DK/DK]; Indertoften 5, DK-2720 Vanløse (DK).

(72) Inventor; and
(75) Inventor/Applicant *(for US only) :* HALSKOV, Søren [DK/DK]; Parcelvej 111, DK-2830 Virum (DK).

(74) Agent: HOFMAN-BANG & BOUTARD A/S; Adelgade 15, DK-1304 Copenhagen K (DK).

(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.
With amended claims.
In English translation (filed in Danish).

(54) Title: A PROCESS FOR PRODUCING SUPPOSITORIES BY COMPRESSION AND SUPPOSITORIES OBTAINED BY THE PROCESS

(57) Abstract

Suppositories which may have a considerably higher content of an active drug than ordinary suppositories, are produced by compressing a suppository mass, which contains a considerable amount of a polyethylene glycol having a molecular weight of at least 4000, preferably 6000. The polyethylene glycol constitutes 20-50 % by weight of the suppository mass, which moreover contains microcrystalline cellulose and/or other additives common in the production of drugs. The obtained suppositories are more convenient to store and use, easier to produce and considerably more concentrated with respect to active substance (up to 75 % by weight) than traditional melt-moulded suppositories.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

A process for producing suppositories by compression and suppositories obtained by the process

The present invention concerns a special process for producing suppositories by compression, and the process of the invention is characterized by producing a suppository mixture granulate containing a considerably greater amount of active drug than ordinary suppositories as well as 20-50% by weight of a polyethylene glycol having an average molecular weight of at least 4000, and producing the suppositories in the same manner as tablets, i.e. by compression, instead of by moulding. The invention moreover concerns the suppositories obtained by the process which have a considerably higher percentual content of active drug than ordinary suppositories.

As will be known, suppositories are drugs intended for insertion into the rectum. They contain the active drug in a dosed amount and are produced by pressing, moulding or compression. They can also be produced in the form of capsules for controlled release of the active substance.

Ordinarily suppositories are produced by moulding, the produced mass being melted using the least possible amount of heat, and then the liquid mass is poured into moulds having the desired nominal capacity.

The suppositories produced by moulding are oblong and smooth, and they have a uniform appearance. Melting is intended to provide a uniform distribution of the drug in the basic mass, which, however, can be difficult to obtain because of sedimentation during hardening.

However, traditional moulding is a time-consuming and slow process which involves considerable costs. Moulded suppo-

sitories also have the drawback that too strong heating of certain suppository basic masses result in unstable modifications with a considerably reduced solidification point.

It is well-known to use polyethylene glycols having average molecular weights of 4000-6000 or above as the main component in the basic mass for suppositories produced by traditional melting and moulding. Thus, the DE Offenlegungsschrift 2 248 777 describes melt-moulded indomethacin suppositories whose basic mass contains such polyethylene glycols.

An object of the invention is to provide a process enabling the production of suppositories having a high content of active drug, which are partly more convenient to store and are partly more convenieny to use and easier and cheaper to produce than traditional melt-moulded suppositories.

This is achieved by the process of the invention which is characterized by the subject-matter stated in the characterizing portion of claim 1.

It has previously been attempted to produce suppositories by compression or pressing, i.e. by traditional tabletting methods. However, these suppositories tend to form irregular rough surfaces, which makes them unpleasant to use for the patient. Moreover, in such a production method it has been found impossible to dose the drug in so high doses as is often desirable owing to the prescribed treatment.

Thus, the EP publication 111 137 describes suppositories containing the drug indomethacin in a base consisting of polyethylene glycol having an average molecular weight of

up to 35,000. It is stated that the content of the active drug may be up to 50% by weight, but preferably the content is 2-40% by weight and in particular 2-26% by weight. All the examples in the publication concern rectal tablets having a content of indomethacin of 2.8 - 5.8% by weight and rectal capsules having a content of indomethacin of 5.25 - 10.5% by weight, i.e. rather low concentrations. Further, the suppositories thus known contain quite high amounts of polyethylene glycols, typically 1600-1730 mg per unit, which is a drawback, because it has been found that a content of polyethylene glycols in suppositories of 1 - 1.5 g per unit may cause bowel disorders.

It has now surprisingly been found that a composition which can easily be compressed to suppositories by an ordinary tabletting method can be obtained by using a suitable amount, more particularly 20-50% by weight of a polyethylene glycol having an average molecular weight of at least 4000 in the suppository basic mass. The use of such a polyethylene glycol in the basic mass results in suppositories having a uniform appearance and having an extremely smooth and regular surface, which is moreover sufficiently slippery for the suppository to be inserted without difficulty. It is moreover possible in such suppositories to incorporate up to 75% by weight of active drug, which is far above normal.

Polyethylene glycols, more particularly mixtures of condensation polymers of ethylene oxide and water, are also called "macrogols". Macrogols having average molecular weights of 200-700 are liquids, while macrogols having average molecular weights above 1000 vary in consistence from soft oily substances to hard wax-like solid substances. The average molecular weight is stated as a number after the name. "Macrogol 6000", which it is preferred to use according to the invention, thus has an ave-

rage molecular weight of about 6000.

The macrogols have the general formula

$$H(CH_2OCH_2)_nOH$$

where n is greater than or equal to 4. In "Macrogol 6000" n has an average value of between 158 and 204. It is a white or cream-coloured solid wax-like substance which is in the form of a powder or flakes. The melting point is 56-63°C, i.e. considerably above the body temperature. Mixtures of various polyethylene glycols having melting points above the body temperature have frequently been used as a base in suppositories from which the drug is released by dissolution.

Since the melting points of the macrogols increase with increasing average molecular weight, macrogols having high average molecular weights, such as "Macrogol 6000", have not previously been a natural choice as a suppository base material.

Mixing a granulate of the drug with "Macrogol 6000" and compressing the mixture to suppositories by a method which is known per se for the production of tablets for oral administration provide the following advantages:

1) The suppositories do not melt under normal temperature conditions, but only at about 60°C.

2) The suppositories are cheaper to produce.

3) The drug can be incorporated in very high concentrations and is considerably easier to dose uniformly.

4) The product is more convenient and more pleasant to use for the patient.

5) Avoidance of drug decomposition during the heating which is necessary in traditional moulding of suppositories.

6) It is easier to obtain and maintain a homogeneous mixture, and the risk of sedimentation is eliminated.

All active drugs which lend themselves for rectal administration may be incorporated in the suppositories produced according to the invention. One of the interesting drugs in this respect is 5-aminosalicylic acid (5-ASA), which is used particularly for the treatment of colitis ulcerosa and Crohn's disease, but which has moreover been found to be of interest for the production of suppositories for treatment of hemorrhoids. Suppositories containing 5-aminosalicylic acid are known e.g. from the EP patent application 83 775, these suppositories being produced by moulding and containing max. 500 mg of 5-aminosalicylic acid per dose unit. The suppositories of the invention may contain considerably larger amounts of 5-ASA, which is absolutely an advantage for the patient.

An example of the many active drugs which may be used is steroids for various applications.

In addition to a polyethylene glycol or a mixture of polyethylene glycols having an average molecular weight of at least 4000, preferably "Macrogol 6000", in an amount of 20-50% by weight, the suppositories produced according to the invention contain microcrystalline cellulose and/or other additives common in the production of drugs. These additives and the active drug together amount to 45-75% based on the gross weight of the suppositories. Finally,

the suppositories contain one or more of the substances talc, magnesium stearate and polyvinyl pyrrolidone in an amount of 2-5% by weight.

The suppositories are typically compressed to symmetrical units having an approximately elliptic longitudinal section, i.e. the two ends are uniform (in contrast to the ordinary "torpedo-shape" where one end is pointed while the other is blunt).

The following example illustrates the invention:

EXAMPLE

A suppository basic mass for the production of 1000 suppositories consists of the following ingredients:

"Macrogol 6000"	572 g
Microcrystalline cellulose and active drug	1000 g
Magnesium stearate	4 g
Talc	4 g
Polyvinyl pyrrolidone + ethanol (1:19)	q.s.

A granulate is made from the microcrystalline cellulose, the active drug, e.g. 5-aminosalicylic acid (5-ASA) and the mixture of polyvinyl pyrrolidone and ethanol.

The resulting granulate is mixed with "Macrogol 6000", and then magnesium stearate and talc are added.

The granulate can then be compressed to suppositories in a tabletting machine in a manner known per se.

Patent Claims:

1. A process for producing suppositories by compression, characterized by producing a suppository mixture granulate containing a considerably larger amount of active drug than ordinary suppositories as well as 20-50% by weight of a polyethylene glycol having an average molecular weight of at least 4000, and then compressing the produced mass to suppositories by a method known per se for the production of tablets.

2. A process according to claim 1, characterized by producing a suppository mass having the following composition:

polyethylene glycol:	20-50%
active drug as well as microcrystalline cellulose and/or other additives common in the production of drugs:	45-75%, preferably at least 50%
talc, magnesium stearate and/or polyvinyl pyrrolidone:	2-5%

the stated percentages being percentages by weight.

3. A process according to claim 1 or 2, characterized in that the polyethylene glycol used has an average molecular weight of 6000.

4. A process according to any of the preceding claims, characterized in that the polyethylene glycol used is selected from "Macrogol 4000", "Macrogol 6000" and mixtures thereof.

5. Suppositories, c h a r a c t e r i z e d in that they are produced by a process according to any of claims 1-4.

6. Suppositories according to claim 5, c h a r a c - t e r i z e d in that they have the following composition:

polyethylene glycol having an average molecular weight of at least 4000:	20-50%
active drug as well as microcrystalline cellulose and/or other additives common in the production of drugs:	45-75%, preferably at least 50%
talc, magnesium stearate and/or polyvinyl pyrrolidone:	2-5%

the stated percentages being percentages by weight.

7. Suppositories according to claim 5 or 6, c h a r a c - t e r i z e d in that the polyethylene glycol used is "Macrogol 6000".

8. Suppositories according to any of claims 5-7, c h a - r a c t e r i z e d in that they contain 5-aminosalicylic acid (5-ASA) as an active drug in an amount of up to 75% of the gross weight of the product.

9. Suppositories according to any of claims 5-7, c h a - r a c t e r i z e d in that they contain a steroid as an active drug.

AMENDED CLAIMS

[received by the International Bureau on 23 October 1992 (23.10.92); original claims 1-9 replaced by amended claims 1-8 (2 pages)]

1. A process for producing suppositories by compression, c h a r a c t e r i z e d by producing a suppository mixture granulate containing 50-75% active drug as well as optionally microcrystalline cellulose and/or other additives common in the production of drugs, 2-5% talc, magnesium stearate and/or polyvinyl pyrrolidone as well as 20-50% by weight of a polyethylene glycol having an average molecular weight of at least 4000, and compressing the produced mass to suppositories by a method known per se for the production of tablets.

2. A process according to claim 1, c h a r a c t e r i z e d in that the polyethylene glycol used has an average molecular weight of 6000.

3. A process according to claim 1 or 2, c h a r a c t e r i z e d in that the polyethylene glycol used is selected from "Macrogol 4000", "Macrogol 6000" and mixtures thereof.

4. Suppositories, c h a r a c t e r i z e d in that they are produced by a process according to any of claims 1-3.

5. Suppositories according to claim 4, c h a r a c t e r i z e d in that they have the following composition:

polyethylene glycol having an average molecular weight of at least 4000:	20-50%
active drug as well as microcrystalline cellulose and/or other	

additives common in the production of drugs:	50-75%
talc, magnesium stearate and/or polyvinyl pyrrolidone:	2-5%

the stated percentages being percentages by weight.

6. Suppositories according to claim 4 or 5, c h a r a c t e r i z e d in that the polyethylene glycol used is "Macrogol 6000".

7. Suppositories according to any of claims 4-6, c h a r a c t e r i z e d in that they contain 5-aminosalicylic acid (5-ASA) as an active drug in an amount of up to 75% of the gross weight of the product.

8. Suppositories according to any of claims 4-6, c h a r a c t e r i z e d in that they contain a steroid as an active drug.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 92/00187

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[8]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 9/02, A 61 J 3/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; A 61 J

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	DE, A, 2248777 (MERCK & CO. INC.) 19 April 1973, see the whole document --	1-9
X	EP, A2, 0111137 (TROPONWERKE GMBH & CO. KG) 20 June 1984, see the whole document --	1-9
	---	

* Special categories of cited documents:[10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21st September 1992	22 -09- 1992
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Anneli Jönsson

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 92/00187

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 28/08/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-A- 2248777	73-04-19	AT-B-	336188	77-04-25
		AU-B-	472229	76-05-20
		AU-D-	4708472	74-04-04
		BE-A-	789726	73-04-05
		CA-A-	985625	76-03-16
		FR-A-B-	2158209	73-06-15
		GB-A-	1384760	75-02-19
		NL-A-	7212626	73-04-10
		SE-B-C-	384134	76-04-26
		US-A-	3849549	74-11-19
EP-A2- 0111137	84-06-20	DE-A-	3241263	84-05-10
		JP-A-	59101420	84-06-12