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(72) Feltaláló(k):
RIBEIRO DOS SANTOS, Isabel, F-31600 Eaunes (FR)
SOURNAC, Michel, F-31400 Toulouse (FR)

(73) Jogosult(ak):
Pierre Fabre Médicament, 92100
Boulogne-Billancourt (FR)

(74) Képviselő:
Danubia Szabadalmi és Jogi Iroda Kft.,
Budapest

(54) **Porózus mikrorészecskéket tartalmazó transzdermális eszköz**

TRANSDERMAL DEVICE INCLUDING POROUS MICROPARTICLES

The present invention relates to the field of porous polymeric microparticles and the use thereof in association with nicotine in a transdermal delivery system. The present invention also relates to a transdermal device containing said porous microparticles and the use thereof as a drug.

Several families of solid polymers (polyamides, polyacrylonitriles, polyacrylic, polyvinylidene chloride, cross-linked copolymers, vinyl chloride, etc.) are known for their cosmetic uses as structuring agents, texturing agents, sebum-absorbing agents and mattifying agents. In each of these cases, it is a matter of formulating a cosmetic product to facilitate application, to give it a particular organoleptic property or to enable the local delivery of an active principle.

The technology disclosed in the patent of Advanced Polymer Systems Inc. makes it possible to obtain solid porous particles (or microparticles) by polymerisation (for example US 5,145,675 and US 5,156,843).

The polymers according to these patents of Advanced Polymer Systems Inc. are in particular comprised of monomer units such as styrene, divinylbenzene, methyl methacrylate, ethylene glycol dimethacrylate, 4-vinylpyridine, lauryl methacrylate, allyl methacrylate, glycol dimethacrylate. A particular polymer based on cross-linked methyl methacrylate/ethylene glycol dimethacrylate copolymers in microparticle form is marketed under the name Microsponge®.

Said porous particles have a unit size varying between 10 and 400 µm and they can thus physically entrap large quantities of active principles and then release them in an essentially controlled manner over time. For example, a typical 25 µm Microsponge® sphere may have up to 250,000 pores, resulting in a total pore volume of nearly 1 ml/g. More often, this capacity is characterised by a specific surface measurement expressed in m^2/g of product. Owing to their size, these microparticles cannot cross the stratum corneum. Said active agents are released by simple diffusion or via several stimuli (mechanical friction, hydration, pH, temperature) which have been disclosed.

This technology is more particularly adapted to the formulation of topical drug products (creams, gels, lotions, powders, soaps, etc.) or beauty care products. In both cases, the Microsponge® products improve skin tolerance. For example, in medical dermo-cosmetics, several products are marketed in the form of gels or creams, based on benzoyl peroxide (NeoBenz®), tretinoin (Retin-A® Micro), fluorouracil (Carac® 0.5%) or retinol and hydroquinone (EpiQuin® Micro). For each of these drugs, an additional advantage is being able to maximise the presence of active principle on the surface of the skin or in the epidermis, while reducing its transfer into the dermis.

Compositions using Microsponge® technology have been reported, and in this respect reference is made to US 5,145,675 and EP 0306236 which disclose how to deliver locally to the skin, and in an extended and controlled manner, certain substances such as sunscreens, repellents, cutaneous steroids such as fluocinonide or benzoyl peroxide, anti-irritants, hair-loss prevention products such as minoxidil or vitamins, essentially. The porous supports used are those disclosed for example in WO 88/01164, that is a copolymer of styrene and divinylbenzene or a copolymer of methyl methacrylate and ethylene glycol dimethacrylate or a copolymer of 4-vinylpyridine and ethylene glycol dimethacrylate. These microparticles are obtained in a first step by polymerisation in suspension in the presence of a porogenic agent, followed by a step of extraction of this porogen before final incorporation of the active principle.

Microsponge® technology is not used in the formulation of transdermal devices.

The transdermal delivery system, or transdermal device, or patch, uses the cutaneous pathway to provide direct administration of active principle to the blood system without passing through the digestive system, as is the case with tablets or syrups.

A transdermal delivery system is an adhesive device which can administer, for medical purposes, an active substance through the skin.

This system, besides the ease of use it offers, has many advantages.

Firstly, it eliminates the risk of degradation of the drug by gastric juices, hepatic metabolism or the intestinal tract. It is particularly advantageous for providing in patch form molecules that the liver tends to retain. Indeed, if it removes or stores them when they are administered orally, they are diverted from their therapeutic purpose and lose any effectiveness. In parallel, the patch eliminates the risk of digestive disorders related to the ingestion of a substance. Lastly, unlike other devices which result in concentration peaks in the blood system, the patch releases the active substances contained therein with good regularity hour after hour. Consequently, it can maintain a relatively constant concentration of the drug in the body.

It thus reduces the side effects to a maximum (digestive irritation, for example), the hepatic metabolism (first pass effect) and the intestinal degradation of the drugs in question. Today, a significant number of patches are available for various treatments. For giving up smoking, nicotine in particular is administered using patches.

There are several types of nicotine patches which can be categorised (in "Topical Drug Bioavailability, Bioequivalence and Penetration", V. P. Shah and H. I. Maibach, published by Springer, 1993, page 53) according to the mechanism by which the active principle is released and to the patch design. Among the six categories listed, nicotine-based patches are those of categories II, IVa and IVc, alone or in combination. By directly incorporating nicotine into the adhesive, the type IVa patch, like the one of the present invention, has the advantage of having a small thickness and of being able to be cut to size exceptionally by virtue of the homogeneous distribution of the active principle across its entire surface, unlike, for example, type II patches comprising a deposit region.

The transcutaneous absorption of a substance needs to comply with very precise rules which take advantage of patches to control dosage throughout the duration of use. The phenomenon corresponds to the migration of the substance considered from the skin surface to the first capillary layer. However, molecules capable of penetrating the epidermis are rare. At present, there are only a dozen known ones which can be administered by patch.

Indeed, their physicochemical characteristics must be such that the skin does not constitute an impassable obstacle; among other things, their molecular mass must be less than 500 daltons and their melting point must be below 100°C. Furthermore, the candidate substances within the patch must of course be tolerated by the skin, in order to avoid any allergic reaction.

The physicochemical properties of nicotine are problematic for transcutaneous administration; indeed, nicotine base is an oily substance which very quickly penetrates the skin surface to the first capillary layer. Moreover, it is a highly toxic substance. Thus, when the patch is affixed, all of the nicotine contained therein should not pass into the body in just a few minutes: its concentration in the blood needs to remain constant, at a therapeutic dose, for 12 or so hours. For that, nicotine is formulated in a patch whose composition regulates the transfer of the nicotine. Furthermore, Fick's law of diffusion can be used to determine a nicotine administration rate, expressed in micrograms per hour and per square centimetre of patch, according to the composition of the patch with which it is associated. The dose injected and the consistency of its administration hour after hour can thus be controlled very precisely. Generally, after a latency period corresponding to the time required for the active principle to cross the epidermis and to reach circulating blood, its concentration rapidly increases exponentially until a state of equilibrium corresponding to the value determined by the patch is reached. This concentration is maintained until the patch is removed or the reserve of active substance is exhausted.

Furthermore, with a patch, treatment may be stopped very easily if the patient exhibits intolerance. It is sufficient to remove it to terminate the delivery of the drug or the palliative substance, in the case of nicotine. The principal advantage of the patch remains its ease of use and the regulated delivery over time of the active principle.

In view of the difficulties controlling the release kinetics of nicotine, several devices containing control membranes or solid microparticles have been disclosed. Reference is made, for example, in EP 708627, to a nicotinic patch including a support layer, a matrix layer comprised of a mixture of nicotine and polymer, said patch being characterised by an average nicotine delivery rate greater than 50 $\mu g/cm^2/h$. The compositions of patent EP 708627 are characterised by the use of adhesive of the silicone type and solid particles of the silica type.

Other nicotine patch compositions are also known, such as US 5,725,876 disclosing an acrylic-type matrix nicotine patch comprised of clays for improving the cohesion of the device. For these two examples, the solid microparticles disclosed are not porous polymers such as those of the present invention.

The prior art also includes WO 95/01766.

The applicant sought to design a self-adhesive transdermal device as a substitute for the existing devices. The applicant sought to design a transdermal device capable of controlling the release of nicotine while preserving the attributes of a matrix patch of the "drug in adhesive" type such as small thickness and reduced size, as well as a manufacturing method that is simpler and less expensive than those already known in the prior art.

The applicant sought to solve a certain number of technical problems which existing self-adhesive transdermal devices did not address:

- obtain a patch characterised by a homogeneous distribution of nicotine in the adhesive matrix, which in an exceptional case allows the patch to be cut to size;
- control plasticisation induced by the presence of nicotine, which amounts to maintaining the cohesion of the adhesive matrix;
- improve comfort by having a thinner, more flexible patch that is thus more comfortable to use.

Moreover, preferably a certain number of constraints need to be respected concerning the transdermal device to be obtained:

- control the release of nicotine (to the minimum, avoid a release that is too fast, synonymous with side effects, notably addiction, likely cardiac effect and cutaneous type effect) with a novel matrix support;
- have good qualities in terms of adhesion and skin tolerance;
- obtain a patch whose ageing is of no consequence to the initial physicochemical characteristics of the product;
- select nicotine-compatible components;

- obtain a transparent patch (making it possible to observe possible irritation or local sensitisation effects).

In a surprising and unexpected manner, the applicant has shown that the use of porous microparticles of solid polymers filled with nicotine in a transdermal delivery system has many advantages, particularly in terms of the controlled release of nicotine and the homogeneous distribution of active principle in the adhesive matrix. Moreover, the use of these microparticles, in a completely unexpected manner, increases the cohesion of the patch (notably reducing the risk of leaking and the quantity of matrix residues remaining on the skin after the patch is removed) and reduces the adhesive aggressiveness of the patch.

The present invention also has as subject matter a method for preparing a transdermal device according to the invention.

The use of microporous solid polymers, in particular those comprised of monomer units such as methyl methacrylate and ethylene glycol dimethacrylate have shown very good dispersion within the adhesive and better compatibility with nicotine (no degradation of the active principle, no colouring observed).

Moreover, the method of manufacturing the composition according to the present invention is simpler than that of manufacturing some existing self-adhesive transdermal devices such as the Nicotinell® patch, notably described in "Topical Drug Bioavailability, Bioequivalence and Penetration" (V. P. Shah and H. I. Maibach, published by Springer, 1993, page 53), since unlike the latter, the nicotine patch according to the present invention is a monolayer patch which requires only one pass through a coating/drying system.

Furthermore, the subject matter of the present invention differs from certain transdermal nicotine-release devices existing up to now. Indeed, the latter cannot be cut, and moreover, over time, the distribution of nicotine in the patch becomes heterogeneous. Due to maturation, on some patches of the prior art it has been shown that there is a decreasing and concentric distribution of nicotine from the centre towards the periphery.

A transdermal patch according to the invention contains a homogeneous distribution of nicotine throughout its matrix part. This characteristic allows better use of the device by patients, in particular because the patch is thinner, but also because the patch may be cut to size in order to decrease the dose absorbed without altering its functions.

The characteristics and advantages of the compositions according to the present invention are described in the following.

Description of the drawings:

Figures 1 and 2: in vitro permeation kinetics showing the effect of the presence of microporous solid polymer (Microsponge®) in the composition according to the invention.

Figure 3: adhesive monolayer compositions and permeation results according to the adhesive used.

Figure 4: in vitro permeation kinetics showing the equivalence of the effect of the presence of solid microporous polymer Microsponge® or Polytrap® in the composition according to the invention.

The present invention thus relates to a self-adhesive transdermal device, characterised in that it includes the association of a support layer and a self-adhesive matrix layer, and a detachable protective film, said self-adhesive matrix layer including, in relation to the total weight of the self-adhesive matrix layer:

a. 65 to 93% by weight of at least one self-adhesive polymer selected from the group comprising polymers of the acrylic or acrylate type, polymers of the silicone type, polymers of the vinyl acetate type, natural or synthetic gums, copolymers thereof and mixtures thereof;

b. 2 to 15% by weight of at least one microporous solid polymer capable of containing an active principle, said polymer being comprised of monomer units selected from the group of monomers comprising methyl methacrylate and

c. 5 to 20% by weight of active principle.

The term by "association" means that the layers of the device according to the invention are directly in contact with each other and that once assembled they form a whole which cannot come apart easily and in particular which cannot come apart without human will and intervention.

Preferably, the patch according to the invention is of the adhesive monolayer type.

The term "support layer according to the invention" means any support layer typically used in the field of patches. Preferably, the support layer is a multilayer film at least one layer of which is a polyester layer and at least one other layer is a polyethylene-based or vinyl acetate ethylene-based layer. Preferably, the support layer is transparent.

The term "detachable protective film" means all detachable protective films capable of protecting the device's matrix before the device is used. These films typically used in the field of transdermal devices are well-known to a person skilled in the art. Preferably, this film is made of siliconised polyester.

The matrix layer according to the invention is self-adhesive. The term "self-adhesive" means that the matrix layer is able to keep the device according to the invention bound to a support, for example the skin, in a stable manner, with no need for the use of other means of bonding. Preferably, "self-adhesive" means that the matrix layer allows the device to adhere to the skin for at least 12 hours, preferably for about 12 to 48 hours, more preferably for about 24 hours.

The matrix layer according to the invention comprises from 65 to 93%, preferably between 75 and 85% by weight of at least one self-adhesive polymer selected from the group comprising polymers of the acrylic or acrylate type, polymers of the silicone type, polymers of the vinyl acetate type, natural or synthetic gums, copolymers thereof and mixtures thereof.

The term "synthetic gum" means, particularly in the context of the present invention, gums selected from the family of elastomers, for example styrene, styrene-isoprene-styrene (SIS), polystyrene-butadiene-styrene (SBS) or styrene-ethylene/butylene-styrene (SEBS). The term "natural gum" means all types of natural gums such as carrageenan gum or guar gum, for example.

Preferably, the matrix layer includes at least one polymer of the acrylic or acrylate type.

The polymer of the acrylic or acrylate type according to the invention is preferably comprised of monomers selected from the group comprising or consisting of vinyl acetate, 2-ethylhexyl acrylate, butyl acrylate, acrylic acid, methyl methacrylate, methyl acrylate, tert-octyl acrylamide, 2-hydroxy ethyl acrylate, glycidyl methacrylate, or mixtures thereof, more preferably from the group comprising or consisting of acrylic acid, butyl acrylate, 2-ethylhexyl acrylate, vinyl acetate, and mixtures thereof.

In one embodiment, the self-adhesive polymer according to the invention is an acrylate-vinyl acetate copolymer.

The matrix layer according to the invention further includes from 2 to 15%, preferably from 5 to 12% by weight in relation to the total weight of the self-adhesive matrix layer of at least one microporous solid polymer capable of containing an active principle.

The phrase "capable of containing an active principle" according to the invention means that the microporous solid polymer may be charged with active principle by adsorption, the active principle is thus associated with the polymer. Preferably, the microporous solid polymer according to the invention may be charged with 15% to more than 400%, preferably more than 50%, for example between 50 and 150%, even for example around 100% or around 140% by weight of active principle in relation to the weight of free microporous solid polymer. The microporous solid polymers according to the invention are preferably charged by simple contact (adsorption) with the active principle by mixing.

The microporous solid polymer capable of containing an active principle according to the invention is preferably solid porous microparticles of the polymer type or the cross-linked copolymer type (microporous solid polymer).

Said microporous solid polymer is comprised of monomer units selected from the group of monomers comprising or consisting of methyl methacrylate and ethylene glycol dimethacrylate.

The microporous solid polymer is comprised of monomer units of methyl methacrylate and ethylene glycol dimethacrylate. One such polymer may in particular be obtained commercially under the Microsponge® brand. The self-adhesive transdermal device according to the invention does not contain a microporous solid polymer other than the microporous solid polymer comprised of monomer units of methyl methacrylate and ethylene glycol dimethacrylate.

Preferably, the microporous solid polymer according to the invention is provided in the form of microparticles of average size comprised between 1 μm and 100 μm, preferably between 5 μm and 50 μm, more preferably between 15 μm and 30 μm. The average size can in particular be measured by an apparatus of the laser particle-size analyser type, for example the Malvern Mastersizer 2000 which, in particular, measures particles ranging from 0.2 μm to 2000 μm in a dry system.

In one embodiment of the invention, the microporous solid polymer according to the invention has a total pore volume comprised between 0.5 and 3 ml/g, preferably between 1 and 2 ml/g.

In another embodiment, said microporous polymer has a granular pore volume comprised between 0.2 and 3 ml/g, preferably between 0.5 and 1.5 ml/g, more preferably between 0.7 and 1.0 ml/g.

The total pore volume and granular pore volume may in particular be measured by a mercury porosimeter, for example the Autopore IV (Micromeritics). Said porosimeters make it possible in particular to carry out an intrusion of mercury at constant pressure and thus to be able to determine the total pore volume and granular pore volume of microporous solid polymers. At low pressure (3.45 kPa to 186 kPa, for example), the intrusion volumes obtained correspond to packed powder and total porosity (intergranular and granular). At high pressure (186 kPa to 20.7 MPa, for example), the mercury intrusion values observed correspond to granular porosity.

According to one advantageous characteristic of the present invention, the microporous solid polymer, which is advantageously provided in the form of microparticles, is distributed homogeneously within the self-adhesive polymer mass. According to another characteristic of the invention, the active principle is adsorbed homogeneously in the microporous solid polymer mass. The result is thus regular distribution within the self-adhesive matrix layer of the device of the invention and, therefore, regular release of the active principle.

Preferably, the device according to the invention is characterised in that the basis weight of the self-adhesive matrix layer is between 50 and 300 g/m^2, preferably between 100 and 200 g/m^2.

The active principle according to the invention is nicotine.

The active principle may be charged into the microporous solid polymer in liquid form. The active principle, in particular nicotine, is preferably charged in base form or in the form of a solution of a salt thereof, more preferably in base form. The quantity of active principle charged in the particles will depend in particular on the desired quantity of active principle released by the transdermal device according to the invention and on the desired release time. For example, the device according to the invention including nicotine may include between 10 and 100 mg of nicotine, preferably between 15 and 90 mg of nicotine, for example 15, 30, 45 or 90 mg of nicotine.

The inventors noted that the release of nicotine was particularly well controlled when the microporous solid polymer is as defined in the present invention, preferably, a methyl methacrylate and ethylene glycol dimethacrylate copolymer, and that the adhesive matrix has a basis weight between 50 and 300 g/m^2, preferably between 100 and 200 g/m^2.

The rate of nicotine released by the microporous solid polymers depends in particular on the nature of the polymer and the pore size. Preferably, the devices according to the invention allow the release of nicotine from the matrix layer by an average delivery rate comprised between 5 and 100 µg/cm^2/h, in one embodiment between 10 µg/cm2/h and 50 µg/cm^2/h, for a time interval comprised between 1 and 24 hours. The release rate may be measured by any permeation technique known to the person skilled in the art, in particular via permeation kinetics, for example on abdominal skin of nude mouse arranged on the surface of a glass (Franz) cell, such as in particular described in Example 3.

The matrix layer according to the invention can also include other excipients or components such as antioxidants, for example. In one embodiment, the self-adhesive matrix layer includes at least one antioxidant agent in particular selected from the group comprising or consisting of butyl hydroxy toluene (BHT), butyl hydroxy anisole (BHA), ascorbyl palmitate, alpha tocopherol and esters thereof, citric acid, propyl gallate and mixtures thereof, preferably BHT. The antioxidant agent is then preferably present in said self-adhesive matrix layer in a proportion comprised between 0.01 and 1% by weight in relation to the total weight of said self-adhesive matrix layer.

In another embodiment, the self-adhesive transdermal device according to the invention is characterised in that it consists of the association of a support layer and a self-adhesive matrix layer, and a detachable protective film, said self-adhesive matrix layer consisting of, in relation to the total weight of the self-adhesive matrix layer:

a. 65 to 93% by weight of at least one self-adhesive polymer selected from the group comprising polymers of the acrylic type, polymers of the silicone type, polymers of the vinyl acetate type, natural or synthetic gums, copolymers thereof and mixtures thereof;

b. 2 to 15% by weight of at least one microporous solid polymer capable of containing an active principle, said polymer being comprised of monomer units selected from the group of monomers comprising methyl methacrylate and ethylene glycol dimethacrylate;

c. 5 to 20% by weight of nicotine as active principle;

d. optionally from 0.1 to 1% of an antioxidant agent; and

Preferably, the patch according to the invention is transparent. The term "transparent" means that it is possible to sufficiently observe the skin through the patch in order to rapidly identify any possible skin intolerance.

The present invention also relates to a method for preparing a transdermal device according to the invention, characterised in that it comprises or consists of the following steps:

a. mixing the self-adhesive polymer, the microporous solid polymer, the active principle, preferably nicotine, and optionally the oxidizing agent, until a homogeneous mixture is obtained;

b. coating the homogeneous mixture obtained in step a. on a detachable protective film;

c. gradually drying the coated mixture;

d. laminating the product obtained in step c onto a support layer; and

e. optionally, cutting the product obtained in step d, in such a way as to obtain transdermal devices or patches of the desired size.

Mixing the self-adhesive polymer and the microporous solid polymer according to the invention "until a homogeneous mixture is obtained according to the present invention" means that the microporous solid polymer must be distributed uniformly in the self-adhesive polymer. This distribution can in particular be evaluated by visual observation (absence of aggregates).

Nicotine may or may not be mixed with the microporous support according to the invention before step a. In a preferred embodiment, nicotine is not mixed with the microporous support prior to step a., the nicotine, the microporous support and the self-adhesive polymer thus being brought into contact independently and concomitantly in step a.

Preferably, the coating step b. is carried out at a temperature comprised between 30°C. and 50°C.

The term "gradually drying" means the creation of a temperature gradient. It is preferable that drying occurs gradually in order to avoid crusting. For example, the temperature gradient may be a gradient of 5 to 20°C in a temperature range from 30°C to 80°C, preferably from 40 to 60°C.

After coating and drying, the product obtained in step c is laminated onto a support layer according to the invention. The lamination operation may be carried out by any method known to a person skilled in the art.

The coated support layer obtained in step d of the method according to the invention can then optionally be cut to the desired size. For example, the support layer may be cut into transdermal devices or patches (or units) of between 5 cm^2 and 80 cm^2, for example 10 cm^2, 20 cm^2, 30 cm^2 or 60 cm^2.

The transdermal device according to the invention may be packaged in a packaging under a protective (inert) atmosphere, preferably in nitrogen, in particular when the patch according to the invention does not contain an antioxidant agent. The preparation of inert packaging for patches is well-known to a person skilled in the art and can be carried out using any known method.

The present invention further relates to a self-adhesive transdermal device according to the invention for use as a drug.

In particular, the present invention relates to a self-adhesive transdermal device according to the invention, preferably a transdermal device according to the invention containing nicotine, for use in the treatment of nicotine addiction, in particular in so as facilitate giving up smoking.

In another embodiment, the present invention relates to a self-adhesive transdermal device, preferably a transdermal device according to the invention containing nicotine, for use in the treatment of neurodegenerative diseases such as in particular Parkinson's disease or Alzheimer's disease.

The present invention is illustrated by the examples below.

EXAMPLES

Example 1: Characterisation of adsorption supports

Example 1A: Adsorption capacity tests (Table 1)

Comparative tests for measuring the adsorption capacity of nicotine by various microporous solids were carried out. The tests consisted of determining the maximum quantity of nicotine that could be adsorbed on the microporous supports according to the following procedure:

- weighing the microporous support, between 0.3 and 2.0 g depending on its density, to have an identical volume,
- adding nicotine in an iterative manner by weighing out about 0.1 g,
- impregnating the support with nicotine using a spatula after each addition of nicotine; the appearance of the mixture is then noted.

The maximum adsorption capacity is thus determined: it is the quantity of nicotine adsorbed by the microporous support expressed in grams of nicotine per gram of support, with nicotine seepage not observed.

The results were as follows: Table 1:

Support type	Trade name	Adsorption capacity (quantity of nicotine in grams/1 gram of support)	Comments - visual appearance
Cross-linked MMA/GDMA polymer	Microsponge ®	1.40	Significant swelling of particles; light yellow colour maintained
Silica	Silica shells	2.70	Very small particles forming clusters once impregnated
Silica	MSS-500/3H4 ®	3.00	Difficult homogenisation with formation of lumps
Densified fumed silica	Aerosil ®V200	2.75	Nicotine penetrates but is not spread out; particles form irregular heaps
Polyurethane/ silica	BPD 800 ® microspheres	1.05	Significant swell-ing of particles; light yellow colour maintained
Crospovidone	Polyplasdone ® XL-10	0.15	Nicotine penetrates but is not spread out; significant yellowing
Silicone resin/POE lauryl ether 98/2	DC 9506 ®	0.60	Powders that wet well, but tendency to ooze

As may be noted, the majority of the supports tested combined with nicotine have a large number of disadvantages that make them unusable: spreading is impossible; seepage; formation of aggregates, clusters or lumps.

The cross-linked MMA/GDMA polymers (cross-linked polymer of methyl methacrylate and ethylene glycol dimethacrylate) allow good adsorption of nicotine and have after adsorption a suitable appearance.

Example 1B: Adsorption support release capacity test (Table 2)

The adsorption supports are charged with nicotine at 50% or 80% of their maximum adsorption capacity determined beforehand (see preceding Table 1). A wash test is then carried out in order to determine their release capacity expressed in % of nicotine released in relation to the quantity of nicotine added.

The results were as follows:

Table 2:

Support type	Charge (%)	Part in the wash (%)
Silica (Silica shells)	80%	90
	50%	96
Cross-linked MMA/GDMA polymer (Microsponge ®)	80%	79
	50%	69
Polyurethane/silica (BPD800 ® microspheres)	80%	91
	50%	84
Crospovidone (Polyplasdone ® XL-10)	80%	99
	50%	89
Silicone resin/POE lauryl ether 98/2 (DC9506 ®)	80%	72
	50%	69

The wash test is carried out on 200 mg of charged microparticles, with rinsing carried out with 1 ml of water for a period of 10 seconds with shaking, followed by filtration.

These results show that the cross-linked MMA/GDMA polymers and DC9506® silicone resin retain more nicotine via better adsorption than the other supports.

Example 1C: Adsorption support dispersion tests

Tests of dispersion of the microporous supports are carried out in solvents constituting the majority phase of the adhesive mixtures before coating. These dispersion tests make it possible to verify the technical feasibility of the adhesive mixtures.

These tests are carried out according to the following procedure:

- in a 9 ml glass vial, weigh the microporous support, between 0.2 and 1.25 g depending on its density,
- add solvent (ethyl acetate or heptane) so as to have a mass ratio of solvent to microporous support equal to about three,

- mix with a spatula and immediately observe the mixture; the mixture is also observed after resting for 48 hours.

The results are presented in Table 3:

Table 3:

Support type	Observations with ethyl acetate	Observations with heptane
Polyurethane/silica (BPD800 ® microspheres)	Liquid suspension	Liquid suspension
Crospovidone (Polyplasdone ® XL-10)	Liquid suspension	Liquid suspension
Cross-linked MMA/ GDMA polymer (Microsponge ®)	Pasty suspension	Liquid suspension
Silica (Silica shells)	Support remains dry	Support remains dry
Densified fumed silica (Aerosil ® 200VV)	Support changes appearance: presence of translucent agglomerates	Support remains dry
Silica (MSS-500/3H4 ®)	Support changes appearance: presence of translucent agglomerates	Support changes appearance: formation of a gel
Silicone resin/POE lauryl ether 98/2 (DC9506 ®)	Support changes appearance: formation of a kind of translucent gel	Support changes appearance: formation of a kind of gum

The supports of greatest interest at the conclusion of these dispersion tests in solvents are the supports that remain in suspension in either liquid or paste form: cross-linked MMA/GDMA polymers (Microsponge®), BPD800 or Polyplasdone XL10.

Surprisingly, only the cross-linked MMA/GDMA microporous support provides advantageous characteristics in all 3 characterisation tests carried out. Cross-linked MMA/GDMA microporous polymers are thus, unexpectedly, a support which is particularly suitable for nicotine (charge, release, compatibility).

Example 2: Method for preparing a monolayer transdermal composition containing nicotine and a Microsponge®-Type Microporous Polymer

The preparations according to the invention are prepared in the following way:

The adhesive, then the nicotine, microporous polymer and optionally BHT are added into a mixing vessel. The stirring parameters (time and speed) are set so as to avoid the formation of lumps and to obtain a homogeneous mixture, and depend in particular on the size of the vessel. After resting for 24 hours, the adhesive mass is coated onto a silicone film in a proportion of 150 ±5 g/m^2 before proceeding to drying at

45°C., which is intended to evaporate the solvents in the adhesive, followed by transfer of the matrix onto a transparent polyester support. The product thus obtained is cut into the desired sizes.

Example 3: Permeation tests (Figures 1 and 2)

The following compositions A and B are obtained according to the method of Example 2:

Table 4

	KG209	KG243
Composition	A	B
Nicotine base	11.2%	11.2%
Polymethyl methacrylate/ethylene glycol dimethacrylate copolymer (Microsponge ®)		8.1%
Silicone adhesive	9.0%	8.1%
Acrylate-vinyl acetate copolymer	79.8%	72.6%

In vitro permeation kinetics were carried out on abdominal skin of a nude mouse arranged on the surface of a glass (Franz) cell. The results obtained express the comparative cumulative quantities (CQ) from 0 to 48 hours in μg/cm^2 between a preparation not containing microporous polymer (formula A) and the reference product (Nicotinell®) (Fig. 1).

CQ

	1	3	6	9	12	16	20	24	48
KG209	140.47	399.50	687.86	876.30	1018.01	1176.65	1235.77	1302.11	1504.50
Nicotinell	67.47	249.09	514.86	737.75	933.88	1156.95	1310.09	1449.56	1908.67

The same preparation is then prepared but containing a quantity of microporous polymer of the cross-linked MMA/GDMA polymer (Microsponge®) type according to the invention (formula B). In vitro permeation kinetics are then carried out on abdominal skin of a nude mouse arranged on the surface of a glass (Franz) cell. The results obtained express comparative cumulative quantities (CQ) from 0 to 48 hours in μg/cm^2 between this preparation according to the invention (formula B) and the reference product (Nicotinell® comprised of a gelled nicotine depot on an adhesive layer) (Figure. 2).

CQ

	1	3	6	9	12	16	20	24	48
KG243	106.06	347.84	614.78	854.52	1024.88	1143.59	1268.95	1313.79	1515.68
Nicotinell	171.45	540.27	869.15	1166.56	1382.27	1567.33	1690.11	1849.09	2242.83

These results show how the presence of a microporous support of the cross-linked MMA/GDMA polymer (Microsponge®) type is able to control the permeation kinetics of nicotine from the matrix patch according to the invention. In particular, the presence of microspheres makes it possible to reduce the quantity of nicotine released in the first 12 hours ("burst" effect observed in Figure 1 for composition KG209, the curve which crosses that of Nicotinell®) not observed in Figure 2 for the composition according to the invention.

Reduction of the "burst" effect is very important in the case of nicotine in order to avoid a too rapid release of a too large amount of nicotine, an event which may prove to be irritating or toxic.

A comparative experiment was repeated with a formula C differing from formula B wherein the 8.1% of cross-linked MMA/GDMA polymer (Microsponge®) was replaced with 8.1% of lauryl methacrylate/glycol dimethyl methacrylate crosspolymer (Polytrap®). The permeation kinetics results obtained with this formula C were compared with those of formula B and those of Nicotinell obtained during the same experiment so that the results could be directly compared.

Time (hours)	0.5	1	1.5	3	6	12	18	24
POLYTRAP	7.6	32.7	63.9	156.5	293.5	461.8	547.3	599.3
MICROSPONGE	6.2	28.3	55.8	139	266.4	438.9	530.5	587.6

As noted in the table above and in the appended Figure 4, the results obtained are comparable when using Microsponge® or Polytrap®.

The following examples illustrate the influence of the microporous support on the adhesive and cohesive properties of the adhesive matrix containing nicotine.

The following adhesive monolayer compositions C, D and E were obtained following the protocol of Example 2:

Table 5:

	SME416	SME417	SME418
Composition	C	D	E
Nicotine base	0%	5.0%	5.0%
Polymethyl methacrylate/ ethylene glycol dimethacrylate copolymer (Microsponge ®)		4.1%	
Butylhydroxytoluene		0.1%	0.1%
Acrylate-vinyl acetate copolymer	100.0%	90.8%	94.9%

These compositions are then characterised by adhesion tests, respectively a shear test and a tack test. The shear test comprises measuring the capacity of an adhesive or a self-adhesive formulation such as a patch to resist a static force applied in the same plane. The criterion measured is that of the time required to separate by sliding the material tested from a standard surface such as a steel plate. The longer this time, the stronger the cohesion. The tack test consists in measuring the force required to unstick, at a given rate, an adhesive or a self-adhesive formulation such as a patch from a standard surface with which it was brought into contact under the effect of low pressure (by setting-up a loop in contact with a probe). The criterion measured is force expressed in Newton. The greater this force, the greater the tack.

The results were as follows (Table 4):

Table 6

	Maximum tack force (Newton)	Shear time
Composition C	19.2	More than 168 hours
Composition D	16.6	112 hours
Composition E	23.1	86 hours

It is thus shown that the addition of nicotine, by a plasticising effect, within an adhesive decreases the cohesion of the system (reduction in shear time) and increases its tack (compared between compositions C and E). The addition of porous microparticles of the cross-linked MMA/GDMA polymer (Microsponge®) type improves the cohesion of the system and reduces tack strength (compared between compositions D and E). The addition of porous microparticles of the cross-linked MMA/GDMA polymer (Microsponge®) type thus unexpectedly reduces the plasticizing effect of nicotine.

Example 5: Influence of adhesive on nicotine release

The following examples illustrate, for the preparations of compositions according to the invention, the influence of the adhesive on nicotine release.

The following adhesive monolayer compositions were obtained following the protocol of Example 2:

Table 7

	KG427	KG428	KG429
Nicotine base	10.0%	10.0%	10%
Polymethyl methacrylate/ethylene glycol dimethacrylate copolymer	8.3%	8.3%	8.3%
Butylhydroxytoluene	0.1%	0.1%	0.1%
Self-cross-linking acrylate-vinyl acetate adhesive (Duro-Tak ® 2052)	81.6%		
Non-cross-linked acrylic adhesive (Duro-Tak ® 9088)		81.6%	
Self-cross-linking acrylate-vinyl acetate adhesive (Duro-Tak ® 2196)			81.6%

The in vitro permeation test was performed according to the description provided in preceding Example 3 and the results obtained are those of Figure 3.

CQ	1	3	6	9	12	16	20	24
KG427	90	294	547	735	860	983	1076	1137
KG428	118	319	501	613	687	776	842	888
KG429	87	271	493	639	749	847	924	982

The use of porous microparticles of the cross-linked MMA/GDMA polymer (Microsponge®) type makes it possible to obtain for a patch a similar in vitro kinetics profile, regardless of which adhesive is used.

Szabadalmi igénypontok

1. Öntapadó transzdermális eszköz, **azzal jellemezve,** hogy tartalmazza egy hordozó réteg és egy öntapadó mátrix réteg és egy leválasztható védőfilm asszociációját, amely öntapadó mátrix réteg tartalmaz az öntapadó mátrix réteg teljes tömegére vonatkoztatva

a) 65-93 tömeg%-ban legalább egy öntapadó polimert, amely akril vagy akrilát típusú polimerek, szilikon típusú polimerek, vinil-acetát típusú polimerek, természetes és szintetikus gumik, ezek kopolimerei, és mindezek keverékei csoportjából vannak kiválasztva,

b) 2-15 tömeg%-ban legalább egy mikropórusos szilárd polimert, amely a hatóanyagot képes magába foglalni, amely mikropórusos szilárd polimer metil-metakrilát és etilén-glikol-dimetakrilát monomer egységeket tartalmaz, és

c) 5-20 tömeg%-ban nikotint hatóanyagként.

2. Az 1. igénypont szerinti eszköz, **azzal jellemezve,** hogy az öntapadó polimer akril vagy akrilát típusú és vinil-acetát, 2-etilhexil-akrilát, butil-akrilát, akrilsav, metil-metakrilát, metil-akrilát, *terc*-oktil-akrilamid, 2-hidroxi-etil-akrilát, glicidil-metakrilát vagy ezek keverékei csoportjából kiválasztott monomereket tartalmaz.

3. A 2. igénypont szerinti eszköz, **azzal jellemezve,** hogy a monomerek akrilsav, butil-akrilát, 2-etilhexil-akrilát, vinil-acetát vagy ezek keverékei csoportjából vannak kiválasztva.

4. Az 1-3. igénypontok bármelyike szerinti eszköz, **azzal jellemezve,** hogy a mikropórusos szilárd polimer 1 µm és 100 µm közötti, előnyösen 5 µm és 50 µm közötti, még előnyösebben 15 µm és 30 µm közötti közepes méretű mikrorészecskék formájában van jelen.

5. Az 1-4. igénypontok bármelyike szerinti eszköz, **azzal jellemezve,** hogy a mikropórusos szilárd polimer teljes pórustérfogata 0,5 ml/g és 3,0 ml/g közötti, előnyösen 1 ml/g és 2 ml/g közötti.

6. Az 1-5. igénypontok bármelyike szerinti eszköz, **azzal jellemezve,** hogy a mikropórusos szilárd polimer szemcse pórus térfogata 0,2 ml/g és 3,0 ml/g közötti, előnyösen 0,5 ml/g és 1,5 ml/g közötti.

7. Az 1-6. igénypontok bármelyike szerinti eszköz, **azzal jellemezve,** hogy a mikropórusos szilárd polimer az öntapadó polimer tömegében egyenletesen van eloszlatva.

8. Az 1-7. igénypontok bármelyike szerinti eszköz, **azzal jellemezve,** hogy a hatóanyag a mikropórusos szilárd polimer tömegében egyenletesen van adszorbeálva.

9. Az 1-8. igénypontok bármelyike szerinti eszköz, **azzal jellemezve, hogy** az öntapadó mátrix réteg alaptömege 50 g/m^2 és 300 g/m^2 közötti, előnyösen 100 g/m^2 és 200 g/m^2 közötti.

10. Az 1-9. igénypontok bármelyike szerinti eszköz, **azzal jellemezve**, hogy az öntapadó mátrix réteg tartalmaz legalább egy antioxidáns anyagot, amely butilhidroxitoluol (BHT), butil-hidroxi-anizol (BHA), aszkorbil-palmitát, alfa-tokoferol és ezek észterei, citromsav, propil-gallát és ezek keverékei csoportjából van kiválasztva.

11. A 10. igénypont szerinti eszköz, **azzal jellemezve**, hogy az öntapadó mátrix rétegben az antioxidáns anyag az öntapadó mátrix réteg teljes tömegére vonatkoztatva 0,01 tömeg% és 1 tömeg% közötti arányban van jelen.

12. Az 1-11. igénypontok bármelyike szerinti eszköz, **azzal jellemezve**, hogy a szilárd mikropórusos polimer alaptömege 100 g/m^2 és 200 g/m^2 közötti.

13. Az 1-12. igénypontok bármelyike szerinti eszköz, **azzal jellemezve**, hogy a mátrix rétegből a nikotin közepes bejutási aránya 10 $\mu g/cm^2$/óra és 50 $\mu g/cm^2$/óra között van 1 és 24 óra közötti időtartam alatt.

14. Eljárás az 1-13. igénypontok bármelyike szerinti transzdermális eszköz előállítására, **azzal jellemezve**, hogy az tartalmazza következő lépéseket:

a) az öntapadó polimert, a mikropórusos szilárd polimert, a nikotint és adott esetben az oxidálószert összekeverjük homogén keverék képződéséig,

b) az a) lépésben kapott homogén keveréket egy leválasztható védőfilmen szétterítjük,

c) a szétterített keveréket fokozatosan megszárítjuk,

d) a c) lépésben kapott terméket egy hordozó rétegre rétegezzük, és

e) adott esetben a d) lépésben kapott terméket kívánt méretű transzdermális eszközökre vagy tapaszokra szétvágjuk.

15. Az 1-13. igénypontok bármelyike szerinti eszköz gyógyszerként történő alklamazásra.

16. A 15. igénypont szerinti eszköz nikotinfüggőség kezelésében történő alkalmazásra.

17. A 15. igénypont szerinti eszköz neurodegeneratív betegeségek kezelésében történő alkalmazásra.

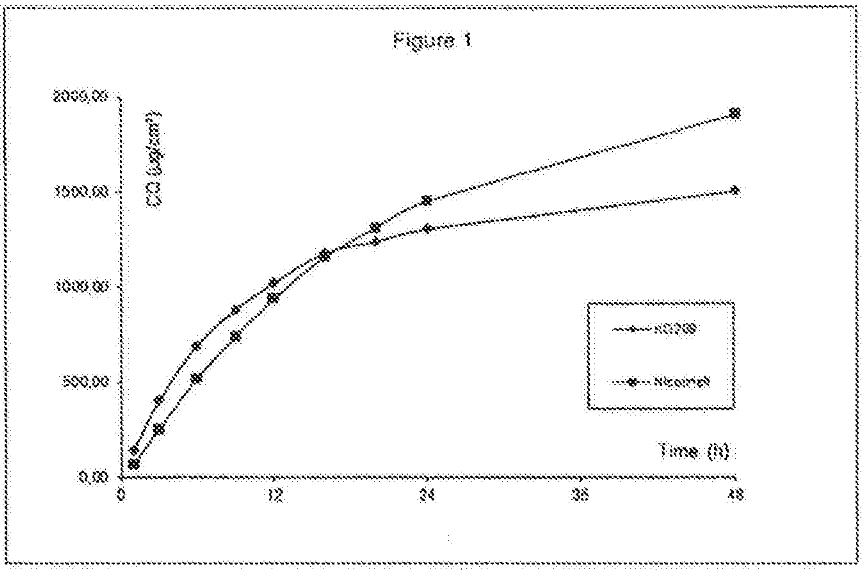
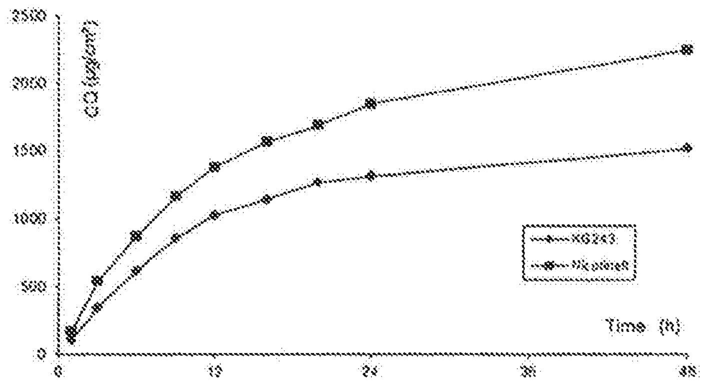


Figure 1

Figure 2



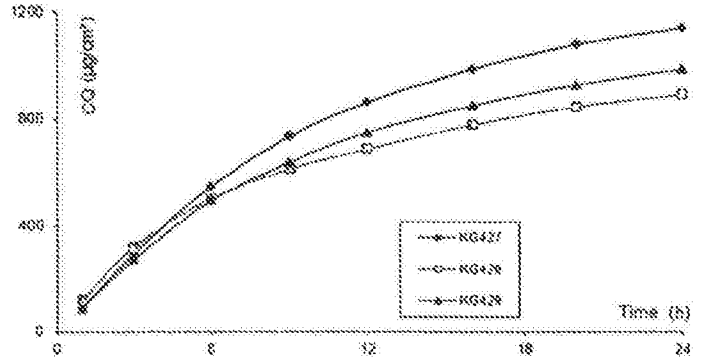
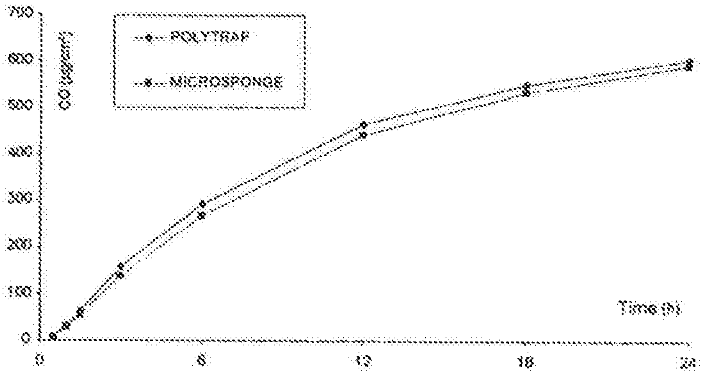


Figure 3

Figure 4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600
500
400
300
200
100
0
CO (µg/cm²)
POLYTRAP
MICROSPONGE
Time (h)
0
6
12
18
24