Title: IMPROVED METHOD FOR PREVENTING CRYSTAL FORMATION IN A SCOPOLAMINE TRANSDERMAL DEVICE

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(71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]: Lichtstrasse 35, CH-4002 Basel (CH).

(72) Inventor; and


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IMPROVED METHOD FOR PREVENTING CRYSTAL FORMATION IN A SCOPOLAMINE TRANSDERMAL DEVICE

This invention relates to scopolamine transdermal drug delivery devices in which the scopolamine is dispersed in a polymer matrix. The invention further relates to a method for the prevention or eradication of crystals of scopolamine in the polymer matrix.

Transdermal devices for the administration of scopolamine have been used extensively for the prevention of motion sickness. By transdermal device is meant a laminar item, e.g. a patch comprising a backing layer, drug reservoir layer, a release liner layer and adhesive means for providing an adhesive surface for attaching to a patient's skin. However, it has been reported that in known transdermal scopolamine devices, hydrated scopolamine base crystals begin to form within a week of manufacture of said systems (see USP 4,832,953).

The formation of crystalline hydrates in large enough quantities in transdermal devices can affect the release rate of scopolamine base due to their slower rate of dissolution.

It is known that the scopolamine hydrate crystal formation could be prevented by heating finished transdermal devices, preferably which are already packaged, e.g. in foil packaging to a temperature of 60°C (the hydrate was observed to melt at 59°C) and maintain the transdermal device at this temperature for a period of 24 hours (see USP 4,832,953).

It has recently been discovered, however, that scopolamine transdermal devices, despite being formed according to a manufacturing process incorporating the heating step referred to in the paragraph immediately above, nevertheless develop crystalline hydrates of scopolamine base during the manufacturing process.
Accordingly, it is an object of the present invention to provide a process of forming scopolamine base transdermal devices which prevents formation of crystalline hydrates in, or eliminates crystalline hydrates from, said devices.

Thus, one aspect of the invention provides a process of making a scopolamine base-containing transdermal device in the form of a laminar item substantially free of crystalline hydrates comprising the step of annealing scopolamine base-containing layers before or during the lamination process wherein the scopolamine base-containing adhesive layer is annealed for 3 to 6 minutes and wherein the annealing step is carried out above the melting point of the crystalline hydrates of the scopolamine base.

According to another aspect of the present invention, there is provided a scopolamine base transdermal device in form of a laminar item substantially free of crystalline hydrates of scopolamine base obtained by a process comprising the step of annealing scopolamine base-containing layers before or during the lamination process wherein the scopolamine base-containing adhesive layer is annealed for 3 to 6 minutes and wherein the annealing step is carried out above the melting point of the crystalline hydrates of the scopolamine base.

It is another object of the invention to provide a scopolamine base transdermal device which is substantially free of crystalline hydrates of scopolamine base.

By "substantially free" is meant that the devices are either completely free of any crystalline hydrates and nucleation sites or they are free to the extent that any crystals or nucleation sites which may be present are sufficiently small and/or sufficiently few in number that their presence does not adversely affect the release rate of
scopolamine base from the device.

We have now found that these and other objects of the invention are achieved if immediately before or during the lamination process, layers containing scopolamine base are subjected to an annealing step above the melting point of crystalline hydrates of scopolamine base.

The appearance of scopolamine base crystals in devices made according to the methodology of USP 4,832,953 is attributed not to the reappearance of the hydrated scopolamine base crystals with a melting point of 59°C previously eradicated by the heating step. Rather the applicant surprisingly discovered that the newly appearing crystals were in fact a previously unencountered polymorph of hydrated scopolamine base having a higher melting point (approximately 70°C) than the previous hydrated form.

Transdermal delivery devices according to the invention comprise a backing layer, drug reservoir layer, release rate-controlling membrane layer, adhesive means for releasably fixing the device to the skin of a patient to be treated and a release liner.
Transdermal devices according to the invention may be storage stable for up to 3 years, e.g. 2 years at 25°C.

A preferred delivery device according to the invention comprises in sequence (1) a backing layer which is impermeable or substantially impermeable to scopolamine, (2) a scopolamine reservoir layer which is itself made of a dispersion of scopolamine in a polymer matrix, preferably a polyisobutylene (PIB)/mineral oil (MO) matrix, (3) a release rate controlling membrane layer, (4) an adhesive layer, and (5) a removable release liner which is removable prior to applying the device to the skin of the user.

The backing layer is made of a polymer impermeable or substantially impermeable to scopolamine. Preferably it is made of a polyester foil. Preferably the polyester foil is vapour coated with aluminium. The polyester foil may be coated, with an outer coating of medium density polyethylene and a heat-sealable inner coating.

The backing layer should be thick enough to resist wrinkling which may arise through prolonged periods in storage and through the movement of a patient's skin. Preferably the thickness of the backing layer is about .06 to .07 mm, more preferably .068 to .069 mm.

The drug reservoir consists of scopolamine base dispersed or dissolved in a polymer matrix. Said polymer matrix preferably consists of polyisobutylene (PIB) and a light mineral oil (MO). The polyisobutylene polymer is preferably chosen from those having a molecular weight Mw of 1,200,000 to 35,000.

The release rate controlling membrane is preferably formed of a polypropylene film. Preferably the thickness of said film is from .02 to .03 mm, more preferably .025 mm, e.g. .0254 mm.
The release liner is a disposable element which serves to protect the device prior to its application. Typically the release liner is chosen from a material which is impermeable or substantially impermeable to scopolamine and the adhesive means. The release liner should be easily stripped away from the adhesive means. A preferred release liner is made from a polyester foil. The release liner may be silicone-coated, in which case the silicone coating is preferably made from a fluorosilicone compound known in the art, e.g. a polyfluoroalkylsiloxane. It is particularly preferred to use a silicone coated release liner when the adhesive means is not itself a silicone adhesive.

The release liner is preferably about .07 to .08 mm thick, more preferably .076 mm, e.g. .0762 mm.

The adhesive means is preferably formed as a discrete layer disposed between the release liner and the release rate controlling membrane. The adhesive may be chosen from any adhesive which is suitable for skin contact and is preferably an adhesive wherein scopolamine is at least partly soluble. Preferably the adhesive is a contact adhesive which is pressure sensitive. The preferred adhesive consists of PIB having a molecular weight of about 1,200,000 to 35,000. It is particularly preferred if some active agent is dispersed or dissolved in an adhesive layer.

The transdermal devices according to the invention may be made according to techniques known in the art. A solvent-evaporation technique may be used to make the various layers of the device. Thus the components of a particular layer may be mixed in a solvent, e.g. acetone, ethyl acetate, hexane or chloroform, preferably chloroform and cast onto a substrate, e.g. impermeable webbing to form said layer.
Conveniently, reservoir and adhesive layers may be made by casting a chloroform solution of scopolamine base in PIB and MO onto impermeable webs and the chloroform evaporated to create said layers.

The release rate controlling membrane layer may be formed from MO impregnated microporous polymer film.

The invention provides in another of its aspects a process of making the aforementioned transdermal devices comprising the step of annealing scopolamine base-containing layers before or during the lamination process.

This annealing step is additional to the heating step carried out on the packaged device as described in USP 4,823,953.

Lamination of the various layers which make up the final laminate may be carried out according to known methods.

Conveniently, the reservoir layer may be laminated to one side of the release rate controlling membrane. The adhesive layer may be laminated to the other side of the release rate controlling membrane. These lamination steps may be conducted without regard to the particular sequence or they may be conducted simultaneously. The laminate device is completed by laminating the drug reservoir layer to the backing layer and laminating the release liner to the adhesive layer.

Thereafter, the finished laminate may be cut, e.g. into patches, and packaged, e.g. in aluminum foil pouches according to techniques known in the art. Preferably however, the die cutting operation should be cyclical compared to the continuous pouching operation. The die
cutting/pause cycle is preferably repeated in order to keep pace with the slower pouching operation. This procedure is preferred as the applicant surprisingly discovered that the mechanical stress associated with the die cutting may form nucleation sites for crystal growth. This procedure therefore minimizes the time for growth of crystals by pacing the die cutting operation to the pouching operation.

The annealing step which serves to eliminate or prevent formation of crystalline hydrates is preferably carried out on the scopolamine base-containing layers either before or during the lamination of the scopolamine containing layers to the control membrane.

The step of annealing the laminates containing scopolamine base preferably should occur within about 24 hours, more preferably within about 18 hours of casting the scopolamine base-containing films.

The annealing step preferably takes place in a heating chamber at a temperature of between at least 67° to about 90°C, preferably at about 70°C to about 90°C, more preferably about 80°C to about 90°C, and most preferably at about 82°C. The residence time in the heating chamber may vary between 2 to 15 minutes depending on the nature of the annealing step. Preferably the annealing step is carried out on the drug reservoir layer and the scopolamine base containing adhesive layer independently as well as on the final laminate. Preferably the drug reservoir layer is annealed for a period of 6 to 11 minutes; the scopolamine base containing adhesive layer is preferably annealed for 3 to 6 minutes; whereas the final laminate may be annealed for a period of 2 to 5 minutes.

The annealing step may be carried out at the same time as the solvent drying step, although it is preferred that the annealing step is distinct from the drying step.
In a preferred process according to the invention, drug reservoir and adhesive films are cast onto webs and introduced into an oven to drive off the solvent, e.g. chloroform. The two webs may then be brought together, preferably while still in the oven and the annealing step takes place. In situations where the manufacturing equipment is not suited to a single oven (largely due to space limitations), each of the cast webs may be introduced into a single oven or into two separate drying ovens. The dried webs emerging from the drying ovens may be brought together and introduced into an annealing oven. In other situations, where only one oven is available and which can only accommodate a single web at a time, the drug reservoir film may be coated with scopolamine base-containing formulation and dried. The dried web may be rolled and preferably rewound onto another roller while the adhesive is cast onto a web and dried. As aforementioned, the adhesive may or may not have scopolamine base in it, and preferably does contain scopolamine base. The dried adhesive web may be rolled. Thereafter, the rolled dried adhesive layer and the rolled (preferably rerolled) drug reservoir layer are brought in contact and introduced into the oven for the annealing process. This separate processing may also be needed when the throughput speeds of the various films differ.

It will be understood by the person skilled in the art that the lamination procedure may be accomplished in many different ways. Accordingly, one can, for example envisage an alternative embodiment to that described above wherein the release rate-controlling membrane is coated with the with the scopolamine base solution and dried to drive off the solvent and annealed prior to being rolled on a roller. The scopolamine base-containing adhesive solution may be coated on the release liner, dried, annealed and rolled. The coated membrane and release liner may thereafter be brought into contact and optionally annealed again.

In the case where the reservoir/control membrane and adhesive layer/release liner are formed, laminated, and annealed in a single process, the above conditions can be optimized to give the
best results, but the oven traveling speeds of the respective layers should be adjusted so that the adhesive/release liner speed matches the reservoir/control membrane speed and the annealing speed. In the single assembly alternative here mentioned, the overall processing speed of the various webs is preferably 3.5 feet/minute through the various heating zones.

The heating step carried out on the finished and optionally pouched device may be carried out according to the methodology described in USP 4,832,953. The temperature of the heating step is preferably at least 67°C to 90°C, more preferably 75°C plus or minus 2°C. The heating step is carried out for as long as it takes to ensure that crystalline hydrates and any nucleation sites therefor are destroyed; this may be for up to 24 hours.

Scopolamine transdermal devices are useful for the treatment of symptoms of motion sickness, such as nausea, vomiting and vertigo.

The exact amount of active agent required and the release rate thereof may be determined on the basis of known in vitro or in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

In a preferred transdermal device, 0.5 mg to 1.0 mg of scopolamine is delivered from the device over a 3 day period.

The invention will be more fully explained, but is not limited, by the following example:

EXAMPLE
A chloroform solution containing mineral oil (MO), polyisobutylene (PIB), and scopolamine is coated, using an appropriate casting head, onto an ethylene/vinyl acetate (EVA) surface of a moving multi-layered polymer film (polyethylene, polyester, aluminum, EVA). The film is passed through an oven to remove the chloroform. The drug reservoir film exiting the oven is wound onto a core with a polyester interleaf. The roll of film of 1,250 ft is rewound and re-passed through the oven at a temperature of 67-90°C at a speed of 2 feet/minute and again wound onto a core.

A similar chloroform solution containing scopolamine at a lower concentration is coated onto a moving polyester film and passed through an oven to remove chloroform. As the film exits the oven, a polypropylene film, saturated with MO, is pressure laminated to the contact adhesive film and a roll of 1,250 ft of laminate is wound on a core with a polyester interleaf.

The drug reservoir film previously made is then pressure laminated to the contact adhesive film while removing the interleaving films. The final laminate is passed through an oven at a temperature range of 67-90°C at a speed of 3.5 ft per minute and wound onto a core.

The heat treated final laminate is die cut into individual systems, placed in pouches and placed in an oven at 75°C for 24 hours.
CLAIMS:

1. A process of making a scopolamine base-containing transdermal device in the form of a laminar item substantially free of crystalline hydrates comprising the step of annealing scopolamine base-containing layers before or during the lamination process wherein the scopolamine base-containing adhesive layer is annealed for 3 to 6 minutes and wherein the annealing step is carried out above the melting point of the crystalline hydrates of the scopolamine base.

2. A process according to claim 1 wherein the transdermal device is packaged and heated to at least 67°C to about 90°C for a period of about 12 to about 24 hours.

3. A process according to claim 2 wherein the transdermal device is packaged and heated at a temperature of 75°C.

4. The process according to any one of claims 1 to 3 wherein a drug reservoir layer containing scopolamine base and an adhesive layer containing scopolamine base are each separately annealed and then contacted and sealed together.

5. The process of claim 4 wherein the drug reservoir layer containing scopolamine base and the adhesive layer containing scopolamine after being sealed together are further annealed prior to packaging.

6. The process of claim 1 wherein said annealing takes place at least at about 67°C to about 90°C.

7. The process of claim 1 wherein said annealing takes place at about 82°C.
8. The process according to claim 4 or 5, wherein the drug reservoir layer is annealed for a period of 6 to 11 minutes.

9. The process according to claim 4 or 5, wherein a final laminate is annealed for a period of 2 to 5 minutes.

10. A scopolamine base transdermal device in form of a laminar item substantially free of crystalline hydrates of scopolamine base obtained by a process comprising the step of annealing scopolamine base-containing layers before or during the lamination process wherein the scopolamine base-containing adhesive layer is annealed for 3 to 6 minutes and wherein the annealing step is carried out above the melting point of the crystalline hydrates of the scopolamine base.

FETHERSTONHAUGH & CO.

OTTAWA, CANADA

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