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(71) Applicant(s)
LTS Lohmann Therapie-Systeme AG

(72) Inventor(s)
Hans-Werner Wolf; Thomas Hille

(74) Agent/Attorney
HODGKINSON OLD McINNES,Level 3, 20 Alfred Street,MILSONS POINT NSW 2061

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(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: LTS LOHMANN THERAPIE-SYSTEME ~~GMBH~~ AG [DE/DE]; ~~Irlicher Strasse 55, D-56567 Neuwied~~ Lohmannstrasse 2 D-56626 Andernach (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder *(nur für US)*: WOLF, Hans-Werner [DE/DE]; Im Höstert 6, D-56567 Neuwied (DE). HILLE, Thomas [DE/DE]; Am Moogsberg 2A, D-56568 Neuwied (DE).

(74) Anwalt: FLACCUS, Rolf-Dieter; Bussardweg 10, D-50389 Wesseling (DE).

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(54) Title: METHOD FOR RECOVERING MEDICAMENTS FROM PREPARATIONS, AND FROM THE PRECURSORS OR WASTES THEREOF

(54) Bezeichnung: VERFAHREN ZUR RÜCKGEWINNUNG VON ARZNEISTOFFEN AUS ZUBEREITUNGEN, DEREN VORPRODUKTEN ODER ABFÄLLEN

(57) Abstract

The invention relates to a method for recovering medicaments or active ingredients from preparations, and from the precursors or wastes thereof, especially in the form of a flat starting material. The invention uses film provided with an adhesive, and a material containing an active ingredient. The starting material is produced with surface areas preferably ranging between 5 and 50 cm^2. The starting material comprising a basic active ingredient is introduced into an aqueous extraction liquid having a pH range between 7 and 1, and the starting material comprising an acidic active ingredient is introduced into an aqueous extraction liquid having a pH range between 7 and 13. The extraction liquid is permitted to act until the supporting film detaches from the laminate or until the active ingredient detaches from the supporting film during which a solution containing active ingredients is formed. The extracted medicament or active ingredient is isolated by precipitating it out of the solution containing active ingredients.

(57) Zusammenfassung

Bei einem Verfahren zur Rückgewinnung von Arznei- oder Wirkstoffen aus Zubereitungen, deren Vorprodukten oder Abfällen, insbesondere in Form von flächigem Ausgangsmaterial, enthaltend abhäsiv ausgerüstete Folie und wirkstoffhaltiges Gut, wird das Ausgangsmaterial in Flächenbereichen vorzugsweise zwischen 5 und 50 cm^2 vorgelegt, Ausgangsmaterial mit basischem Wirkstoff in eine wäßrige Extraktionsflüssigkeit mit einem pH-Bereich zwischen 7 und 1, und Ausgangsmaterial mit saurem Wirkstoff in eine wäßrige Extraktionsflüssigkeit mit einem pH-Bereich zwischen 7 und 13 eingebracht, darin die Extraktionsflüssigkeit bis zum Ablösen der Trägerfolie vom Laminat oder des Wirkstoffs von der Trägerfolie unter Bildung einer wirkstoffhaltigen Lösung einwirken gelassen, und der extrahierte Arznei- oder Wirkstoff durch Fällung aus der wirkstoffhaltigen Lösung isoliert.

ABSTRACT

In a process for recovering medicinal substances or active substances from preparations, their initial products or waste, especially in the form of flat-shaped starting material, containing abhesively equipped film and active substance-containing material, the starting material is provided in area sizes of preferably between 5 and 50 cm^2; starting material with basic active substance is placed into an aqueous extraction liquor with a pH range of between 7 and 1, and starting material with acidic active substance is placed into an aqueous extraction liquor with a pH range of between 7 and 13;
the extraction liquor is then allowed to take effect until the carrier sheet is detached from the laminate or the active substance is detached from the carrier sheet under formation of an active substance-containing solution;
and the extracted medicinal substance or active substance is isolated from the active substance-containing solution by means of precipitation.

Process for the recovery of medicinal substances from preparations, their initial products or waste

The present invention relates to a process for recovering medicinal substances or active substances from preparations, their initial products or waste, especially in the form of flat-shaped starting material, containing abhesively equipped film and active substance-containing material.

The process is especially suited for active substances from unused or discarded devices for the transdermal application of active substances and/or their process waste, whereby the active substances contained in said devices are usually present in combination with polymer films and polymer sheets.

Devices for transdermal application can be subdivided into two categories:

a) systems releasing active substances to the skin or to the organism by passive diffusion, and
b) systems releasing active substances to the skin or to the organism under the action or by the aid of electric currents.

Systems based on passive diffusion are so-called transdermal therapeutic systems (TTS).

These can be further subdivided into so-called matrix systems and reservoir systems.

In matrix systems, the active substance is dissolved in polymer films or partially suspended in crystalline form or in the form of microcapsules. In the simplest case, such systems therefore consist of a backing layer which is impermeable to the active substance, an active substance-

containing and preferably self-adhesive matrix, and a protective sheet to be removed prior to use.

Reservoir systems contain the active substance in a fluid reservoir. The active substance may be present in a completely or only partially dissolved form. In the simplest case, these systems consist of a backing layer impermeable to the substances contained in the reservoir and a membrane at least permeable to the active substance and preferably provided with an adhesive film for application of the system to the skin.

Systems which release the active substance to the skin or the organism under application of electric current can have various structures. They are particularly used for active substances which - owing to their chemo-physical properties - cannot penetrate the skin in a sufficient amount by means of passive diffusion.

A portion of unspent active substance remains in every worn TTS. Such active substance-containing waste products represent a toxicological or ecological risk and must therefore be disposed of as hazardous waste at extremely high expense. On the other hand, these waste products contain expensive and valuable ingredients or active substances originating from medicinal preparations, the recovery of which appears economically sensible. One reason why the economic considerations to be taken into account hereby result in favor of recovering active substances is that the carrier material, which is then substantially free of active substance, is not regarded as hazardous waste and can therefore be disposed of at a low cost.

A number of recycling methods are known from the state of the art, in particular also for recycling waste products containing adhesive-coated sheet material.

DE-OS 42 21 681 describes a method for recycling polyethylene, polypropylene or polystyrene adhesives on label waste products.

DE-OS 40 37 562 describes a recycling of adhesive-coated plastic films by repeated kneading in a solvent, drainage in a screw conveyor, and repeated passage of the remaining material in the same procedure. This publication also teaches a process for recycling plastic sheets coated with adhesive and present in shredded form by separating the plastic material and the adhesive. In a first stage, the sheet shreds are placed in a solvent for the adhesive and agitated under mechanical action for a predetermined period of time in order to disperse the adhesive adhering to the sheet shreds in the solvent. Subsequently, the adhesive dispersed in the solvent is separated from the sheet shreds under mechanical action. In a second, similar stage, fresh solvent is supplied to the sheet shreds of the first stage and the solvent-adhesive dispersion of the second stage is fed to the first stage.

DE-OS 195 24 083 describes a method for recycling TTS in which active substance is dissolved in a solvent and recovered from this solvent. However, the disclosure only states that the methods on which the invention is based are known to the person skilled in the art. In addition, this document suggests that the person skilled in the art submit the TTS to a pretreatment in order to sort out carrier and/or protective sheets, packaging material, etc.

It is the object of the present invention to provide, on this basis, a process with which it is possible to reprocess waste products of medical preparations and in particular of devices - unused or discarded after wearing - for the transdermal application of active substances, so-

called TTS, in a cost-efficient manner in order to recover active substances contained therein.

According to the present invention there is disclosed a process for the recovering of medicinal substances or active substances from preparations, their initial products or waste, especially in the form of flat-shaped starting material, containing adhesively equipped film and active substance-containing material, said method comprising the following process steps in sequence:

- in a first step, separating carrier material and active substance-containing material by avoidance of expensive separation of starting material into pure-grade fractions and without costly size reduction by total leaching of the initial material,
- leaching for 60 to 72 hours while agitating in an extraction liquor that is selected according to whether an acidic or alkaline active substance is being extracted,
- in a further step, separating the carrier material from the active substance-containing solution,
- in a further step, filtering off the active substance-containing solution and further purifying the medicinal substance solution by salification and/or recrystallization,
- in a further step, precipitating the differently solved medicinal substances by differential fractionation, and
- in a last step, filtering off the precipitated medicinal substances.

The above method is environmentally beneficial, feasible with economical means, and enables the isolation of valuable raw active substances on the one hand and of an environmentally neutral and thus easily disposable fraction of residue of solids or carrier materials, substantially freed of active substances, on the other hand.

The carrier materials or residue from the process can be further recycled and disposed of according to known methods.

The process according to the invention avoids expensive process steps such as e.g. processing the materials in a pretreatment through sorting and separation into pure-grade fractions, whereby foreign materials such as carrier and/or protective sheets are sorted out and the active substance-containing material is concentrated. In the present invention, the separation is achieved by means of a complete dissolution of the active substances. An expensive size reduction of the material e.g. in a shredder, which is problematic even after embrittlement due to the pressure-sensitive adhesive characteristics, is not necessary. Rather, the dissolution and thus the prerequisite for the extraction of the active substance takes place in a liquid.

To recover the active substance from the solution, it is advantageously provided that the recovery is carried out by precipitation.

If the active substances are extracted by means of solvents or solvent mixtures, it is advisable to use water with an

acidic pH or an acidified water/alcohol mixture in the case of basic active substances and to set a basic pH value for acidic active substances. Inorganic acids or bases are particularly suitable, and especially aqueous solutions of sulfuric acid or sodium hydroxide solution with a concentration of 1%, because these substances are not volatile. The use of substantially aqueous solutions has the additional advantage that substantially lipophilic auxiliary agents are coextracted to only a small extent.

After filtering off the sheets or films, the active substances are precipitated by means of a pH shift. The thus obtained solution is filtrated and the medicinal substance is purified by means of salification and/or recrystallization.

The process is effective and economically advantageous and it achieves the object stated above in an optimum manner.

In particular the following substances can be recovered by a selection of the processing parameters: active substances with hormonal action, estradiol, estradiol derivatives, gestagens, gestagen derivatives or their mixtures, morphine or morphine derivatives, buprenorphine, physostigmine, scopolamine and galanthamine. The recovered substances can then be reused, according to their pharmaceutical action, as analgesics as well as for the treatment of senile dementia, high blood pressure, arrhythmia, vascular diseases, addictions, hyperlipidaemia, psychological disturbances, to influence blood coagulation, eating disorders, or dysglycemia.

The invention is illustrated with the help of the following examples:

Example 1:
10 m² of laminate, consisting of a siliconized polyester sheet (PET) with a thickness of 100 µm, a self-adhesive matrix containing 80 g of buprenorphine, and a PET sheet with a thickness of 23 µm is cut into strips with a width of 5 cm. These strips are cross-cut at intervals of approximately 50 cm. The resulting rectangles are stirred in sulfuric acid with a concentration of 0.1% for 60 hours. Hereby, the siliconized PET sheet becomes detached. The solution becomes cloudy because the sulfuric acid partly disintegrates the PET sheets and the matrix. After the stirring is completed, filtration is performed through a filter. The solution is brought to a pH of 8 with sodium hydroxide solution. Buprenorphine precipitates and is filtered off.
Yield: 63.2 g of buprenorphine = 79% of theoretical value
Content: >98% (determined by HPLC)

Example 2:
150 buprenorphine-containing TTS from process waste (= 3 g of buprenorphine) were processed as in Example 1. The TTS were extracted from the primary packaging by hand. The protective sheet, however, was not removed. Shredding did not occur.
Yield: 1.44 g of buprenorphine = 48% of theoretical value

Example 3:
0.05 m² of laminate (= 4 g of buprenorphine) according to Example 1 were cut into strips with a length of 5 cm and a width of 0.1 cm by hand. The processing was carried out as in Example 1. The relative yield was not higher than in Example 1. This clearly illustrates that leaving out the

shredding process of the process waste is, surprisingly, of advantage.

Example 4:
1000 estradiol-containing TTS (= 4g of estradiol), unpacked but with protective sheet, are stirred in sodium hydroxide solution with a concentration of 0.1% for 72 hours. The protective sheet was a siliconized PET sheet with a thickness of 100 µm and the backing layer was a transparent PET sheet with a thickness of 15 µm which was partially detached during stirring. After completion of the stirring, the sheet rests were separated through a filter. The filtrate is brought to a pH of 1 with diluted sulfuric acid. Hereby, estradiol and terephthalic acid precipitate. They are separated from one another through absorptive precipitation with acetone.
Yield: 2.23 g of estradiol hemihydrate = 50% of theoretical value

Example 5:
1000 TTS of Example 2 (= 20 g of buprenorphine) and 1000 TTS of Example 4, unpacked but with protective sheet, are stirred in sodium hydroxide solution with a concentration of 0.1% for 72 hours. The sheet rests are separated through a filter. Estradiol (and terephthalic acid) are precipitated at a pH of 1. Buprenorphine is precipitated from the filtrate at a pH of 8 by adding sodium hydroxide solution. While the yield of estradiol corresponds to the value of Example 4, the yield of buprenorphine is 26%, i.e. less than in Example 2.

By means of HPLC analyses it can be shown that no mutual impurities of the two medicinal substances can be observed after recrystallization.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the recovering of medicinal substances or active substances from preparations, their initial products or waste, especially in the form of flat-shaped starting material, containing adhesively equipped film and active substance-containing material, said method comprising the following process steps in sequence:

   - in a first step, separating carrier material and active substance-containing material by avoidance of expensive separation of starting material into pure-grade fractions and without costly size reduction by total leaching of the initial material,
   - leaching for 60 to 72 hours while agitating in an extraction liquor that is selected according to whether an acidic or alkaline active substance is being extracted,
   - in a further step, separating the carrier material from the active substance-containing solution,
   - in a further step, filtering off the active substance-containing solution and further purifying the medicinal substance solution by salification and/or recrystallization,
   - in a further step, precipitating the differently solved medicinal substances by differential fractionation, and
   - in a last step, filtering off the precipitated medicinal substances.

2. The process according to claim 1, wherein the extraction liquor is sulfuric acid or sodium hydroxide solution.
3. The process according to claim 2 wherein 1% sulfuric acid or 1% sodium hydroxide solution is used.
4. The process according to any one of claims 1-3, wherein the process of dissolution of the active substance is intensified through additional heat treatment and/or ultrasound in the extraction liquor.
5. The process according to any one of claims 1-4, wherein precipitation of an acidic active substance is carried out through a pH shift in the extraction liquor by adding a basic solution to the active substance-containing solution that raises the pH of the active substance-containing solution.
6. The process according to claim 5, wherein the pH of the active substance - containing solution is raised to a value of approximately 8.
7. The process according to claim 5 or 6, wherein the basic solution is aqueous sodium hydroxide solution or soda solution.
8. The process according to any one of claims 1-4, wherein precipitation of an alkaline active substance is carried out through a pH shift in the extraction liquor by acidification of the active substance-containing solution to a pH value less than 6.
9. The process according to claim 8, wherein sulfuric acid or phosphoric acid is used to acidify the active substance-containing solution.
10. A process for the recovery of medicinal substances or active substances from preparations, their initial products or waste, especially in the form of flat-

shaped starting material, containing adhesively equipped film and active substance-containing material, said process being substantially as herein described and exemplified.

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LTS LOHMANN THERAPIE-SYSTEME AG

BY:

HODGKINSON OLD McINNES

Patent Attorneys for the Applicant