(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/09653 A1

(51) International Patent Classification[7]: A61K 7/00, 9/70

(21) International Application Number: PCT/GB01/03418

(22) International Filing Date: 27 July 2001 (27.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0018467.1 27 July 2000 (27.07.2000) GB

(71) Applicant *(for all designated States except US)*: **STRAKAN PHARMACEUTICALS LIMITED** [GB/GB]; Buckholm Mill, Buckholm Mill Brae, Galashiels TD1 2HB (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAMITYAMA, Fumio** [JP/GB]; Strakan Pharmaceuticals Limited, Buckholm Mill, Buckholm Mill Brae, Galashiels TD1 2HB (GB). **QUAN, Ying-shu** [CN/GB]; Strakan Pharmaceuticals Limited, Buckholm Mill, Buckholm Mill Brae, Galashiels TD1 2HB (GB).

(74) Agent: **LORD, Hilton, David**; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/09653 A1

(54) Title: ADHESIVE COSMETIC PATCHES

(57) Abstract: Dispensing means for cosmetic agents advantageously comprise an adhesive material suitable as a bioadhesive and which comprises an adhesive polymer and a plasticiser therefor, wherein the adhesive is cross-linked, the adhesive comprising ketone groups cross-liked by a polyamine cross-linking agent. Such adhesives have good cohesion and low dermal irritation.

ADHESIVE COSMETIC PATCHES

The present invention relates to adhesive substrates, particularly patches and strips, for the delivery of cosmetics, the adhesive being a cohesive bioadhesive comprising both adhesive polymer and plasticiser.

Various applications for bioadhesives exist, including medical tape and dermal patches, for example. Methods of manufacture of these products are well advanced, but the nature of the adhesive remains a problem.

If the adhesive on medical tape is too strong, then removal can be painful, and will also serve to exfoliate the skin, which can cause irritation and may even lead to sensitisation to any drugs that the patient might be taking.

If the bioadhesive is too weak, then the patch or tape will tend to come away from the skin before it should. This has led to bioadhesives being developed which have merely been adapted so as not to be too strong to be painful, and not so weak as to be relatively useless.

More recently, it has been established that strong adhesives can be tempered with plasticisers. These generally take the form of oily substances introduced into the adhesive polymer. The effect of the introduction of such oily substances is to soften the physical structure of the adhesive whilst, at the same time, acting at the interface between the adhesive and the skin, thereby helping to somewhat weaken the adhesive, and to prevent exfoliation. Such a beneficial type of adhesive was first noted in certain types of electrical insulating tape.

The problem with such softened, or plasticised, adhesives is that, once they are weak enough to be medically acceptable, their cohesive strength is poor. Thus, such adhesives, when used in dermal patches or surgical tape, for example, have insufficient integrity, and tend to tear, leaving bits of adhesive behind on the skin.

EP-A-450986 discloses an acrylic adhesive plasticised with isopropyl myristate (IPM) and which also contains nitroglycerine, which can further serve as a plasticiser. In order to improve cohesion of this adhesive, cross-linking was effected with aerosil silica. The problem with such cross-linking is the technical difficulty involved in sufficiently finely dividing the aerosil silica and incorporating it uniformly throughout the adhesive. Such cross-linking would not be generally practical.

US-A-5298258, more generally, seeks to solve the problems noted above, and discloses acrylic adhesives containing substantial amounts of plasticisers. Various methods for cross-linking the adhesive are mentioned, including irradiation and exposure to UV, but chemical cross-linking with a metal alcoholate, metal chelate or trifunctional isocyanate is preferred. The cross-linking of such an adhesive requires the presence of active hydrogen, generally in the form of a carboxyl or hydroxyl group, typically provided by a co-monomer having the required functionality.

The problem with such a system is with regard to the nature of the cross-linking, where there is necessarily involved an active chemical reagent, either on the adhesive (carboxyl groups, for example) or in the cross-linker (such as aluminium in aluminium alcoholate). Many drugs can react or interact with such groups, which can lead to problems, such as breakdown of the drug, or simple blocking of the cross-linking. For example, where a drug is weakly basic, then this can interact with the carboxyl groups present on the adhesive, thereby competing with the cross-linker.

WO 99/02141 discloses block copolymers wherein the soft segments are cross-linked, these copolymers being suitable for use as drug-retaining bioadhesives in dermal patches. These adhesives tend to suffer a loss of cohesion, however, when a plasticiser is incorporated.

In co-pending WO 00/44846 we show that it is possible to provide a satisfactory medical adhesive with good cohesion and adhesive properties, together with low irritation, and which comprises an adhesive polymer and a plasticiser, wherein the

polymer is cross-linked by a polyamine reacting with ketone groups present in the adhesive.

The desirability of delivering cosmetics using skin patches has led to some investigation of suitable systems. The problems noted above are then compounded by having to load sufficient cosmetic in the patch to have activity. Such patches need a soft, gentle adhesive, as they will tend to be used on a frequent basis, and any patch that is difficult to remove may cause a rash or other irritation, thereby counteracting any beneficial effects realised by the cosmetic.

EP-A-953348 to L'Oréal discloses skin patches for cosmetics wherein the adhesive should be soft. EP-A-450986 (Sekisui) discloses nitroglycerine patches which are intended to be non-irritant. WO00/45785 (Acutek), an intermediate document, discloses cosmetic patches wherein the adhesive contains an oil as a softener.

WO99/26572 (Theratech) discloses anti-wrinkle patches wherein a pressure sensitive adhesive comprises glycerine and a polydiorganosiloxane adhesion-adjusting agent. FR-A-2735024 (Sanofi) discloses cosmetic patches and US-A-5298258 (*supra*, Nitto Denko) discloses a cross-linked acrylic adhesive whose properties are modified by a plasticiser, but no further cross-linking is disclosed.

It has now, surprisingly, been discovered that cosmetics can be delivered to the skin by cohesive bioadhesives comprising sufficient plasticiser to reduce discomfort on removal, especially when the adhesive is cross-linked. Substrates bearing the cosmetic-containing adhesive, generally in the form of tape or dermal patches, are particularly useful.

Thus, in a first aspect, the present invention provides dermally attachable dispensing means comprising a substrate upon which is disposed an adhesive material, the adhesive material comprising a cross-linked, adhesive polymer and a plasticiser therefor, ketone groups in the adhesive being cross-linked by a polyamine cross-linking agent, the adhesive comprising plasticiser sufficient to reduce discomfort on dermal

detachment, characterised in that the substance to be dispensed comprises a cosmetic agent.

By the term "dermally attachable" is meant that the dispensing means of the invention is attachable to the hair, skin, or epidermis, of the intended user. Attachment to the mucosae, such as the inside of the mouth, is also considered as skin herein, and provides an embodiment of the invention. Attachment to hair is not especially preferred but is encompassed herein, there being little requirement for therapeutic acceptability in such uses. Indeed, in such cases, the dispensing means may comprise a tape carrying bleach or hair colourant, for example.

In general, the dispensing means of the invention is intended for secure attachment for a period of hours, with substantially pain-free, or painless, removal at the end of the period of use. The adhesives used in the dispensing means, or patches, of the present invention are advantageous in that they provide secure attachment, low to virtually no irritation, and can be removed substantially or completely painlessly. In addition, this is generally and preferably achieved without leaving a residue on the user's skin.

The dispensing means of the present invention will often take the form of a patch or other adhesive dressing or cosmetic vehicle. The term "patch" is used interchangeably herein with "dispensing means" and extends equally to other forms of dispensing means, such as tape, unless otherwise apparent.

It will be appreciated that the essential features of the present invention lie in the adhesive and the cosmetic, and that the substrate may be any that is suitable to carry the adhesive and permit attachment to the skin of the user. Thus, a preferred substrate is flexible and preferably thin, for comfort, although it may comprise a rigid, shaped support for a specific region of the body, for example. The substrate may simply comprise a flexible web on which the adhesive is disposed. In an alternative, the substrate may comprise a backing and a reservoir for the cosmetic agent attached thereto. The reservoir may comprise any adsorbent or absorbent substance capable of

carrying the cosmetic agent chosen, and is preferably adhered to the backing, such as by adhesion, the cosmetic agent generally being loaded after adhesion.

In such a construction, the adhesive of the present invention may then be layered around or over the reservoir, although it is preferred to layer the adhesive over the reservoir for ease of manufacture. In addition, the adhesives used in the patches of the invention are capable of high loading of cosmetic agents, so that any cosmetic agent in the reservoir passes through the adhesive onto the skin once *in situ*.

As noted above, the adhesives used in the present invention are capable of high levels of loading of cosmetic agent, so that it is not necessary to provide a separate reservoir, the adhesive serving the purpose. Suitable quantities of the adhesive may be selected to carry the cosmetic, and such matrix patches are preferred embodiments of the present invention.

The cross-linking of the adhesives of the invention is readily achieved, as illustrated further below. In general, the adhesive polymer comprises a minority of monomeric sub-units exhibiting free keto groups with little tendency to enolisation after polymerisation. At least some of these groups are cross-linked with a polyamine, two free amine groups on the cross-linking agent reacting with keto groups on separate monomers to effect a cross-link. By "free" amine groups is meant that there is at least one hydrogen substituent on the nitrogen.

Suitable plasticisers are illustrated below, but may be any that is suitable for use in topical administration. Such considerations apply to any of the components of the patches of the invention likely to come into prolonged contact with the skin of a user. The plasticiser may be one and the same as the cosmetic agent, where the agent is suitable for such use. In such a case, it will be appreciated that the amount of cosmetic agent will be in excess of that otherwise required for simple cosmetic application, in order to provide the qualities of the adhesive.

Where the plasticiser is not the same as the cosmetic, then it should be miscible with the adhesive. In this respect, "miscible" indicates that the plasticiser, once mixed with the adhesive and after cross-linking, exhibits little or no tendency to seep out of the patch, with time. Naturally occurring organic substances are preferred, while many mineral oils are unsuitable. Examples of preferred plasticisers are given hereinbelow.

The amount of plasticiser required is what is sufficient to reduce discomfort on dermal detachment, that is, when the patch is removed from the skin of the user the plasticiser lends those qualities of ready and painless removal. If there is too little plasticiser, then irritation and redness can result, and removal made painful. Suitable levels are readily determined by those skilled in the art but, for guidance, are generally between 17% and 200% by weight (w/w). More preferred ranges are illustrated and discussed hereinbelow.

The adhesive used in the present invention is preferably a bioadhesive, in that there is little or no appreciable long-term toxicity. In addition, as noted above, it is a particular advantage of the adhesives used herein that they are cohesive so that, while they have good properties of adhesion, they are readily removed and without leaving a residue. Other adhesives removable without pain have far less adhesive qualities and have poor cohesion, often leaving substantial amounts of adhesive on the skin, requiring an alcoholic swab for removal of the residue.

It is also particularly advantageous that the adhesives of the present invention are contact adhesives, in that the patches of the invention can be prepared and stored on a release layer for long periods, and then simply applied to the skin of the user where they will adhere as required without any further preparation or wetting, for example.

There is also provided an adhesive of the invention which is loaded with a cosmetic agent. The adhesive may be provided between two sheets of release layer and applied as required. Such substance may be useful where it is desired to apply a decoration or other object or material over the patch area other than a standard backing.

By "loaded" is meant that the adhesive has been impregnated with the agent, or is otherwise carrying the agent. It is not necessary that the levels of agent be at saturation.

In one embodiment of the invention, there is provided a patch or tape comprising a cosmetic agent for delivery to the skin and an adhesive material suitable for use as a bioadhesive, the adhesive material comprising an adhesive polymer and a plasticiser therefor, wherein the adhesive is cross-linked, characterised in that the adhesive comprises ketone groups cross-linked by a polyamine cross-linking agent.

The dermal dispensing means is generally any that is capable of delivering the cosmetic agent onto, into, or through, any or all layers of the skin. In general, however, most cosmetic agents suitable to be administered by delivery in accordance with the present invention are for administration into or onto the dermis and epidermis, especially the epidermis, including the stratum corneum.

It will be appreciated that the dispensing means may take any suitable form, provided that the adhesive is used for adhesion to the skin. Particularly suitable forms are tapes and patches, especially dermal delivery patches, but other forms, such as plasters and bandages, for example, are also envisaged. Simple tapes, for example, may to be cut to desired shapes and sizes for application, the adhesives of the invention being capable of holding substantial amounts of the agent. As noted above, where specific forms of dispensing means, such as tapes and patches, are referred to herein, such reference includes reference to other forms of dispensing means, unless otherwise apparent.

Thus, at its simplest, the means of the present invention comprises a backing layer bearing the adhesive which, in turn, comprises the cosmetic agent. For storage and handling purposes, the exposed face of the adhesive will generally be covered with a readily removable protective layer, such as a paper, plastics or a metal foil.

Use of such adhesives of the present invention in combination with a cosmetic agent allows the agent to be delivered to the skin *via* a matrix patch, for example,

without causing skin trauma when the patch is removed. This is especially important in cosmetic applications, for example, to the face. Such patches will often be applied daily, for example, and it is important that there be minimum irritation and skin surface removal, and minimal adhesive residue on removal.

In addition, the use of an adhesive as described herein allows optimum delivery of the cosmetic agent to the skin. The presence of the plasticiser in the adhesive allows the adhesive to closely follow the contours of the skin, such that the maximum surface area of the dermal dispensing means is in contact with the skin.

Additionally, the invention provides a method of cosmetic treatment, comprising applying a dispensing means of the invention to skin or mucosae that it is desired to treat.

Cosmetic agents used in the patches of the present invention are any agents which generally serve to enhance appearance, especially of the skin or hair, and may generally function so as to improve skin tone, or by reducing or reversing skin wrinkles, or by masking or reducing skin blemishes, for example. Preferred agents are those which serve to reduce or reverse the effects of ageing upon the skin, such as wrinkles and age- or liver-spots, especially facial skin, or which, at least, appear to do so, either temporarily or permanently. Other suitable cosmetic effects are well known in the art.

Examples of preferred cosmetic agents include vitamin C, vitamin D2, vitamin D3, vitamin A, vitamin E, natural and synthetic ceramides, alpha hydroxyacids, retinoids, agents changing (darkening or lightening) skin pigmentation, tyrosine, essential fatty acids, tocotrienols, herb extracts, phospholipids, squalene, urea, olive oil, lauric acid, isopropyl myristate, cetyl alcohol, essential oils such as tea tree oil, peppermint oil, rosemary oil, avocado oil, almond oil, palm kernel oil, babassu oil, hemp seed oil, mango seed oil, brazil nut oil, grape seed oil, jojoba oil, sandlewood oil, carrot oil, peach kernel oil, wheat germ oil, macadamia nut oil, lavender oil and eucalyptus oil, plant and herb extracts such as Aloe vera, elderflower, cucumber, witch hazel, green tea, seaweed, algae, watermelon, hawthorn flower, orchid, orange flower

and sea plant, sodium hyaluronate, lanolin, glycerin, zeolites, cocoa butter, and pro-vitamin B5. Of the above, the oily vitamins are preferred. In general, all of the above agents are individually envisaged in the present invention, and other cosmetic agents will be readily apparent to those skilled in the art.

It will be appreciated that patches and tapes of the invention may comprise more than one cosmetic agent, if so desired, in which case they are most preferably compatible. The cosmetic agents, such as those exemplified, may also be used in the form of salts or esters, or other derivatives or analogues. For example, vitamin E acetate and vitamin A palmitate are preferred compounds for use in the present invention. Of the more hydrophilic compounds, it is generally preferred to provide these as derivatives, where they are to be incorporated directly into the adhesive. In this respect, vitamin C mono- and di- palmitate are preferred for use in the present invention.

Where the cosmetic is a hydrophilic compound, it may be used in combination with additional delivery systems such as liposomes, for example, to enhance delivery to and into the dermis and epidermis. Alternatively, hydrophilic compounds may be ground to a fine powder and then mixed into the adhesive solution for delivery, or may be admixed with an amphiphilic agent such as a surfactant, for example a poloxamer such as P407 or P188, to assist in uptake by the adhesive.

It will also be appreciated that it is not essential that the cosmetic agent be transdermally delivered. Many agents act on the upper skin surface or penetrate only into the first few skin cell layers, such that all that is necessary is for the tape or patch to deliver the agent into or onto the skin surface. In general, patches and tapes of the invention generally deliver to a localised area of the skin. If it is desired to enhance uptake in the skin, then enhancers, such as are well known in the art, may be used.

The cosmetic agent may be present in any suitable concentration in the patch, and is preferably comprised in the adhesive. When in the adhesive, the concentration may be any that is suitable, generally over very wide ranges, and is preferably present in

a concentration of 0.001-100% by weight of the adhesive, more preferably 0.1-70% by weight of adhesive. The lower ranges may be appropriate for highly active compounds, such as tretinoin, for example, while the higher ranges may be appropriate for such compounds as vitamin E and its derivatives. Similar considerations apply to situations where other means are used for cosmetic agent retention. In general, suitable concentrations will depend upon the nature of the cosmetic agent used and the intended effect, so that suitable concentrations will be readily apparent to those skilled in the art.

In certain circumstances, however, as noted above, the cosmetic agent may act as a plasticiser. In such cases, the amount of plasticiser may be reduced, or even eliminated altogether, and the amount of cosmetic agent increased above 30% by weight, for example, of the adhesive. Suitable adjustments to the proportions of plasticiser and cosmetic agent are readily determined by those skilled in the art.

It has been found that vitamin E, particularly the acetate, for example, can act as a plasticiser for the adhesive of the present invention. In addition, it has also surprisingly been shown to act to enhance the adhesive strength of the adhesive component of the present invention. Thus, vitamin E serves to increase adhesive strength, so that less cross-linking is needed in the adhesives of the invention, and can enable a greater range of useful adhesives to be prepared.

The amount of cosmetic agent used will vary widely according to the effect it is intended to have, where it is intended for use, and the nature of the agent, as well as its solubility or other uptake characteristics in the adhesive. Such considerations are moot where the agent is borne in reservoir patch. In matrix patches, however and for guidance, the amount of cosmetic agent may be anywhere from about 1% to about 30% by weight, where the agent does not also serve as plasticiser. More preferred are concentrations between 5% and 25%, especially 10% and 20% w/w.

For the avoidance of doubt, the present invention employs adhesive materials, as disclosed herein, wherein the polymer and/or copolymer constituents thereof are cross-linked, wherein at least a portion of the cross links comprise a moiety

>C=N-(X)-N=C<

in which the carbon atoms are each a part of the respective polymer and/or copolymer constituents and each X is the same or different, preferably the same, and is directly equivalent to any group that would serve to carry the necessary amine groups of a polyamine cross-linking agent of the present invention.

Accordingly, it will be appreciated that -(X)-, at its simplest, need only represent a direct bond, in the instance of hydrazine, for example. It will also be appreciated that more than two suitable amine groups may be attached to X, although X may often be of the form X^1-N<, or of the form $X^2(NA-)_2$, wherein X^1 and X^2 represent the kernel of X, and the groups -N< and NA represent the links with -N=C< groups, with each A representing a hydrogen or a direct bond with X^2.

The adhesive materials used in the present invention have been found to possess good water vapour permeabilities, which allows the skin to breathe when the tape or patch is in place, especially if the substrate is also breathable, which is preferred. In addition, the lack of any necessary reactive groups in the adhesive is useful for the stability of active agents, and also in providing certain sorts of patch that could not previously be made, as the adhesives of the invention are generally susceptible to very little interaction with other materials.

The term "polymer" is used generically herein to relate to polymers, copolymers and mixtures thereof. In general, it is preferred that the polymer should be a synthetic polymer, in order to be able to provide adequate quality control and predictability of results. It is also advantageous to use synthetic polymers, as they can be controlled to contain desired side-groups, as necessary. In the present invention, the adhesive polymer, or a substantial component thereof, has at least one ketone group which is able to react with a polyamine.

Ketone groups are capable of tautomerisation, where there is an equilibrium between the ketone and the corresponding enol compound. This equilibrium is generally in favour of the ketone. In the present invention, it is strongly preferred that

the ketone-containing polymer should have at least one ketone group with little or substantially no tendency to enolisation. Hence, it is preferred that the ketone group should not be part of a larger functionality, and it is particularly the case that the ketone group should not be part of a carboxyl group or any derivative thereof, such as an esteric linkage or amide group, although it may be linked to or adjacent such a group. It is also strongly preferred that the ketone group should not be part of an aldehyde group.

It appears that, in the present invention, the cross-linking reaction takes place between the keto form of the carbonyl group and the amine group of the cross-linking agent. It has been found that, if the ketone group is not stable in the keto form, then it reacts only poorly, if at all, with the cross-linking agent. Preferred compounds are those in which the keto form is at least 100 fold more stable than the enol form, preferably more stable by a factor of 10^4, most preferably more stable by a factor of 10^6 or greater. Preferably the equilibrium constant K (enol/keto), when measured in water, is less than 10^{-2}, more preferably less than 10^{-4}, and most preferably less than 10^{-6}, or even smaller. In this way, the equilibrium is strongly biased in favour of the keto form. Other factors aside, the more strongly biased the equilibrium toward the ketone group, the better.

Given the preference for the ketone group to not readily be able to form an enol group, then it will be appreciated that functionalities in the proximity of the reactive ketone group are preferred which do not encourage the keto group to enolise. In fact, such functionalities are preferred where stabilisation of the keto group is encouraged.

Block copolymers are useful in the present invention. Suitable block copolymers consist of a mixture of 'hard' (A) and 'soft' (B) segments, which may be combined in an A-B-A or $(A\text{-}B)_n$ type structure (*c.f.* Block Copolymers: Overview and Critical Survey, Noshay and McGrath, 1977). Association of the hard segments is thought to provide a degree of physical cross-linking, which improves the cohesive properties of the adhesive. Acrylic block copolymers, comprising soft and hard segments, having a degree of chemical cross-linking between the soft segments, are preferred.

More specifically, the term 'block copolymer', as used herein, refers to a macromolecule comprised of two, or more, chemically dissimilar polymer structures, terminally connected (Noshay and McGrath, *supra*). These dissimilar polymer structures, sections or segments, represent the 'blocks' of the block copolymer, the A and B segments comprising the chemically distinct polymer segments of the block copolymer. In the present invention, the A-B-A structure is preferred.

In general, it is preferred that the adhesive agent used in the invention possesses a minimum number of functionalities having active hydrogen, in order to avoid undesirable reactions/interactions, such as with any active agent that it is desired to incorporate into the bioadhesive material. It will be appreciated that this is only a preferred restriction, and that any adhesive may be tailored by one skilled in the art to suit individual requirements. For example, it may be desirable to incorporate certain active groups into the adhesive in order to encourage uptake of a hydrophilic cosmetic agent, for example. However, limiting such functionalities generally helps to reduce irritation and, so, is preferred.

Limiting active functionalities, especially those with active hydrogen, is also advantageous, in order to permit wide use of any given formulation of adhesive without having to take into account how it is likely to interact, chemically, with its environment. However, as stated above, an adhesive required for any individual purpose may be tailored as seen fit by one skilled in the art. Thus, a generally chemically inert adhesive is preferred, in the absence of requirements to the contrary.

If means other than the adhesive are used to carry the cosmetic agent, then the substance having active agent retention properties is taken herein as being a substance capable of absorbing or adsorbing active agent. In the instance where the substance is loaded with active agent for dispensing *via* a dermal patch, then it will be appreciated that such absorbance and/or adsorbance should be at least partially reversible.

Tapes employing the adhesives of the invention exhibit good adhesion and cohesion, and release freely from the subject without painful exfoliation. It may also be

beneficial for a tape of the present invention to carry such additional agents as antimicrobial agents, although adhesives of the invention, especially those comprising IPM as plasticiser, exhibit antimicrobial properties.

Preferred adhesives for use in the present invention are those which, in tests, can be applied to newspaper and readily removed therefrom without tearing the paper. Particularly preferred are those adhesives which can be removed from, and reapplied to, newspaper repeatedly, without losing adhesion or damaging the paper. Tapes having such properties are particularly useful, and are preferred embodiments of the present invention.

Suitable examples of impermeable backings which may be used for dermal patches include films or sheets of polyolefins, polyesters, polyurethanes, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chloride, polyamides, ethylene-vinyl acetate copolymer (EVA), ethylene-ethylacrylate copolymer (EEA), vinyl acetate-vinyl chloride copolymer, cellulose acetate, ethyl cellulose, metal vapour deposited films or sheets thereof, rubber sheets or films, expanded synthetic resin sheets or films, non-woven fabrics, fabrics, knitted fabrics, paper and foils. Other backings will be readily apparent to those skilled in the art. The backing must be secured to the adhesive more strongly than to the skin, in order that the patch come away from the skin cleanly on removal.

As noted above, in a preferred embodiment, patches of the invention are breathable, and it is generally preferred that, while the backing material is strong and impermeable to the cosmetic agent, it should also be able to allow the passage of water vapour, at least in cosmetic applications. In the case of dermal patches, water vapour permeability can be tempered by the requirement for impermeability to cosmetic agent.

Highly preferred adhesives for use with the present invention correspond to those disclosed in WO 99/02141 (*supra*), incorporated herein in its entirety. Where these adhesives do not already possess suitable ketone groups, these can readily be provided by the incorporation of a suitable monomer when preparing the polymer. The

adhesives of WO 99/02141 already possess good cohesion and adhesion, but addition of plasticiser compromises cohesion. Cross-linking in accordance with the present invention enables the use of these adhesives with plasticiser, retaining their superior active agent retention properties and allowing control of the level of adhesion, while allowing painless and irritation-free removal of the patch.

Many adhesives are known, and it will be apparent to those skilled in the art which adhesives will be useful in the present invention. In general, those based on acrylates and methacrylates are preferred and alkyl acrylates and alkyl methacrylates provide properties of tack and adhesion. Suitable alkyl acrylates and alkyl methacrylates include n-butyl acrylate, n-butyl methacrylate, hexyl acrylate, 2-ethylbutyl acrylate, isooctyl acrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate and tridecyl methacrylate, although other suitable acrylates and methacrylates will be readily apparent to those skilled in the art. Acrylate block copolymers are suitably used in the present invention, and it is preferred that the acrylic block copolymer comprises at least 50% by weight of alkyl acrylate or alkyl methacrylate (co) polymer.

Particularly where the adhesive is for use in a dermal patch, it is often preferred that a polar monomer is copolymerised with an alkyl acrylate or alkyl methacrylate, in order to enhance the solubility of certain active agents. Suitable such polar monomers include hydroxyethyl acrylate, hydroxypropyl acrylate, vinyl pyrrolidone, acrylamide, dimethylacrylamide, acrylonitrile, diacetone acrylamide and vinyl acetate.

Diacetone acrylamide, or a combination of diacetone acrylamide and vinyl acetate, is useful in the present invention. The diacetone acrylamide component enables more advantageous loading capabilities than vinyl acetate, but vinyl acetate enhances the rate of polymerisation, which is of commercial importance. In such a case, where two polar monomers are used in an adhesive, it will be appreciated that the levels of each monomer may be manipulated in such a way as to provide optimum retention and delivery properties.

Where used, it is preferred that diacetone acrylamide, or other polar monomer, such as hydroxyethyl methacrylate or vinyl acetate, be present in no more than 50% w/w of the monomeric mix, as this can lead to reduced adhesion, for example. However, where adhesion is not important, good levels of cosmetic agent loading may be obtained with an excess of polar monomer.

In general, it is preferred to provide the adhesive in the form of a copolymer. In the preferred block copolymers, it is preferred that at least the soft segment should be a copolymer. This not only has the advantage of giving a greater variety of polymers from which to select, but is also useful in providing the necessary ketone groups. Suitable monomers (comonomers) will be readily apparent to those skilled in the art and, essentially, are only otherwise limited to compounds which are copolymerisable in the system of choice and which provide the necessary ketone group.

Examples of suitable ketone-providing monomers include aliphatic, olefinically unsaturated keto, preferably monoketo, compounds such as vinyl esters or allyl esters of aliphatic monobasic or dibasic acids containing a keto group and having a suitable number of carbon atoms, such as three to eight. Suitable such acids include pyruvic acid, acetoacetic acid and levulinic acid, a suitable ester of such being the vinyl alcohol ester. For example, one suitable compound, pyruvic acid vinyl alcohol ester, has the formula H_2C=CH-O-CO-CO-CH_3.

Other suitable compounds include aliphatic amides substituted at the nitrogen by a vinyl or allyl group and other suitable monomers are the olefinically unsaturated ketones, such as vinylmethyl ketone and vinylethyl ketone. However, a preferred monomer is diacetone acrylamide, which is readily commercially available and which has the structure CH_2=CH-CONH-$C(CH_3)_2$-CH_2-$COCH_3$. A particularly preferred embodiment of the adhesive of the present invention uses a combination of butyl acrylate, 2-ethylhexyl acrylate and diacetone acrylamide, preferably in a ratio of about 4 : 4 : 3, either as the adhesive, or as the soft segment of the block copolymer, although other suitable preparations will be apparent to those skilled in the art.

In general, unless otherwise specified, ratios and percentages, as given herein, are by weight.

The present invention is not limited to specific plasticisers. The only requirement for the plasticiser is that it be appropriate to the adhesive. For example, using the preferred adhesive noted above, naturally occurring castor oil has been found not to be appropriate, for example, as it leaks out of the adhesive, thereby preventing adhesion. However, appropriate plasticisers are readily established by those skilled in the art. In particular, a simple mixture of a plasticiser with the adhesive should provide a bioadhesive material, or material suitable for use as a bioadhesive (which expressions are used interchangeably herein), which does not separate, and which is adhesive, within the broad general ranges that have generally been noted. Too little plasticiser will generally result in an adhesive material which is too strong and insufficiently soft, while too much plasticiser will generally lead to disruption of the adhesive and permit insufficient adhesive quality.

In general, the plasticiser may be used in an amount generally between about 20 and 200% of the adhesive, preferably between 20% and 150%, more preferably between about 30 and 120%, with about 100% generally providing good results. It will be appreciated, however, that different plasticisers will have different optima for different adhesives.

Plasticisers are generally liquids having high boiling points, and suitable examples include glycols, such as ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, polyethylene glycol and polypropylene glycol; fats and oils such as olive oil, jojoba oil, squalene and lanolin; organic solvents such as dimethyl decyl sulphoxide, methyl octyl sulphoxide, dimethyl sulphoxide, dimethylformamide, dimethylacetamide, dimethyllaurylamide, dodecyl pyrrolidone and isosorbitol; liquid surfactants; specific plasticisers such as diisopropyl adipate, phthalates and diethyl sebacate; hydrocarbons such as liquid paraffin; ethoxylated stearyl alcohol, glycerol esters, isopropyl myristate, isotridecyl myristate, ethyl laureate, N-methylpyrrolidone,

ethyl oleate, oleic acid, isopropyl adipate, isopropyl palmitate, octyl palmitate and 1,3-butanediol. Of the above, phthalates, isopropyl myristate, isotridecyl myristate and octyl palmitate are currently preferred. These substances can be used either alone or as a mixture or mixtures thereof.

Polyamines for use in the present invention should have two or more free amine groups to react with the ketone moiety of the adhesive. In the simplest embodiment, hydrazine, or hydrazine hydrate, may be used as the polyamine. However, we have established that it is highly preferable that the reactive amine should be bound directly to another nitrogen, or to another group providing the same or generally equivalent electronegativity as another nitrogen. Thus, dihydrazine compounds and linked amine compounds are particularly preferred. Examples of the latter include dialkylene triamines, such as di-C_{2-6} alkylene triamines wherein the alkylene groups are preferably the same length as each other, especially diethylene triamine [2-(2-aminoethylamine)ethylamine] or bishexamethylene triamine, but other suitable triamine and polyamine compounds will be readily apparent to those skilled in the art.

Dihydrazine compounds are especially preferably dihydrazides of polybasic organic acids, especially dicarboxylic acids. Examples of aromatic dicarboxylic acids include phthalic acid, isophthalic acid and terephthalic acid, although others will be readily apparent to those skilled in the art. Particularly preferred dihydrazides are those of aliphatic saturated dicarboxylic acids, especially those having 2-10 carbon atoms, and dihydrazides of oxalic acid, adipic acid, and sebacic acids are suitable examples, while the diamino derivatives of medium chain alkanes are useful (C_{5-12}), especially the straight chain alkanes, of which the hexane and dodecane derivatives are currently preferred, especially 1,6-diaminohexane and 1,12-diaminododecane. It will be apparent that polyhydrazides, as well as the dihydrazides, may also be employed.

We prefer that the polyamines be used in an amount generally between about 0.05% and 2% of the adhesive, more specifically between about 0.3% and 1%, although individual polyamines will have different optima for different adhesives. In addition, it will be appreciated that the quantity of the polyamine that is required may vary

depending upon the amount of plasticiser that is used. We prefer that the amount of cross-linker that is added results in gelation of the adhesive, and is such that the adhesive cannot be subsequently dissolved by a solvent after cross-linking.

In general, polymers suitable for use as the hard portion of the block copolymer possess glass transition temperatures above room temperature. Suitable monomers for use in forming the hard segment polymer include styrene, α-methylstyrene, methyl methacrylate and vinyl pyrrolidone, although other suitable monomers will be readily apparent to those skilled in the art. Polystyrene and polymethyl methacrylate have been found to be suitable for the present invention.

It is preferred that the hard portion of the block copolymer forms from 3-30% w/w of the total block copolymer, particularly preferably from 5-15% w/w.

Particularly suitable block copolymers have soft portions which have been at least partially chemically cross-linked prior to cross-linking with polyamine. Such initial cross-linking may be effected by any suitable cross-linking agent. It is particularly preferable that the cross-linking agent be in the form of a monomer suitable for incorporation into the soft segment during polymerisation. Preferably the cross-linking agent has two, or more, radically polymerisable groups, such as a vinyl group, per molecule of the monomer, at least one tending to remain unchanged during the initial polymerisation, thereby to permit cross-linking of the resulting block copolymer.

Suitable initial cross-linking agents for use in the present invention include divinylbenzene, methylene bis-acrylamide, ethylene glycol di(meth)acrylate, ethylene glycol tetra(meth)acrylate, propylene glycol di(meth)acrylate, butylene glycol di(meth)acrylate, or trimethylolpropane tri(meth)acrylate, although other suitable cross-linking agents will be readily apparent to those skilled in the art. A preferred initial cross-linking agent is tetraethylene glycol dimethacrylate. It is preferred that the initial cross-linking agent comprises about 0.01-0.6% by weight of the block copolymer, with 0.1-0.4% by weight being particularly preferred.

Methods for the production of block copolymers from their monomeric constituents are well known. Block copolymer portions may be produced by any suitable method, such as step growth, anionic, cationic and free radical methods (Block Copolymers, *supra*). Free radical methods are generally preferred over other methods, such as anionic polymerisation, as the solvent and the monomer do not have to be purified.

Suitable initiators for polymerisation include polymeric peroxides with more than one peroxide moiety per molecule. One suitable initiator has been found to be 'Perhexa MC' (1,1'-di-*tert*butyl-peroxy-2-methyl cyclohexane, Nihon Yusi C.C.). This compound contains two tertiary butyl peroxy groups which allow stepwise polymerisation of the hard and soft segments of the block copolymer. The initiator CH-50-AL (Peroxid-Chemie GmbH) has also been found to be suitable in the manufacture of compounds of the present invention. Choice of reaction conditions is well within the skill of one in the art, once a suitable initiator has been chosen.

The initiator is preferably used in an amount of 0.005-0.1% by weight of the block copolymer, with 0.01-0.05% by weight being particularly preferred, although it will be appreciated that the amount chosen is, again, well within the skill of one in the art. In particular, it is preferred that the amount should not be so much as to cause instant gelling of the mix, nor so low as to slow down polymerisation and to leave excess residual monomers. A preferred level of residual monomers is below 2000 ppm. It will also be appreciated that the amount of initiator will vary substantially, depending on such considerations as the initiator itself and the nature of the monomers.

It will be appreciated that there is no particular restriction on further substances being used in association with the adhesive used in the invention. For example, suitable agents may be used to inhibit crystallisation of a cosmetic agent in the adhesive, where the adhesive is to be used in a patch, for instance. Many agents will be apparent to those skilled in the art, and polyethylene glycol is generally particularly effective. However, in general, it has been found that compounds to be delivered from patches of the invention are generally less likely to crystallise than they are in prior art systems.

A patch comprising a bioadhesive material and cosmetic of the present invention may be additionally used in combination with a drug, where necessary, to complement the cosmetic action. Suitable drugs are biologically active compounds or mixtures of compounds that have therapeutic, prophylactic or other beneficial pharmacological or physiological effects.

Transdermal patches and other dermal delivery means of the present invention may be suitably shaped to provide optimal delivery of the agent to the skin. For example, semi-circular patches may be suitable for delivery of cosmetics to a region on the face under the eye, where wrinkles may be present. Other suitably shaped patches will be readily apparent to the skilled person.

In general, the adhesive polymer for use in the invention may be prepared in any suitable manner as known in the art. This will generally comprise the adhesive being prepared in a solvent and, prior to removal of the solvent, it is preferable to involve, as a final step, the polyamine. This is mixed with the prepared adhesive solution and then applied to the tape or patch, or any other suitable application requiring such an adhesive material. A further advantage of the present invention is that the cross-linking time is generally substantially reduced, so that manufacture is easier. The solvent can be removed as known in the art.

The preferred adhesive strength of the bioadhesive material is such that, when applied to a tape or patch, the tape or patch can be applied to the skin and then removed without removing the stratum corneum layer of the skin surface. In particular, an adhesive strength of about 30g/inch (~1.2g/mm) to about 300 g/inch (~12g/mm), more preferably about 40g/inch (~1.6g/mm) to about 200 g/inch (~8g/mm), is preferred for the bioadhesive, although the skilled person will recognise appropriate strengths. Materials with adhesive strength greater than about 300 g/inch (~8g/mm) are likely to cause skin irritation when the tape is removed, as the outer skin layer is concomitantly removed.

The present invention will now be illustrated further with reference to the following, non-binding Examples.

Example 1

Preparation of Suitable Block Copolymeric Adhesives

An adhesive compound suitable for use in the invention was prepared in a "2 + 1" synthesis. The first step effectively provides the soft segment of the block copolymer, while the second step completes formation of the block copolymer. In the third step, cross-linking occurs, to form an insoluble product.

Step 1:

115g of 2-ethylhexyl acrylate, 84g of diacetone acrylamide, 115g of butyl acrylate and 0.72g tetraethylene glycol dimethacrylate were mixed, in order to obtain a homogeneous solution. The solution was placed in a flask, and 200 ml of ethyl acetate along with 200 ml of toluene were added. The solution was heated to 80°C under nitrogen, then 0.05 g of 1,1'-di-*tert*-butylperoxy-2-methyl cyclohexane dissolved in 10 ml of ethyl acetate were added. Polymerisation was allowed to proceed for 24 hours at this temperature. This step produced the soft segments.

Step 2:

After 24 hours, 45g methyl methacrylate and 300 ml of toluene were added to the mix of Step 1. The solution was then heated to 99°C in order to initiate the second stage polymerisation step, which was continued for 12 hours at 99°C.

After this time, the polymer was transferred to a bottle for cooling. The resulting solution contains the pre-crosslinked polymer, and can be stored for substantial periods. The average molecular weight of the polymer produced in this way was estimated to be 358,000 Da by gel permeation chromatography. This solution can be used, *per se*, but the solids content of the solution generally varies between about 30 and 50%. Accordingly, it is preferred to dry the solution, with heating, in order to

obtain a first stage adhesive. This adhesive generally corresponds to that of WO 99/02141, and, after the evaporation stage, already possesses a degree of cross-linking between the soft segments of the block copolymer. This adhesive is then dissolved at a rate of 1.0 g *per* 2.0 g of a 2 : 5 v/v mixture of ethyl acetate and toluene.

Step 3:

3.0g of the solution of step 2 (containing 1.0g of solid adhesive) were mixed with plasticiser, as specified [*e.g.* isopropyl myristate (IPM), 1.0g], and cross-linker [1.0 ml of a solution of adipic acid diamine in 3 : 1 v/v methanol/water (0.5g in 100ml), unless otherwise specified] was mixed and coated onto substrate, generally a PET (polyethylene terephthalate) film measuring 20 x 20 cm. This was then heated at 80°C for 20 minutes, covered with a PET release liner, and then allowed to stand at 40°C for 24 hours to complete cross-linking. The 20 x 20 PET film is then typically cut into strips measuring 10 x 2.5 cm.

EXAMPLE 2

Mixed Vitamin Patch

3.0 g of the solution obtained in Example 2, step 2, 0.70 g of IPM (plasticiser), 500 mg of vitamin E acetate, 25 mg of vitamin A palmitate and 2.0 ml of cross-linker mix (0.1 g adipic acid diamine dissolved in 20 ml of a 15 : 5 v/v mixture of methanol and water) were mixed well, and the resulting solution coated onto a 60 μm thickness polyethylene terephthalate release liner. The coated sheet was heated at 85°C for 10 minutes to remove solvents.

Non-woven fabric (100g/m^2) was laminated onto the dried adhesive layer, and rectangular skin softening patches cut from the sheet (10 cm x 6 cm). These patches are suitable for night time application, during sleep, to the skin of the heel or elbow, for example, as skin softeners.

EXAMPLE 3

Rejuvenating Patch

The patches were prepared as in Example 2, except that 40 mg of vitamin D2 was used in place of vitamin A palmitate. Suitable patches were ellipsoid (longer diameter = 6.0 cm, shorter diameter = 2.5 cm), for applying to the skin of face below the eyes, for example for 8 hrs at sleeping time.

EXAMPLE 4

Whitening Patch

The patches were prepared as in Example 2, except that 100 mg of kojic acid was used in place of vitamin E acetate. Suitable patches are circular (diameter of 2.0 cm, for example) for application to the skin over birthmarks or age-spots, for example.

EXAMPLE 5

Alternative Skin Whitening Patch

3.0 g of the solution obtained in Example 1, step 2, 0.60 g of octyl palmitate (plasticiser), 25 mg of vitamin A palmitate, 100 mg of ascorbic acid dipalmitate in 3.0 ml of ethanol, and 2.0 ml of cross-linker (*c.f.* Example 2) were mixed well. A further 2 ml of tetrahydrofuran was added in order to bring the solution to homogeneity. The solution was further mixed and then coated onto a 60 μm thickness polyethylene terephthalate release liner. The coated sheet was dried at 85°C for 10 minutes to remove solvents.

40 μm PET film was laminated onto the dried adhesive, and circular patches cut from the sheet (2 cm of diameter). These patches may be applied to birthmarks.

EXAMPLE 6

In Vivo Permeation Studies In Rabbit And Human

Patch Composition (% of total patch weight):

Vitamin E acetate 22%

Vitamin A palmitate 1%

Three Japanese White rabbit (body weight 2 ~ 3 kg) were used. Patches were applied for 3, 5 and 8 hours. After application, the patches were removed and the vitamins remaining therein were extracted with ethanol at 37°C overnight and analysed with HPLC. The results are shown in Figure 1.

It can be seen from Figure 1 that 20 % of vitamin E and 30% of vitamin A are released from the patch by 3 hours.

Claims:

1. Dermally attachable dispensing means comprising a substrate upon which is disposed an adhesive material, the adhesive material comprising a cross-linked, adhesive polymer and a plasticiser therefor, ketone groups in the adhesive being cross-linked by a polyamine cross-linking agent, the adhesive comprising plasticiser sufficient to reduce discomfort on dermal detachment, characterised in that the substance to be dispensed comprises a cosmetic agent.

2. Dispensing means according to claim 1, which is a patch or a tape.

3. Dispensing means according to claim 1 or 2, wherein the substrate is flexible and thin.

4. Dispensing means according to any preceding claim, wherein the substrate comprises a backing and a reservoir for the cosmetic agent.

5. Dispensing means according to any preceding claim, wherein the cosmetic agent is loaded in the adhesive.

6. Dispensing means according to any preceding claim, wherein the plasticiser and the cosmetic agent are the same.

7. Dispensing means according to any preceding claim, wherein the amount of plasticiser is between 17% and 200% by weight.

8. Dispensing means according to any preceding claim, wherein the adhesive is a contact adhesive.

9. Dispensing means according to any preceding claim, wherein the cosmetic agent is one used to visibly reduce or reverse the effects of ageing upon the skin.

10. Dispensing means according to any preceding claim, wherein the cosmetic agent is selected from: vitamin C, vitamin D2, vitamin D3, vitamin A, vitamin E, pro-vitamin B5, natural and synthetic ceramides, alpha hydroxyacids, and retinoids; agents altering skin pigmentation; tyrosine; essential fatty acids; tocotrienols; herb extracts; phospholipids; squalene; urea; olive oil; lauric acid; isopropyl myristate; cetyl alcohol; essential oils including tea tree oil, peppermint oil, rosemary oil, avocado oil, almond oil, palm kernel oil, babassu oil, hemp seed oil, mango seed oil, brazil nut oil, grape seed oil, jojoba oil, sandlewood oil, carrot oil, peach kernel oil, wheat germ oil, macadamia nut oil, lavender oil and eucalyptus oil; plant and herb extracts, including Aloe vera, elderflower, cucumber, witch hazel, green tea, seaweed, algae, watermelon, hawthorn flower, orchid, orange flower and seaweed; sodium hyaluronate; lanolin; glycerin; zeolites; and cocoa butter.

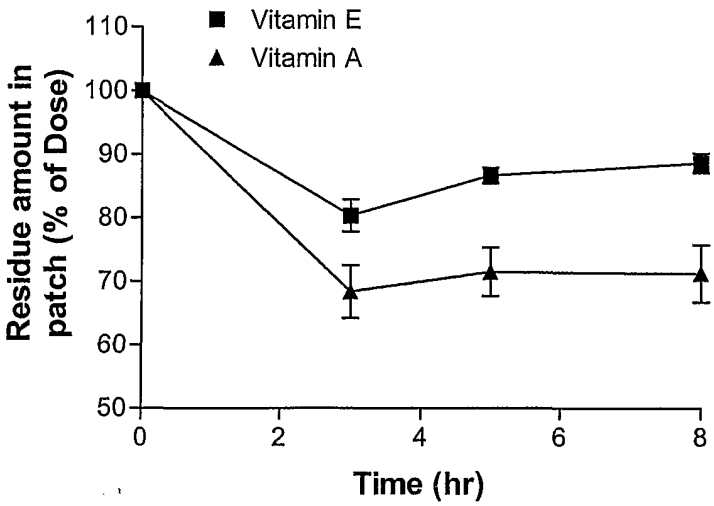
11. Dispensing means according to claim 10, wherein the cosmetic agent comprises vitamin E acetate and/or vitamin A palmitate.

12. Dispensing means according to any preceding claim, wherein the adhesive has an adhesive strength such that, when after said means has been applied to the skin, removal can be effected without removing the stratum corneum layer of the skin surface.

13. An adhesive as defined in any preceding claim, loaded with a cosmetic agent.

14. An adhesive according to claim 13, laminated between release layers.

15 A method of cosmetic treatment, said comprising applying a dispensing means or adhesive according to any preceding claim to hair or skin that it is desired to treat.



Results are expressed as the mean ± SE of 3 rabbits.

Fig. 1

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 01/03418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/00 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 44846 A (STRAKAN LIMITED) 3 August 2000 (2000-08-03) cited in the application the whole document page 11, line 3 - line 6 page 51; example 22	1-15
Y	WO 97 43325 A (E.I. DU PONT DE NEMOURS AND COMPANY) 20 November 1997 (1997-11-20) claims 1,15,16	1-22
Y	WO 99 26572 A (THERATECH, INC.) 3 June 1999 (1999-06-03) cited in the application page 11, line 4 - line 29 page 16; example 2	1-22

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"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 when the document is taken alone

"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

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 2002	16/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Benz, K

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03418

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 14822 A (OSMOTICS CORPORATION) 23 May 1996 (1996-05-23) page 5, line 1 - line 15 page 18; example 3 claims 1-5,7	1-22

INTERNATIONAL SEARCH REPORT

'ormation on patent family members

Inter nal Application No
PCT/GB 01/03418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0044846 A	03-08-2000	AU 2121600 A	18-08-2000
		EP 1165716 A1	02-01-2002
		WO 0044846 A1	03-08-2000
		NO 20013691 A	24-09-2001
WO 9743325 A	20-11-1997	AU 720670 B2	08-06-2000
		AU 2825797 A	05-12-1997
		EP 0897399 A1	24-02-1999
		JP 2000510187 T	08-08-2000
		WO 9743325 A1	20-11-1997
		US 5798426 A	25-08-1998
		ZA 9703975 A	09-11-1998
WO 9926572 A	03-06-1999	US 6180133 B1	30-01-2001
		AU 1705299 A	15-06-1999
		AU 1800099 A	15-06-1999
		WO 9926572 A1	03-06-1999
		WO 9926571 A1	03-06-1999
WO 9614822 A	23-05-1996	AU 4282096 A	06-06-1996
		CA 2204777 A1	23-05-1996
		EP 0799017 A1	08-10-1997
		JP 10508856 T	02-09-1998
		US 5968533 A	19-10-1999
		WO 9614822 A1	23-05-1996
		US 5785978 A	28-07-1998