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(54) Title: TRANSDERMAL DELIVERY OF 5-HT3 ANTAGONISTS

(57) Abstract: Adhesive dressings have adhesive comprising a cross-linked block copolymer and a plasticiser, the block copolymer having hard and soft segments, there being chemical cross-linking between the soft segments, the plasticiser being present in an amount of at least 10% by weight of the adhesive, wherein the plasticiser is a high molecular weight, oily ester, are able to carry and deliver enhanced quantities of 5-HT_3 antagonists, especially ondansetron and granisetron.

TRANSDERMAL DELIVERY OF 5-HT3 ANTAGONISTS

The present invention relates to patches for the transdermal delivery of antiemetic substances.

Nausea and vomiting are frequently the most debilitating and discouraging symptoms of medications administered to cancer patients. The side effects of emesis are not just unpleasant because of the condition, *per se*, they can lead to serious dehydration and even malnutrition.

Patients on regimens of anti-cancer drugs that have high associated emetigenic potential (*e.g.* cisplatin, streptozotocin, carmustine, procarbazine, mechlorethamine and dactinomycin) are particularly affected and, therefore, particularly benefit from aggressive, concomitant administration of antiemetic drugs to curb intractable nausea and vomiting. Other patient groups that benefit from such treatment regimens are those suffering from post-operative nausea and vomiting.

Cytotoxic chemotherapy is thought to release serotonin from certain cells of the small intestine. The released serotonin may stimulate the vagal afferent nerves through the 5-HT_3 (5-hydroxytryptamine$_3$) receptors, thus stimulating the vomiting reflex. Accordingly, it is assumed that 5-HT_3 receptor antagonistic drugs, such as ondansetron, granisetron and tropisetron, exert their effects by blocking serotonin, both peripherally, on vagal nerve terminals, and centrally, in the chemo-receptor trigger zone.

5-HT_3 receptor antagonistic antiemetics are currently administered intravenously, orally, or rectally. Intravenous administration can only be performed under medical supervision and causes significant patient discomfort, such as redness and burning, at the injection site. Problems are compounded in paediatric medicine, owing to children's dislike of needles, and there are always concerns regarding needle-stick injuries. Oral administration has disadvantages associated with its frequency (up to four times daily), as well as the issues resulting from utilisation of such a route of delivery in a patient suffering severe nausea and vomiting and patients

suffering from head and neck cancer can often not swallow properly. The pulsatile nature of oral delivery may also cause problems resulting from deviations from the therapeutic window (often responsible for side effects). Rectal delivery circumvents, to some extent only, the pulsatile nature of oral delivery and is not the most convenient, nor widely acceptable, approach to drug delivery.

Hence, there is a need for a non-oral drug delivery system capable of maintaining constant plasma levels of antiemetic agents over extended periods of time. Indeed, there are other indications for 5-HT_3 receptor antagonists that cannot currently be fully exploited, and that would benefit from more controlled delivery than that currently available.

The 5-HT_3 receptors are located primarily in peripheral and central neurons, and appear to be involved in the depolarisation of peripheral neurons, pain, and the emesis reflex. Thus, other indications include migraine, anxiety, and cognitive and psychotic disorders, and, more specifically, the treatment or prevention of depression, schizophrenia, psychosis in postnatal depression, fibromyalgic pain, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation and eating disorders, such as bulimia.

Transdermal delivery of drugs through the skin is a recognised method for maintaining relatively steady plasma levels of therapeutic agents whilst also circumventing the pain, discomfort and inconvenience of intravenous, oral and rectal drug delivery. Hence, post-chemotherapy and post-operative transdermal anti-emetigenic therapy has the potential to ease the suffering of patients who are not only experiencing nausea and vomiting, resulting from their primary therapy, but also suffering significant discomfort associated with their medical condition *per se*.

Various attempts have been made to provide successful, transdermal administration of 5-HT_3 receptor antagonists. However, the majority of patent publications on the subject simply includes the option of transdermal delivery, as one option among many, as a possible route of administration.

Similarly, various patent publications relating to specific transdermal or iontophoretic devices cite ondansetron, amongst others, for possible inclusion in these devices. US-A-5,372,819 (Minnesota Mining and Manufacturing Company) cites, amongst a large number of other compounds of numerous classes, metoclopramide and ondansetron as antiemetics for inclusion in a transdermal patch. However, there are no specific examples for any of the drugs cited that demonstrate the therapeutic potential of the device, nor which address the issues concerning the transdermal delivery of these compounds. Similarly, WO 94/07468 (Cygnus Inc.) cites granisetron and ondansetron as exemplary antiemetics in a less extensive list of compounds for inclusion in another transdermal device.

Japanese laid-open no. 8-34731 discloses percutaneous preparations of granisetron, using such formulation forms as creams, liniments, lotions, gels, tapes and patches. These formulations comprise a vehicle and a permeation enhancer, which may be selected from alcohols, fatty acids, esters of these, and others. The Examples of this publication use the skin of the hairless mouse to establish likely flux in humans. Despite the skin of these animals having about 10 fold greater permeability than human skin, it was still necessary to employ a 100 cm^2 patch. An object of the present invention is to reduce the size of patch necessary to achieve antiemetic blood plasma levels of drug.

Ondansetron is a widely used $5HT_3$ antagonist. Owing to the systemic nature of the antiemetic effect, relatively high therapeutic plasma levels of ondansetron are required to achieve efficacy. Hence, the successful transdermal delivery of a therapeutically effective amount of ondansetron requires that the transdermal device provide a relatively high flux of the drug across the skin. Such high fluxes can only be maintained over a clinically relevant time period if the drug loading within the patch is great enough to ensure that drug depletion does not reduce delivery rate with time, *i.e.* a high flux is sustained.

High drug loading in transdermal patches is generally achieved by the use of so-called 'reservoir patches'. Reservoir patches contain solutions of drug that allow higher loadings than can normally be achieved in the alternative matrix patch technology. These high drug loadings are achieved by the use of relatively high

volumes of solvents, such as ethanol or propylene glycol, which are often irritating to the skin. By virtue of the volume of their contents, reservoir patches are normally physically and visually bulky and, once applied, are not flush with the skin surface. Such attributes make them cosmetically unacceptable to many patients.

Furthermore, adherence of reservoir patches to the skin can be sub-optimal, as the adhesive is only positioned around only the periphery of the patch, which is intended to allow the drug to permeate from the central reservoir across a rate controlling membrane in contact with the skin.

By way of contrast, matrix patches have the ability to adhere to the skin much more effectively, owing to the fact that the area of adhesive in contact with the skin is coterminous with the total, effective area of the patch, thereby also securing a maximal secure interface between patch and skin. This has implications for the effective utilisation of the skin as a route of drug delivery, as well as simply ensuring that the patch remains in place.

However, the very nature of a matrix patch sets a limit on the amount of active material that can be carried by the patch, as reservoir for the drug is provided by the adhesive matrix, rather than separately. Matrix patches simply are not suitable for drugs that need to be administered in high amounts, such as ondansetron, as they cannot carry sufficient drug. For example, WO 00/47208 (Sam Yang Corporation) and EP-A-1,064,939 (Novosis Pharma AG) disclose transdermal ondansetron reservoir patches, while WO 00/47208 specifically excludes matrix patches on the grounds that the obtainable drug loading is insufficient.

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 offer relatively high drug loading, but are strongly adhesive, and can cause discomfort with repeated administration.

In WO 00/44846 we show that it is possible to provide a satisfactory medical adhesive with good cohesion, drug loading, and adhesive properties, together with low irritation, and which comprises an adhesive polymer and a plasticiser, such as

IPM (isopropyl myristate), wherein the polymer is cross-linked by a polyamine reacting with ketone groups present in the adhesive. These adhesives are suitably those of WO 99/02141, with further cross-linking. They are excellent for dermal administration of drugs, whether topical or transdermal, but it is not possible to achieve sufficiently high loading of ondansetron, for example, to be useful.

Hence, there is a need for a matrix patch capable of high loading of systemic drugs, such as ondansetron.

We have now found, surprisingly, that the use of certain plasticisers enables significantly higher loading than IPM in cross-linked, block-copolymeric adhesives, the patches being able to carry and deliver enhanced quantities of drug.

Accordingly, in a first aspect, the present invention provides an adhesive dressing, wherein the adhesive material has drug retention properties, the adhesive comprising a cross-linked block copolymer and a plasticiser, the block copolymer having hard and soft segments, there being chemical cross-linking between the soft segments, the plasticiser being present in an amount of at least 10% by weight of the adhesive, characterised in that the plasticiser is a high molecular weight, oily ester, the adhesive material being loaded with a 5-HT_3 antagonist.

Preferred dressings comprise at least sufficient 5-HT_3 antagonist such that, when positioned on skin such as to bring a substantial majority of the surface area of adhesive into contact therewith, therapeutically effective levels of antagonist are observed in the patient's bloodstream for a therapeutically useful length of time, optionally after an initial lag time. The lag time may be virtually non-existent, but is the length of time it takes for therapeutically useful levels of drug to become present, systemically.

The lag time is generally observed with patches of the invention, and is discussed in more detail below. After this time, levels of drug are maintained in the bloodstream, generally for a period in excess of 4 hours, although shorter periods, such as 30 minutes, or 1 or 2 hours, may be acceptable for certain conditions. In general, it is preferred to provide patches capable of providing long duration

administration, and to remove the patch after an appropriate length of time, as may be recommended by a skilled physician.

It will also be appreciated that a level of drug suitable for preventing emetigenesis may be higher or lower than required for treating another condition, such as depression, suitable levels being readily determined by those skilled in the art, and it may be desirable to formulate patches accordingly.

Suitable high molecular weight oily esters are preferably those that have long hydrocarbon chains, especially un(hetero)substituted alkanes or alkanoates. Straight and branched chain alkanes and alkanoates are equally preferred, and it is preferred that the total amount of carbons in the ester be at least 18, and more preferably 20. It is particularly preferred that the alkane component, in total, have at least 20 carbon atoms. There is no upper limit, other than the plasticiser be sufficiently oily to be miscible with the adhesive. As a guide, it is preferred that the carbon total not exceed 50, with a range of between 20 and 40 being preferred.

The substituted backbone is preferably a lower alkane substituted with at least two OH groups. These OH groups may be independent or form part of a COOH group in the parent molecule, at least one of the components initially possessing a COOH to form an ester with an OH on the other.

It is particularly preferred that the adhesive further comprises ketone groups cross-linked by a polyamine cross-linking agent. In its free form, the polyamine cross-linking agent has two or more free amine groups able to react with ketone groups on the polymer chains of the adhesive. The resulting cross-linking maintains the structural integrity of the adhesive while allowing the use of greater quantities of plasticiser, thereby helping to elevate drug loading, while the extra plasticiser also assists in reducing exfoliation, for example. Other benefits and of such further cross-linking, as well as further illustration, appears hereinunder.

Preferred plasticisers have two long chain alkane components, at least one of which links directly to an ester grouping. At least one of the alkane components is preferred to have at least 10 carbons and, more preferably 12 or higher. A second

alkane may be attached thereto, or may be linked to a further ester or, less preferably, an ether grouping.

Examples of suitable plasticisers include propylene glycol dipelargonate, octyldodecyl lactate, caprylic acid triglyceride, and diisostearyl malate, of which octyldodecyl lactate is particularly preferred.

Crystals in matrix patches are not desirable, and can greatly reduce adhesion, depending on their size and prevalence, and can place a substantial restriction on drug loading. It is an advantage of the present invention, with ondansetron, for example, that high loading without crystallisation is possible.

Levels of loading with plasticisers of the invention are generally at least 50% better than in the art, with improvements of 500% and more being observed with some combinations. In this respect, it will be appreciated that it is possible to combine plasticisers, such as isopropyl myristate with octyldodecyl lactate, for example. In such a situation, plasticisers of the invention should preferably comprise at least 50% of the total plasticisers present in the patch, by weight.

Dressings of the present invention are preferably in the form of bioadhesive drug delivery systems. Preferred adhesives are pressure sensitive. Suitable systems are any that may be used for the delivery of a drug *in vivo*, and wherein the patch can be removed without excessive pain or discomfort. The dressings of the invention are suitable to be removably secured at any desired location, preferably one which is not sartorially inelegant but which is effective to receive drug, without too much discomfort, such on the back, between the shoulder blades, for example.

The adhesives of the present invention have the advantage of providing good levels of adhesion so that patches or tapes will not come off before desired, but that, on removal, there is minimal pain and substantially no exfoliation.

The dressings of the present invention may take any suitable form. In general, it is preferred that they be in the form of tapes or patches. Reference to "tapes" or "patches" herein will be understood also to incorporate reference to any other style of

dressing, unless otherwise apparent, or indicated. Preferred dressings incorporate a level of flexibility.

Dressings of the present invention may be for the delivery of any 5-HT_3 antagonist, the benzimidazole/benzopyrrole family of 5-HT_3 antagonists being preferred. In particular, it is preferred to deliver drugs that require high loading and which are not suitable for oral delivery, or where benefit may be obtained from transdermal delivery, for example. Drugs such as ondansetron, granisetron, dolasetron and tropisetron are useful in the treatment of emesis, and are preferred drugs of the invention. In particular, it has not previously been possible to provide antiemetic drugs such as ondansetron in a patch, as the required loading meant that any effective patch would be too large and unwieldy. Granisetron is more potent, so that matrix patches containing it can be made, although these have been large and are not preferred. Again, use of the present invention means that small patches can now easily be provided that are easy to apply and remove, and that are just as effective, or more so, than those of the art.

Suitable antiemetic drugs for use in the present invention include; 6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-piperazinyl)benzimidazole, azasetron, dolasetron, granisetron, itasetron, ondansetron, palonosetron, ramosetron, and tropisetron, and mixtures thereof, preferably ondansetron, granisetron or tropisetron.

It will be appreciated that the present invention extends to dressings comprising 5-HT_3 receptor antagonists. Such dressings are advantageously used in the treatment and management of emesis. However, as noted above, dressings of the present invention allow consistent delivery of 5-HT_3 receptor antagonists, so that the invention further allows the prophylaxis and treatment of any one or more of the following conditions: depression, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation and eating disorders, such as bulimia. Other indications are as noted above.

It is particularly preferred that the patches of the present invention be used for the treatment and prophylaxis of emesis, and have the advantage of being able to

sustain antiemetic levels of drug in the blood for up to 24 to 48 hours and beyond, depending on formulation. Advantageously, a patch of the invention will be applied prior to the cause of the emesis, such as chemotherapy, fractionated chemotherapy, wherein the chemotherapy is administered over several days, surgery or radiotherapy, in order that antiemetic levels of drug be present in the bloodstream by the time of expected nausea. Alternatively, and less preferred, the patient may be administered with antiemetics in accordance with current practice, and only given a patch of the invention after treatment.

Patches may be applied the night before treatment, for example, in order to ensure sufficient levels of drug by the time of treatment. In addition, as levels of drug need not necessarily be as high as those achieved by individual doses, which necessarily have to peak at higher levels in order to provide an average which may be about half of the peak, patches of the invention may be applied to other patients, such as terminal cancer patients, and bone marrow transplant patients.

Replacing the intensive regimens of the art with, preferably, just one or two patches of the invention for, for example, the five day treatment period greatly enhances convenience and drug utilisation. Orally administered ondansetron and granisetron suffer from significant pre-systemic metabolism which, therefore, increases the required dose. In many patients, anticipatory emesis occurs prior to chemotherapy and has a very strong psychological aspect to it. Thus, the presence of a patch during the period prior to chemotherapy is of benefit both clinically, to raise levels of drug for treatment of acute emesis, and psychologically.

It is also a particular advantage of the patches of the invention that, not only do they bypass pre-digestion, but that the continued flux through the skin or mucous membrane allows a greater area under the graph, or persistent level of drug, so that it is not necessary for levels of drug to reach the peaks observed when using tablets. Patch formulations can then be tailored to the area under the graph desired.

It will be appreciated that, while the term "patch" is commonly used herein, this term is interchangeable with "dressing" and does not confer any specific meaning thereon.

It is an advantage of patches of the present invention that they are capable of delivering therapeutic amounts of drug across the skin over a period ranging from one to several days. In addition, preferred patches of the invention are able to deliver substantially zero order levels of drug over a period of at least a day. In this respect, by "zero order" is meant that the drug is delivered at substantially the same rate of delivery over a period of about 24 hours. It will be appreciated that rates will take an initial period to stabilise, and this initial period may take between about 40 minutes and up to several hours, depending on the patch and/or drug. This initial period, or lag time, may be reduced by permeation enhancers, for example.

Patches of the present invention are also capable of delivering drug over substantial periods of time, and certain preferred patches can deliver drug for up to 5 days, preferably at zero order rates. Other patches may be tailored for higher rates of delivery, for example, for only two or three days, or less.

Suitable backings are described hereinbelow. They may take any suitable form, and may be in the form of films or materials, for example. Films may be selected for breathability and/or their occlusive properties. It is possible to use metallised films, but it is generally preferred to use plastics, such as polyethylene terephthalate (PET). Materials may be selected from woven and non-woven, with non-wovens generally providing a greater degree of flexibility. Such materials are generally highly porous, and it is preferred to impregnate them with a drug-proofing substance and, optionally, a water-proofing substance, as well known in the art.

The adhesive is generally provided as a layer which is preferably laminated directly onto the backing, although the backing itself may be multilaminate. The adhesive is suitable to directly adhere to most backings, but it may be necessary, or desirable, in some instances, to provide further means for the adhesive to be secured to the backing, such as by a cross-linking layer.

Suitable adhesives are described in detail below, and are block copolymers having both soft and hard segments. Chemical cross-linking between the soft segments provides a large drug-loading capacity and remarkable cohesion in the

adhesive. Such adhesives are also strong, and this is tempered by the addition of 10% or more plasticiser. Such levels of plasticiser have not previously been described in effective adhesives, and it is the unique structure of the adhesives of the invention that permit such levels of plasticiser to be used. The resulting adhesive can then be removed without pain, but remains in place until removed, under conditions of reasonable care.

Levels of plasticiser are described in more detail below, but will generally be between 10 and 30% in adhesives not characterised by any further cross-linking (*infra*). Levels of plasticiser of between 10 and 20% are more preferred, especially 15 and 20%, in such adhesives.

Surprisingly, it has also been found that certain permeation enhancers are capable of substantially increasing delivery of drugs from the patches of the invention. Permeation enhancers, in general, allow greater permeation of drug into the skin, and preferred such enhancers are surfactants, or surface active agents. Compounds suitable for use as permeation agents include compounds containing at least one amide bond, esters of lactic acid, lactic acid, salts of lactic acid, dicarboxylic acids, salts of dicarboxylic acids, citric acid and salts of citric acid, O-alkyl (polyoxyethyl)phosphates and esters of higher fatty acids, terpenes, carboxylic acids of glycerin, such as glycerin monolaurate and glycerin triacetate, and ethers of polyoxyethylene and monoalcohols. Specific examples of enhancers further include lauryl di-methanol amide, polyoxyethylene lauryl ether, PEG (polyethylene glycol), liquid paraffin, Azone and vitamin E. A particularly preferred enhancer is lauric acid diethanolamide [N,N-bis(2-hydroxyethyl)dodecanamide].

Particularly preferred enhancers have at least one amide grouping. The acyl moiety is preferably a medium length, unsaturated alkyl or alkenyl, preferably alkyl, chain, containing from about 8 to about 20 carbon atoms. This may be straight or branched chain, and a length of 10 to 14 atoms is a preferred group, with lauryl being a preferred example.

The nitrogen may be unsubstituted or substituted with at least one alkyl or alkenyl, preferably alkyl, substituent. The number of carbons in the substituent may

vary between one and 20, preferably between 2 and 8, inclusive. Preferred amides have two alkyl substituents, which may be the same or different. These are preferably straight chain, and may be further substituted with at least one substituent selected from hydroxy, amine and halo, with hydroxy being preferred. Hydroxyethyl and hydroxypropyl groups are preferred, especially hydroxyethyl.

Surprisingly, it has been found that, contrary to expectation, salts of effective drugs, and especially ondansetron, are delivered significantly better than the free compounds from patches of the invention. Suitable salts may be from mineral or organic acids, with simple mineral salts, such as the hydrochlorides, nitrates, sulphates, hydrobromides and phosphates, and simple organic salts, such as the acetates, citrates, succinates, malates and oxalates being preferred. Particularly preferred drugs for delivery by patches of the invention are ondansetron hydrochloride and granisetron hydrochloride, individually.

Preferred are 5-HT_3 receptor antagonist drugs, in particular ondansetron, granisetron and tropisetron and other derivatives and mixtures thereof, as well as pharmaceutically acceptable equivalents thereof and pharmaceutically acceptable esters and the salts of such compounds with pharmaceutically acceptable acids and bases as appropriate. Equivalents of the drugs useful in the invention include enantiomers where the compound may be in more than one configuration, although it will be appreciated that those enantiomers are preferred that are specifically associated with 5-HT_3 antagonist activity, given the frequent discrepancy in activity between enantiomers. Particularly preferred compounds are ondansetron and granisetron.

In order to provide a sufficiently strong attachment to the skin, we prefer that the adhesive material is bioadhesive, and in particular that it has an adhesive strength of about 30g/inch (~1.2g/mm) to about 300 g/inch (~12g/mm), preferably, about 40g/inch (~1.6g/mm) to about 200 g/inch (~8g/mm), although the skilled person will recognise appropriate strengths. Materials with an adhesive strength greater than about 300 g/inch (~12g/mm) are likely to cause skin irritation when the patch is removed, as the outer skin layer is concomitantly removed, and should therefore be avoided for any part of the patch to be adhered to skin. The adhesive surface for

attachment to the skin may consist of one or more contact surfaces, as desired, but preferably consists of one contact surface per patch.

The copolymeric adhesive material for use in according to the present invention has drug retention properties to enable the treatment drug to be incorporated into the adhesive material. A substance having drug retention properties is taken herein as being a substance capable of absorbing, adsorbing or otherwise carrying a drug. In order to be able to deliver the drug to the area of skin to be treated, it will be appreciated that the uptake of drug needs to be at least partially reversible when *in situ*, although it is preferred that the drug not weep or otherwise exude from the tape or patch until applied to the skin.

The patch preferably comprises a drug-impermeable backing layer. Suitable examples of drug-impermeable backing layers which may be used for the 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. A preferred drug-impermeable backing material is non-woven polyethylene terephthalate (PET).

For example, for the prevention or treatment of emesis, the patch can be provided in the form of a flexible matrix that contains the drug throughout its extent, suitably for daily application. It will be appreciated that the patches can be provided in any appropriate area and shape, suitably ranging from 1 to 100 cm^2, for example an area of 10 cm^2, 25 cm^2 or 50 cm^2. If necessary, patches can be combined to deliver a therapeutic dose of drug. In one embodiment, the delivery device is in the form of a strip or sheet in which the drug is present throughout the extent of the device.

The term 'block copolymer', as used herein, refers to a macromolecule comprised of two or more chemically dissimilar polymer structures, terminally connected together (Block Copolymers: Overview and Critical Survey, Noshay and McGrath, 1977). These dissimilar polymer structures, sections or segments, represent

the 'blocks' of the block copolymer. The blocks may generally be arranged in an A-B structure, an A-B-A structure, or a multi-block -$(A-B)_n$- system, wherein A and B are the chemically distinct polymer segments of the block copolymer, the A blocks generally being the hard and the B blocks generally being the soft segments.

It is generally preferred that the block copolymer is of an A-B-A structure, especially wherein one of A and B is an acrylic-type polymeric unit. It will be appreciated that the present invention is also applicable using block copolymers which possess three or more different blocks, such as an A-B-C block copolymer. However, for convenience, reference hereinafter to block copolymers will assume that there are only A and B sub-units, but it will be appreciated that such reference also encompasses block copolymers having more than two different sub-units, unless otherwise specified.

It will be appreciated that the properties of block copolymers are very largely determined by the nature of the A and B blocks. Block copolymers commonly possess both 'hard' and 'soft' segments. A 'hard' segment is a polymer that has a glass transition temperature (T_g) and/or a melting temperature (T_M) that is above room temperature, while a 'soft' segment is a polymer that has a T_g (and possibly a T_M) below room temperature. The different segments are thought to impart different properties to the block copolymer. Without being constrained by theory, it is thought that association of the hard segments of separate block copolymer units result in physical cross-links within the block copolymer, thereby promoting cohesive properties of the block copolymer. It is particularly preferred that the hard segments of the block copolymers form such physical close associations.

The block copolymers useful in the present invention preferably are acrylic block copolymers. In acrylic block copolymers, at least one of the blocks of the block copolymer is an acrylic acid polymer, or a polymer of an acrylic acid derivative. The polymer may be composed of just one repeated monomer species. However, it will be appreciated that a mixture of monomeric species may be used to form each of the blocks, so that a block may, in itself, be a copolymer. The use of a combination of different monomers can affect various properties of the resulting block copolymer. In particular, variation in the ratio or nature of the monomers used allows properties such

as adhesion, tack and cohesion to be modulated, so that it is generally advantageous for the soft segments of the block copolymer to be composed of more than one monomer species.

It is preferred that alkyl acrylates and alkyl methacrylates are polymerised to form the soft portion of the block copolymer. Alkyl acrylates and alkyl methacrylates are thought to 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. It is preferred that the acrylic block copolymer comprises at least 50% by weight of alkyl acrylate or alkyl methacrylate (co)polymer.

A polar monomer is advantageously copolymerised with the alkyl acrylate or alkyl methacrylate, in order to enhance the drug solubility of certain, especially hydrophilic, drugs. Suitable polar monomers which can be copolymerised with alkyl acrylates or alkyl methacrylates include hydroxyethyl acrylate, hydroxypropyl acrylate, vinyl pyrrolidone, acrylamide, dimethylacrylamide, acrylonitrile, diacetone acrylamide and vinyl acetate, although others will be apparent to those skilled in the art. Diacetone acrylamide, or a combination of diacetone acrylamide and vinyl acetate, is useful as polar monomer if a drug is incorporated in the adhesive. The diacetone acrylamide component enables more advantageous drug 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 drug retention and delivery.

As stated above, variation in the components of the soft segment affects the overall properties of the block copolymer, although the essential feature remains the cross-linking of the soft segments. For example, soft segments essentially consisting of diacetone acrylamide with either butyl acrylate and/or 2-ethylhexyl acrylate, in approximately equal proportions, work well, and a ratio by weight of about 3 : 4 : 4

provides good results. 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 of the soft segment, as this can lead to reduced adhesion, for example. The acrylate component may generally be varied more freely, with good results observed with both 2-ethylhexyl acrylate and butyl acrylate together or individually.

As noted above, ratios of the various monomers are generally preferred to be approximately equal. For adhesives, this is preferred to be with a polar component of 50% or less of the soft segment, with the apolar portion forming up to about 85% w/w, but preferably between about 50 and 70% w/w. In the example above, this is about 72% (4+4) apolar to about 18% (3) polar.

As discussed above, 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. Styrene and polymethyl methacrylate have been found to be suitable for use in the formation of the hard segment of the block copolymers. 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.

The block copolymer is further characterised in that the soft portions contain a degree of chemical cross-linking. Such 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 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 cross-linking agent is tetraethylene glycol dimethacrylate. It is preferred that the 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. The block copolymer portions of the present invention 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 copolymers suitable for the present invention. An appropriate 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.

The block copolymeric adhesives of the present invention are, typically, pressure sensitive adhesives. Pressure sensitive adhesives can be applied to a surface by hand pressure and require no activation by heat, water or solvent. As such, they are particularly suitable for use in accordance with the present invention.

The block copolymers may be used without tackifiers and, as such, are particularly advantageous. However, it will be appreciated that the block copolymers may also be used in combination with a tackifier, to provide improved tack, should one be required or desired. Suitable tackifiers are well known and will be readily apparent to those skilled in the art.

Without being constrained by theory, it is thought that the combination of chemical cross-links between the soft segments of the copolymer combined with the, generally, hydrophobic interaction, or physical cross-linking, between the hard portions results in a 'matrix-like' structure. Copolymers having only physical cross-linking of the hard segments are less able to form such a matrix. It is believed that the combination of both forms of cross-linking of the block copolymers provides good internal strength (cohesion) and also, if needed, high drug storage capacity.

More particularly, it is believed that the hard segments associate to form 'islands', or nodes, with the soft segments radiating from and between these nodes. There is a defined physical structure in the 'sea' between the islands, where the soft segments are cross-linked, so that there is no necessity for extensive intermingling of the soft segments. This results in a greater cohesion of the whole block copolymer while, at the same time, allowing shortened soft segment length and still having as great, or greater, distances between the islands, thereby permitting good drug storage capacity.

The block copolymer preferably cross-links as the solvent is removed, so that cross-linking can be timed to occur after coating, this being the preferred method. Accordingly, not only can the block copolymer easily be coated onto a surface, but

the complete solution can also be stored for a period before coating. Accordingly, in the manufacturing process of the patches, the process preferably comprises polymerising the monomeric constituents of each soft segment in solution, then adding the constituents of the hard segment to each resulting solution and polymerising the resulting mix, followed by cross-linking by removal of any solvent or solvent system, such as by evaporation. If the solution is to be stored for any length of time, it may be necessary to keep the polymer from precipitating out, and this may be achieved by known means, such as by suspending agents or shaking. It may also be necessary to select the type of polymers that will be subject to substantially no cross-linking until the solvent is evaporated.

In general, it is preferred that the adhesive possesses a minimum number of functionalities having active hydrogen, in order to avoid undesirable reactions/ interactions, such as with any drug that it is desired to incorporate into the adhesive 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 given compound, such as a drug. It is also the case that, where the adhesive is not intended for medical use, restrictions on any medically undesirable function are not so severe. Where the adhesive is used as an adhesive in its own right, without carrying a drug, then it is also less of a requirement to limit active functionalities, although limiting such functionalities generally helps to reduce irritation and, so, is preferred.

Limiting active functionalities, especially those with active hydrogen, is generally preferred, 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.

We have found that it is possible to incorporate between about 10 and 20%, even up to 30%, plasticiser in the adhesives of WO 99/02141, and that the resulting adhesive still has good adhesive properties and develops good release qualities. In

these adhesives, we have found that incorporation of a plasticiser in the copolymer still provides sufficiently good cohesion and adhesion properties and low irritation, as long as the amount of plasticiser is less than about 20% w/w, preferably less than about 10% w/w, of the adhesive. Accordingly, in one embodiment, the adhesive material comprises a plasticiser in an amount of less than 20% w/w, preferably less than 10% w/w, of the adhesive.

Additional plasticisers may be selected by those skilled in the art. These should 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.

The plasticiser may be used in an amount less than 20%, preferably less than 10%, of the adhesive, unless the adhesive copolymer comprises ketone groups cross-linked by a polyamine cross-linking agent in which case the plasticiser may also be used in an amount generally between about 10 and 300%, preferably between 20 and 200% of the adhesive, more specifically between about 40% and 160%, preferably between about 60 and 120%, with about 100% generally providing good results. It will be appreciated, however, that different plasticisers will have different optima for different adhesives. Thus, in one embodiment, the plasticiser comprises between about 17% and 71% w/w, preferably between about 37% and 62% w/w, of the adhesive.

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, propylene glycol dipelargonate 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. These substances can be used either alone or as a mixture or mixtures thereof.

In WO 00/44846, incorporated herein by reference, 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 adhesive used is preferably as disclosed in WO 99/02141, incorporated herein by reference, so that there is cross-linking between soft segments and further cross-linking effected by reacting a polyamine with keto groups contained in the adhesive.

The adhesives of WO 00/44846 are particularly useful in the present invention. Accordingly, in a preferred embodiment, the copolymer of the adhesive comprises ketone groups cross-linked by a polyamine cross-linking agent.

Preferably, the adhesive material has an adhesive strength such that the patch can be applied to the skin and then removed without removing the stratum corneum layer of the skin surface. For example, preferred adhesives 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.

Furthermore, if the patch comprises a central, drug-containing portion and a peripheral, drug-free portion, one of the central and peripheral portions may be formed of an adhesive material that comprises a plasticiser and in which the copolymer comprises ketone groups cross-linked by a polyamine cross-linking agent. Thus, in one embodiment, only the central portion is formed of an adhesive material that comprises a plasticiser and in which the copolymer comprises ketone groups cross-linked by a polyamine cross-linking agent. In another embodiment, only the

peripheral portion is formed of an adhesive material that comprises a plasticiser and in which the copolymer comprises ketone groups cross-linked by a polyamine cross-linking agent.

In the embodiments above in which the copolymer comprises ketone groups cross-linked by a polyamine cross-linking agent, the 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 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.

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 polyamine cross-linked adhesive materials have been found to possess good water vapour permeabilities, which may allow the skin to breathe when the patch is in place. If such permeability is deemed unnecessary then an occlusive backing material can be used. In addition, the lack of any necessary reactive groups is useful for drug stability, and are generally susceptible to very little interaction with other materials. These adhesive copolymers, or a substantial component thereof, have 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 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.

Where the adhesive does not already possess a suitable ketone group, this 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 large amounts of plasticiser compromises cohesion. Cross-linking with a polyamine cross-linker that reacts with ketone groups enables the use of these adhesives, retaining their superior drug retention properties and allowing control of the level of adhesion, while allowing painless and irritation-free removal of the patch.

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, the currently 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 adhesive 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.

Suitable polyamines for use as cross-linking agents should have two or more free amine groups to react with the ketone moiety of the adhesive. By "free" amine groups is meant that there is at least one hydrogen substituent on the nitrogen. 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.

The polyamine cross-linking agent used in plasticised copolymer adhesives is preferably used only after partial cross-linking of the soft segments of the copolymer has been effected using an initial cross-linking agent. Suitable initial cross-linking agents 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, as previously described.

The polyamine cross-linked copolymer 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, for example, to a flat mould surface or drug-impermeable backing for the patch. The solvent can be removed as known in the art. In a preferred process, a copolymeric material comprising substantially non-enolisable ketone groups is blended with a suitable plasticiser therefor and, at the same time, or thereafter, further blended with a polyamine cross-linking agent, and the mixture allowed to complete

the cross-linking reaction. The adhesive material will normally be prepared in solution, prior to the addition of plasticiser and polyamine. Cross-linking will normally be done under conditions of heat.

It will be appreciated that there is no particular restriction on further substances being used in association with the adhesive. For example, suitable agents may be used to inhibit crystallisation of the drug in the adhesive. Many agents will be apparent to those skilled in the art, and polyethylene glycol is generally particularly effective.

The present invention will now be illustrated further with reference to the following, non-limiting Examples, in which the following conditions apply, unless otherwise stated:

Patch size: 8 mm diameter (50 mm^2)

Receptor solution:

Ethanol : water (2:8) for ondansetron salt patch

PEG 400:water (1:3) for ondansetron freebase patch

HPLC condition: Flow rate ----- 1 ml/min

Mobile ----- phosphate buffer (pH = 6) : acetonitrile (73:27)

UV detector----- 220 nm

Where units are shown as "um", it will be appreciated that this is equivalent to "μm", and where units are shown as "ug", this is equivalent to "μg".

OS - ondansetron.

The Examples are illustrated by the accompanying drawings, in which:

Figure 1 shows rate of *in vitro* permeation of ondansetron across rat skin;

Figure 2 shows the permeation of ondansetron HCl through rat skin;

Figure 3 shows the same results as Figure 2, but as % permeation;

Figure 4 shows permeation of ondansetron freebase through rat skin;

Figure 5 shows the same results as Figure 4, but as % permeation;

Figure 6 shows the permeation obtained from ondansetron HCl patches with rat skin;

Figure 7 shows the same results as Figure 6, but as % permeation;

Figure 8 shows the permeation obtained from ondansetron freebase patches with rat skin;

Figure 9 shows the same results as Figure 8, but as % permeation;

Figure 10 shows *in vitro* permeation with different thickness of ondansetron salt patch across rat skin;

Figure 11 shows the same data as Figure 10, but as % permeation;

Figure 12 shows the *in vitro* permeation obtained from ondansetron HCl patches in the presence of IPM, OL and transcutol across rat skin;

Figure 13 shows the same data as Figure 12, but as % permeation;

Figure 14 shows *in vitro* permeation obtained from ondansetron patches using different enhancers;

Figure 15 shows the same results as Figure 14, but as % permeation;

Figure 16 shows *in vitro* permeation of ondansetron from an adhesive patch using rat skin;

Figure 17 shows the same data as Figure 16, but as % permeation;

Figure 18 shows penetration of ondansetron from an adhesive patch with DPPG;

Figure 19 shows the same data as Figure 18, but as % penetration;

Figure 20 shows penetration ($\mu g/cm^2$) of ondansetron from an adhesive patch with ODO;

Figure 21 shows the same data as Figure 20, but as % penetration;

Figure 22 shows permeation of ondansetron through human skin;

Figure 23 shows the same data as Figure 22, but as % permeation;

Figure 24 shows the permeation of ondansetron through rat skin and the effect of drug concentration in the patch;

Figure 25 shows OS penetration from the patch through rat skin with or without oleic acid;

Figure 26 shows ondansetron rat skin permeation from patches with oleic acid and LD; and

Figure 27 shows ondansetron permeation with oleic acid and LD through human skin.

EXAMPLE 1

Preparation of Adhesive

Adhesives used in the following Examples were 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 of the ketone groups occurs, to form an insoluble product. Variations to step 3 are detailed in the Examples, as relevant, otherwise step 3 is performed as detailed below.

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. In the following Examples, "Adhesive A" corresponds to the adhesive prepared to this stage, either as specified in these steps, or as otherwise indicated. This adhesive was dissolved at a rate of 1.0 g *per* 2.0 g of a 2 : 5 v/v mixture of ethyl acetate and toluene, and used in the following Examples, in which weights are by dry equivalent.

Step 3:

The adhesive prepared in Step 3 is referred to as Adhesive C (Crosslinked keto groups), in the following Examples. 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 (also known as adipic acid dihydrazide – AADH) 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 200 x 200 mm. 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 200 x 200 PET film is then typically cut into strips measuring 100 x 25 mm. Other sizes are prepared accordingly.

EXAMPLE 2

Ondansetron Solubility and Patch Preparation

Solubility of ondansetron in organic solvents

The freebase form of any given compound is generally expected to diffuse across skin faster than the salt of that compound. Accordingly, ondansetron freebase was prepared from the hydrochloride. This was achieved by dissolving ondansetron hydrochloride in water, increasing the pH to 10 by the addition of sodium hydroxide, and collecting the resulting precipitate by filtration. The yield was 91% of theory. As expected, the freebase and hydrochloride behaved identically under analytical chromatographic conditions.

In order to establish the most appropriate solvent for use in patch manufacture the solubility of ondansetron hydrochloride and its freebase in several organic solvents was determined. Methanol was shown to be a good solvent for both materials. The freebase had low solubility in ethanol, acetone, ethyl acetate and isopropyl myristate (IPM).

Saturation of Ondansetron Freebase in Adhesive C

Ondansetron / Adhesive C patches with different amounts of drug (0.7 – 2.0%) were prepared, but initial results showed these to have low adhesion.

Saturation of Ondansetron Freebase in Adhesive A

Ondansetron / Adhesive A patches with different amounts of drug were prepared (Tables 1a and 1b). In these Examples, most preparative Tables are shown twice, once by weight, and the second by percentage. Acceptable adhesion and no crystallisation were observed in all cases. The amount of ondansetron was kept at ~2.5% in all Adhesive A patches. Formulation V was the most preferred of these formulations.

Table 1b Ondansetron in Adhesive A

Ingredient	Unit	I	II	III	IV	V	VI
Adhesive (solid)	mg	500	500	500	500	500	500
IPM	mg	100	100	100	250	150	100
Ondansetron	mg	20	15	10	20	17	15

Table 1b Ondansetron in Adhesive A (~% composition)

Ingredient	I	II	III	IV	V	VI
Adhesive (solid)	80.6	81.3	82.0	64.9	75.0	81.3
IPM	16.1	13.6	16.4	32.5	22.5	16.3
Ondansetron	3.2	2.4	1.6	2.6	2.5	2.4

Comparison of Ondansetron Hydrochloride and Freebase in Adhesives A and C

Ondansetron HCl and freebase had both been shown to be soluble in methanol, and patches made with both materials were prepared for comparison (Tables 2a and 2b). In the following Examples, ondansetron HCl was dissolved in methanol prior to mixing, at a rate of 0.07g of ondansetron hydrochloride in 1g of methanol. This amount of methanol can cause phase separation from the adhesive and IPM, so a further 1g of THF is added for efficient mixing.

The Adhesive C patches for both the salt and freebase showed poor adhesion (II, IV) whilst those prepared with Adhesive A showed useful adhesion (I, III). In these Tables, the only difference between Adhesives A and C lies in the presence or absence of crosslinker.

Table 2a Ondansetron HCl and freebase in Adhesive A and C

Ingredient	Unit	I	II	III	IV
Adhesive (solid)	mg	500	500	500	500
IPM	mg	200	200	200	200
Ondansetron HCl	mg	20	20	-	-
Ondansetron freebase	mg	-	-	20	20
Crosslinker*	ml	-	0.5	-	0.5

*0.1 g adipic acid dihydrazide (AADH) in 20 ml of methanol/water (15:5)

Table 2b Ondansetron HCl and freebase in Adhesive A and C (~% composition)

Ingredient	I	II	III	IV
Adhesive (solid)	69.4	69.4	69.4	69.4
IPM	27.8	27.8	27.8	27.8
Ondansetron HCl	2.8	2.8	-	-
Ondansetron freebase	-	-	2.8	2.8
Crosslinker	-	0.07	-	0.07

EXAMPLE 3

In Vitro Permeation Studies With Ondansetron Patches

Ondansetron freebase and hydrochloride patches were prepared as shown in Table 3, using Adhesive A. Unless otherwise indicated, Adhesive A was used in the following Examples.

Table 3 Ondansetron HCl and freebase in Adhesive A

Ingredient	Unit	HCl salt	freebase
Adhesive (solid)	mg	500	500
IPM	mg	200	150
Ondansetron HCl*	mg	20	-
Ondansetron freebase*	mg	-	17

*ondansetron HCl and freebase were dissolved in methanol, then mixed with the adhesive solution.

In vitro permeation of ondansetron across rat (Wistar) skin from the two formulations (8 mm diameter discs) of Table 3 is shown in Figure 1, where permeation is given in $\mu g/cm^2$ of ondansetron from adhesive patches through rat skin (mean ± SE of 2 rats; n=6). The methodology was as described by Keith R. Brain, Kenneth A. Walters and Adam C. Watkinson [Methods for studying percutaneous penetration. In Dermatological and Transdermal Formulations. Kenneth A. Walters (Ed.), Drugs and the Pharmaceutical Sciences, 119, pp 197-269, (2002) Marcel Dekker (NY)]. These results demonstrate that, surprisingly, the greater flux was achieved from the patch containing the salt. This difference in flux was not attributable to the slight difference in concentration of ondansetron in the patches. In addition, during patch preparation, patches made with the salt were also easier to prepare than those containing the freebase.

EXAMPLE 4

Development of ondansetron Adhesive patch

The patches of Example 3 were associated with some crystallisation. Accordingly, ondansetron patches were prepared with various oils, replacing IPM. *In vitro* skin permeation studies were conducted with these patches.

Seven oils, used in cosmetic formulations in Japan, were tested for compatibility with the Adhesive. These were diisostearyl malate, neopentyl glycol dioctanoate, octyldodecyl lactate, triethylhexanoin, cetyl 2-ethtyl hexanoate, 2-octyldodecyl myristate and jojoba oil. Of these, only octyldodecyl lactate (OL) and diisostearyl malate (DM) appeared significantly compatible with the Adhesive.

In order to improve adhesion, a small amount of crosslinker was added (about 40% of normal for Adhesive C). The saturation of ondansetron freebase and salt in Adhesive with each of IPM, OL and DM, was examined. The maximum amount of ondansetron freebase and salt that was attainable in the patch with the levels of oil used was 1.7% (Table 4b). Although both OL and DM are more polar than IPM, neither appeared to increase the loading of ondansetron in the patch.

Table 4a Ondansetron HCl and freebase in Adhesive A

Ingredient	Unit	HCl salt	freebase
Adhesive (solid)	mg	500	500
IPM, OL or DM	mg	200	200
Ondansetron HCl[a]	mg	12	-
Ondansetron freebase[a]	mg	-	12
Crosslinker solution[b]	ml	0.2	0.2

a. Ondansetron HCl and freebase were dissolved in methanol, then mixed with adhesive solution.

b. 0.1g AADH in 20 ml of methanol/water (15:5)

Table 4b Ondansetron HCl and freebase in Adhesive A and C (~% composition)

Ingredient	HCl salt	freebase
Adhesive (solid)	70.1	70.1
IPM, OL or DM	28.1	28.1
Ondansetron HCl	1.7	-
Ondansetron freebase	-	1.7
Crosslinker	0.14	0.14

Results of a rat skin permeation experiment with ondansetron HCl and freebase patches containing IPM, OL and DM are shown in Figures 2 to 5.

Figure 2 shows the permeation of ondansetron HCl through rat skin ($\mu g/cm^2$ mean±SE of 2 rats; n = 4).

Figure 3 shows the same results, but as % permeation.

Figure 4 shows permeation of ondansetron freebase through rat skin ($\mu g/cm^2$ mean±SE of 2 rats; n = 4).

Figure 5 shows the results of Figure 4, but as % permeation.

The highest flux of ondansetron was observed from patches containing Ondansetron HCl and octyldodecyl lactate. After 24 hours, 18%, 25% and 7.2% of drug had permeated from patches containing IPM, OL and DM respectively.

EXAMPLE 5

Effect of Enhancers on Flux

A combination of OL and each of the enhancers pirotiodecane (HPE-101, Hisamitsu, Japan) and lauric acid diethanolamide (LD), separately, on patch preparation and flux, was examined (Tables 5a and 5b).

Table 5a Ondansetron HCl and freebase in Adhesive A

Ingredient	Unit	3% HPE	5% HPE	5% LD	control
Adhesive (solid)	mg	500	500	500	500
OL	mg	200	200	200	200
Ondansetron HCl or freebase	mg	12	12	12	12
HPE-101	mg	20	40	-	-
LD	mg	-	-	40	-
Crosslinker solution[b]	ml	0.2	0.2	0.2	0.2

a. Ondansetron HCl and freebase were dissolved in methanol, then mixed with adhesive solution.

b. 0.1g AADH 20 ml of methanol/water (15:5)

Table 5b Ondansetron HCl and freebase in Adhesive A (~% composition)

Ingredient	3% HPE	5% HPE	5% LD	control
Adhesive (solid)	68.2	66.4	66.4	70.1
OL	27.3	26.6	26.6	28.1
Ondansetron HCl or freebase	1.6	1.6	1.6	1.7
HPE-101	2.7	5.3	-	-
LD	-	-	5.3	-
Crosslinker solution[b]	0.1	0.1	0.1	0.1

Figure 6 shows the permeation ($\mu g/cm^2$) from ondansetron HCl patches.

Figure 7 shows the same results as Figure 6, but as % permeation.

Figure 8 shows permeation ($\mu g/cm^2$) from ondansetron freebase patches.

Figure 9 shows the same results as Figure 8, but as % permeation.

As can be seen from the Figures, when patches are made with the freebase,

HPE-101 provides a greater flux than patches with no enhancer, but the flux appears to be independent of concentration of enhancer. However, it is clear that LD has a significantly greater effect on flux than HPE-101.

Effect of Patch Thickness

The effect of both OL and LD in a thin (130 μm) patch and a thick (>600 μm) patch was investigated. It was noteworthy that the flux through the skin was unaffected by patch thickness (Figure 10), but it could be inferred that levels of flux would continue for longer with the thicker patch (Figure 11). The results shown in Figure11 illustrate the accentuating effect of increased loading due to increased patch thickness.

Figure 10 shows *in vitro* permeation ($\mu g/cm^2$) with different thickness of ondansetron salt patch.

Figure 11 shows the same data as Figure 10, but as % permeation.

EXAMPLE 6

Solubility of ondansetron salt and freebase in several oils

The relative solubility of ondansetron HCl and freebase in several oils (IPM, PEG, OL, transcutol, tea tree oil) was examined. As shown in Table 6, ondansetron salt and freebase are both reasonably soluble in transcutol (~4 mg/ml). In addition, ondansetron HCl was also soluble in OL and in tea tree oil.

Table 6

Solubility of ondansetron in oils

	IPM (2.5ml)	PEG 600 (2.5ml)	PEG 400 (2.5 ml)	OL (2.5ml)	Transcutol (2.5 ml)	Tea tree oil (2.5 ml)
10 mg ondansetron HCl	insoluble	insoluble	insoluble	most soluble	soluble (saturated)	a little soluble
10 mg ondansetron freebase	insoluble	insoluble	insoluble	No test	soluble (saturated)	insoluble

Transcutol and tea tree oil in Adhesive C

Placebo patches were prepared by replacing IPM with transcutol. The patch containing transcutol showed good crosslinking and suitable adhesion. It has previously been reported that tea tree oil might increase the solubility of poorly soluble drugs. However, because it is a mixture of volatile oils, volatilisation was a likely consequence of the heating required during patch preparation. Indeed, 10% loss of tea tree oil was found at room temperature after 20 min, and 30% loss was observed after exposure at 50°C for 20 minutes.

Comparison of skin penetration of ondansetron from Adhesive patch with various oils

The concentration of ondansetron HCl in Adhesive C was raised by using various oils, as shown in Table 7. Although the adhesive is referred to as Adhesive C, it will be appreciated that, as with all Examples herein, the adhesive is effectively defined by the presence or absence of crosslinker. A typical example of Adhesive C has the amount of crosslinker defined in Step 3 of Example 1, above, while the adhesives in this and other Examples have substantially less (~60% less) crosslinker although, when crosslinker is added, the heat treatment steps of Step 3 are applied.

These adhesives may alternatively be considered to be Adhesive A with extra crosslinker.

Table 7a Ondansetron HCl and freebase in Adhesive

	Unit	Transcutol	IPM	OL
Adhesive A (solid)	mg	500	500	500
Transcutol	mg	300	-	-
IPM	mg	-	200	-
OL	mg	-	-	300
OS HCl	mg	22	12	22
AADH solution	ml	0.2	0.2	0.2

AADH solution: 0.1g AADH in the 19.9g of mixture solution of water and methanol (1:3).

The OS content was close to saturation in each plasticiser.

Table 7b Ondansetron HCl and freebase in Adhesive (~% composition)

	Transcutol	IPM	OL
Adhesive A (solid)	60.8	70.1	60.8
Transcutol	36.5	-	-
IPM	-	28.1	-
OL	-	-	36.5
OS HCl	2.7	1.7	2.7
AADH solution	0.1	0.1	0.1

The penetration of ondansetron from patches in the presence of IPM, OL and transcutol was examined. As shown in Figure 12, ondansetron HCl exhibited a higher permeation in the presence of OL than the other oils. Figure 13 shows that the percentage permeation using IPM was the same but, because greater loading is possible with OL, the overall flux is improved when using OL.

Figure 12 shows the in vitro permeation ($\mu g/cm^2$) from ondansetron HCl patches in

the presence of IPM, OL and transcutol (mean ± SE of 2 rats; n = 4).

Figure 13 shows the same data as Figure 12, but as % permeation.

EXAMPLE 7

Comparison of other Penetration Enhancers

As the highest loading and penetration rate was observed with the ondansetron HCl patch containing OL, ondansetron HCl patches containing OL and 3% of one of several other different potential enhancers [oleic acid, glycerol monooleate (GO) and lauric acid diethanolamide (LD)] were examined. The patches were made in accordance with Table 8, below. The presence of crosslinker permits greater amounts of oil to be used than in standard Adhesive A, thereby also permitting greater loading of ondansetron HCl.

Table 8a Ondansetron Adhesive patch with enhancers

Ingredient	Unit	LD	Oleic acid	GO	Control
Adhesive	mg	500	500	500	500
OL	mg	400	400	400	400
Ondansetron[a] HCl	mg	55	55	55	55
LD	mg	30	-	-	-
Oleic acid	mg	-	30	-	-
GO	mg	-	-	30	-
Crosslinker solution[b]	ml	0.4	0.4	0.4	0.4

a. ondansetron HCl was dissolved in methanol, then mixed with the adhesive solution

b, 0.1g AADH was dissolved in 20 ml of methanol/water (15:5)

Table 8b Ondansetron Adhesive patch with enhancers (~% composition)

Ingredient	LD	Oleic acid	GO	Control
Adhesive	50.7	50.7	50.7	50.7
OL	40.5	40.5	40.5	40.5
Ondansetron HCl	5.6	5.6	5.6	5.6
LD	3.0	-	-	-
Oleic acid	-	3.0	-	-
GO	-	-	3.0	-
Crosslinker solution	0.2	0.2	0.2	0.2

Once again, and as shown in Figures 14 and 15, LD showed a much greater enhancing effect on ondansetron flux than the other two enhancers.

Figure 14 shows *in vitro* permeation *($\mu g/cm^2$)* results with ondansetron patches using different enhancers (mean + S.E. of 2 rats; n = 3).

Figure 15 shows the same results as Figure 14, but as % permeation.

EXAMPLE 8

Loading of Ondansetron HCl in Adhesive C with Different Oils

The maximum concentration of ondansetron HCl that can be incorporated into an Adhesive C patch with octyldodecyl lactate (OL), propylene glycol dipelargonate (DPPG) or caprylic/capric triglyceride (ODO) was established, and turned out to be approximately 11-12%, when using the amounts of oil shown in Tables 9a and 9b, below.

Table 9a Saturation of ondansetron salt in Adhesive patch with various oils

Ingredient	Unit	OL	DPPG	ODO
Adhesive A	mg	500	500	500
OL	mg	400	-	-
DPPG	mg	-	300	-
ODO	mg	-	-	300
Ondansetron HCl[a]	mg	130	110	100
Crosslinker[b]	ml	0.4	0.4	0.4

a. ondansetron HCl was dissolved in methanol, then mixed with adhesive solution

b. 0.1g AADH was dissolved in 20 ml of methanol/water (15:5)

Table 9b Saturation of ondansetron salt in Adhesive patch with various oils (%)

Ingredient	OL	DPPG	ODO
Adhesive A	48.4	54.8	55.4
OL	38.8	-	-
DPPG	-	32.9	-
ODO	-	-	33.3
Ondansetron HCl	12.6	12.1	11.1
Crosslinker	0.2	0.2	0.2

To improve permeation further, the higher loading of the OL patches was combined with the use of LD as a penetration enhancer and an *in vitro* permeation study was conducted using the patches described in Table 10. Figures 16 and 17 show the results and illustrate that using a high loading in tandem with 3 and 5% LD produces high fluxes of ondansetron.

Table 10a Ondansetron HCl in OL/LD patches

Ingredient	Unit	Control	3% LD	5% LD
Adhesive	mg	500	500	500
OL	mg	400	400	400
Ondansetron HCl[a]	mg	130	130	130
LD	mg	-	30	55
Crosslinker[b]	ml	0.4	0.4	0.4

a, ondansetron was dissolved in methanol, then mixed with adhesive solution.

b, 0.1g AADH was dissolved in 20 ml of methanol/water (15:5).

Table 10b Ondansetron HCl in OL/LD patches (%)

Ingredient	Control	3% LD	5% LD
Adhesive	48.4	47.1	46.0
OL	38.8	37.7	36.8
Ondansetron HCl[a]	12.6	12.2	12.0
LD	-	2.8	5.1
Crosslinker[b]	0.2	0.2	0.2

Figure 16 shows *in vitro* permeation ($\mu g/cm^2$) of ondansetron from adhesive patch.

Figure 17 shows the same data as Figure 16, but as % permeation.

Ondansetron HCl patches with DPPG and ODO in the presence or absence of LD were prepared and the *in vitro* skin permeation examined. In these studies, the ondansetron HCl patch with OL/LD was also used as a reference.

As shown in Figures 18 to 21, similar penetration results with DPPG/LD and ODO/LD were observed. However, permeation of ondansetron from the OL/LD patch was greater than from patches with DPPG or ODO.

Figure 18 shows penetration ($\mu g/cm^2$) of ondansetron from an adhesive patch with DPPG.

Figure 19 shows the same data as Figure 18, but as % penetration.

Figure 20 shows penetration ($\mu g/cm^2$) of ondansetron from an adhesive patch with ODO.

Figure 21 shows the same data as Figure 20, but as % penetration.

EXAMPLE 9

Human skin permeation studies with ondansetron HCl patch

In the foregoing Examples, the effects of various oils were investigated. Octyldodecyl lactate showed the most significant effects on the permeation of ondansetron HCl, especially in the presence of lauric acid diethanolamide (LD). Accordingly, this combination was used in *in vitro* human skin permeation studies. An irritation study was also conducted in the rabbit model. The patch formulations are shown in Tables 11a and 11b.

Table 11a Compositions of ondansetron salt patches

Ingredient	Unit	Control	3% LD	5% LD
Adhesive	mg	500	500	500
OL	mg	400	400	400
Ondansetron HCl[a]	mg	130	130	130
LD	mg	-	30	55
Crosslinker solution[b]	ml	0.4	0.4	0.4

a, ondansetron HCl was dissolved in methanol, then mixed with adhesive solution.

b, 0.1g AADH was dissolved in 20 ml of methanol/water (15:5)

Table 11b Compositions of ondansetron salt patches (%)

Ingredient	Control	3% LD	5% LD
Adhesive	48.4	47.1	46.0
OL	38.8	37.7	36.8
Ondansetron HCl	12.6	12.2	12.0
LD	-	2.8	5.1
Crosslinker	0.2	0.2	0.2

Human skin: 2 donors

Figure 22 shows permeation ($\mu g/cm^2$) of ondansetron through human skin (expressed as the mean $\pm$ SE of 2 donors n = 4).

Figure 23 shows the same data as Figure 22, but as % permeation.

As can be seen in Figures 22 and 23, penetration of ondansetron through human skin from the formulation containing 5% LD was the greatest (as predicted by earlier rat data). Indeed, the formulation containing 5% LD showed a synergistic effect with OL, as the flux was several times greater than that achieved with 3% LD.

The lag time associated with the permeation was longer, and the overall degree of permeation was lower, than through rat skin (*c.f.* Figures 18 – 21). However, this is in accordance with the known differences between the permeability of skin from the two species.

EXAMPLE 10

In Vitro Permeation Studies with Different Concentrations of Ondansetron HCl

In order to further examine the saturation of ondansetron salt in Adhesive C, permeation studies were carried out with different amounts of ondansetron in the patches. The compositions of the patches are shown in Tables 12a and 12b.

Table 12 Composition of ondansetron salt patch with different amount of drug

Ingredient	Unit	12% OS	8% OS	5% OS	3% OS
Adhesive	mg	500	500	500	500
OL	mg	400	400	400	400
Ondansetron HCl[a]	mg	130	80	50	30
LD	mg	55	54	52	50
Crosslinker solution[b]	ml	0.4	0.4	0.4	0.4

a. ondansetron HCl was dissolved in methanol, then mixed with adhesive solution.

b. 0.1g AADH was dissolved in 20 ml of methanol/water (15:5).

Table 12b Composition of ondansetron salt patch with different amount of drug (%)

Ingredient	12% OS	8% OS	5% OS	3% OS
Adhesive	46.0	48.3	49.8	50.9
OL	36.8	38.6	39.8	40.7
Ondansetron HCl	12.0	7.7	5.0	3.1
LD	5.1	5.2	5.2	5.1
Crosslinker	0.2	0.2	0.2	0.2

Figure 24 shows the permeation ($\mu g/cm^2$) of ondansetron through rat skin and the effect of drug concentration in the patch. Results are expressed as the mean $\pm$ SD of 2 rats (n = 3).

It is clear from Figure 24 that the penetration of ondansetron was, to a large extent, dependent on the amount of drug in the formulation.

EXAMPLE 11

Skin Irritation Studies With OL/LD Ondansetron HCl Patch

Based on the above permeation studies, the OL/LD combination appears to markedly increase the skin penetration of ondansetron. OL is extensively used in cosmetic formulations, and LD has been used in an ointment formulation (OTC product, Meiji Pharmaceutical LTD, Japan) at a concentration of 3%. In some of the current patch formulations, high concentrations of OL (~39%) and LD (~5%) have been used. Therefore, skin irritation studies with these two additives in adhesive patches were conducted.

In this study, OL and OL/LD patches were used for the irritation test, and an Adhesive C patch with IPM was used as a control reference.

Animals:	Japanese White rabbit x 4 (male, body weight 3~4 kg)
Test materials:	(1) Adhesive C patch with IPM (2) Adhesive C patch with OL (3) Adhesive C patch with OL and 3% LD (4) Adhesive C patch with OL, 5% LD
Patch size:	20 mm of diameter

Four rabbits were used, and each test material was applied in one site of each rabbit. The irritation was evaluated according to Draize criteria.

Similar results were observed with Adhesive C containing OL and IPM. With 3% and 5% LD, irritation was only slightly higher than the control patch (1.4 and 1.8 *v.* 1.0, respectively).

EXAMPLE 12

Skin Irritation Studies With Ondansetron Patch

The data from Example 11 were inconclusive. Therefore, further work was conducted to determine whether LD causes irritation.

Animals: Japanese White rabbit x 4 (male, body weight 2 ~ 2.5 kg)

Test materials: 12% ondansetron patch with 3% LD
12% ondansetron patch without LD
Adhesive C with IPM

Patch size: 20 mm diameter

Four rabbits were used and each test material was applied to two sites on each rabbit.

Irritation evaluation: The irritation was evaluated according to the Draize scale and all test patches exhibited slight skin irritation (Table 1). The value of the irritation response was lower for the ondansetron patches than for Adhesive C alone.

EXAMPLE 13

Ondansetron Penetration In The Presence Of Oleic Acid

Ondansetron HCl patches with 5% and 10% oleic acid were prepared. The adhesion was significantly reduced with oleic acid, but *in vitro* permeation studies were performed. The patches were made in accordance with Table 13, below.

Table 13

	Unit	control	+5% oleic acid	+10% oleic acid
Adhesive A (solid)	g	0.5	0.5	0.5
OL	g	0.4	0.4	0.4
OS HCl	g	0.13	0.13	0.13
Oleic acid	g	-	0.055	0.12
AADH solution	ml	0.4	0.4	0.4

AADH solution: 0.1g AADH in 19.9g of mixture of water and methanol (1:3).

12% OS patches can show some crystallisation, but this does not appear to affect permeation behaviour, either before and after several months storage, the values at these times being similar.

A marked enhancing effect was observed with oleic acid (Figure 25). With higher concentration, lag time appears to be reduced, but overall flux, after 24 hours, is substantially equal for both concentrations. From these data, oleic acid may have a similar enhancing effect to 3% LD on ondansetron penetration. Oleic acid has a lower skin irritation than LD, and provides an alternative thereto.

Figure 25 shows OS penetration from the patch through rat skin with or without oleic acid. Results are expressed as the mean $\pm$ S.E. of 2 rats (n = 4).

Ondansetron patches with 5% oleic acid and 5% LD were used for permeation studies (Tables 14a and 14b). All experiments were compared with oleic acid or LD alone.

Table 14a Composition of ondansetron salt patch with different amount of drug

Ingredient	Unit	5% oleic acid	5% oleic acid/5% LD	5% LD
Adhesive	mg	500	500	500
OL	mg	400	400	400
Ondansetron HCl	mg	130	130	130
LD	mg	-	60	55
Oleic acid		55	60	-
Crosslinker solution[a]	ml	0.2	0.2	0.2

a. 0.1g AADH was dissolved in 20 ml of methanol/water (15:5).

Table 14b Composition of ondansetron salt patch with different amount of drug (%)

Ingredient	5% oleic acid	5% oleic acid/5% LD	5% LD
Adhesive	46.0	43.4	46.0
OL	36.8	34.8	36.8
Ondansetron HCl	12.0	11.3	12.0
LD	-	5.2	51
Oleic acid	5.1	5.2	-
Crosslinker	0.1	0.1	0.1

Figure 26 clearly demonstrates that the addition of oleic acid to a system comprising OL and LD results in further enhancement of permeation of ondansetron.

Figure 26 shows ondansetron rat skin permeation from patches with oleic acid and LD. Results are expressed as the mean $\pm$ S.E. of 2 rats (n = 4).

Permeation of ondansetron across human skin was also evaluated using these formulations (Figure 27) and the same pattern of results observed, although the difference between the formulations was less significant.

Figure 27 shows ondansetron permeation with oleic acid and LD through human skin. Results are expressed as the mean ± S.E. of 2 donors (n = 4).

EXAMPLE 14

Stability

The composition of ondansetron LD/oleic acid patches are as shown in Table 1. A good preparation process was found to be:

1) Dissolve ondansetron HCl, LD and oleic acid in methanol;
2) Add crosslinker solution and tetrahydrofuran (THF);
3) Add OL and Adhesive A, mix for 15 min;
4) Coat the mixed adhesive solution onto the PET backing; and
5) Dry at 90 °C for 5 min, and keep at 65°C overnight.

Two layers of adhesive were coated onto a PET backing and the release liner, respectively. After drying at 90°C for 5 minutes, these were laminated together and kept at 65°C overnight.

Other crosslinkers were tested in place of AADH [diaminododecane, bis(hexamethylene)triamine, cyclohexanediamine and bis(aminomethyl)cyclohexane]. Whilst these were useful, it was found that AADH yielded the best adhesion properties in the final product.

The chemical stability of ondansetron in the patch was evaluated by storing at 60°C for three weeks. No change in ondansetron content was observed. The results of this test indicate that the patches will be stable for at least 2 ~ 3 years at room temperature.

EXAMPLE 15

Conclusions on Preferred Patches

Table 15 illustrates currently preferred patch formulations and certain properties associated therewith, as derived from the foregoing Examples.

Table 15

Content	**Ondansetron patch**
Composition *Drug* *Plasticiser* *Enhancer* *Crosslinker*	 11.3% OS 34.8% OL 5% LD/5% oleic acid 0.09% AADH
In vitro permeation studies using rat skin	Flux: 24 ug/cm^2/hr
Human skin studies	Flux: 4 – 6 ug/cm^2/hr
Stability studies	Stable at 60°C for 21 days

CLAIMS:

1. An adhesive dressing, wherein the adhesive material has drug retention properties, the adhesive comprising a cross-linked block copolymer and a plasticiser, the block copolymer having hard and soft segments, there being chemical cross-linking between the soft segments, the plasticiser being present in an amount of at least 10% by weight of the adhesive, characterised in that the plasticiser is at least one high molecular weight, oily ester, the adhesive material being loaded with a 5-HT_3 antagonist.

2. A dressing according to claim 1, wherein the adhesive has a surface area and comprises at least sufficient 5-HT_3 antagonist such that, when positioned on the skin of a person in need thereof so as to bring a substantial majority of the surface area of adhesive into contact therewith, therapeutically effective levels of antagonist are observable in the patient's bloodstream for a therapeutically useful length of time, after a lag time.

3. A dressing according to claim 2, wherein the length of time is in excess of 4 hours.

4. A dressing according to any preceding claim, wherein the high molecular weight oily ester have at least 18 carbon atoms therein, and comprise hydrocarbon chains selected from the group consisting of straight and branched chain alkanes and alkanoates.

5. A dressing according to claim 4, wherein the total amount of carbons in the at least one ester is at least 20.

6. A dressing according to claim 4 or 5, wherein the total amount of carbons in the alkane component is at least 20.

7. A dressing according to claim 4, 5, or 6, wherein the total amount of carbons in the ester does not exceed 50.

8. A dressing according to claim 4, 5, or 6, wherein the total amount of carbons in the ester is between 20 and 40, inclusive.

9. A dressing according to any of claims 4 to 8, wherein the substituted backbone is a lower alkane substituted with at least two OH groups.

10. A dressing according to claim 9, wherein the OH groups may be independent or form part of a COOH group in the parent molecule, at least one of the components initially possessing a COOH to form an ester with an OH on the other.

11. A dressing according to any preceding claim, wherein the oily ester is selected from the group consisting of propylene glycol dipelargonate, octyldodecyl lactate, caprylic acid triglyceride, and diisostearyl malate.

12. A dressing according to claim 11, wherein the oily ester is octyldodecyl lactate.

13. A dressing according to any preceding claim, in the form of a tape or patch.

14. A dressing according to any preceding claim, wherein the 5-HT_3 antagonist is selected from the benzimidazole/benzopyrrole family of 5-HT_3 antagonists.

15. A dressing according to claim 14, wherein the 5-HT_3 antagonist is selected from the group consisting of: 6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-piperazinyl)benzimidazole, azasetron, dolasetron, granisetron, palonosetron, itasetron, ondansetron, ramosetron, and tropisetron, and mixtures thereof.

16. A dressing according to claim 15, wherein the 5-HT_3 antagonist is ondansetron.

17. A dressing according to claim 15, wherein the 5-HT_3 antagonist is granisetron.

18. A dressing according to any preceding claim, for the treatment or prophylaxis of emesis.

19. A dressing according to any preceding claim, for co-administration with cisplatin, streptozotocin, carmustine, procarbazine, mechlorethamine and/or dactinomycin.

20. A dressing according to any preceding claim, for the treatment or prophylaxis of a condition selected from the group consisting of: migraine, anxiety, cognitive and psychotic disorders, depression, schizophrenia, psychosis in postnatal depression, fibromyalgic pain, irritable bowel syndrome, alcoholism, obstructive sleep disturbed breathing, motion sickness, loss of cognitive function, urinary incontinence, dyskinesia, systemic lupus erythematosus, drug-induced pruritus, premature ejaculation and eating disorders.

21. A dressing according to any preceding claim, adapted to sustain antiemetic levels of 5-HT_3 antagonist in the blood for 48 hours, or greater.

22. A dressing according to any preceding claim, wherein the dressing comprises between 10% and 30% oily ester, by weight of the adhesive.

23. A dressing according to claim 22, wherein the dressing comprises between 10 and 20% oily ester.

24. A dressing according to claim 22, wherein the dressing comprises between 15 and 20% oily ester.

25. A dressing according to any preceding claim, wherein the adhesive further comprises ketone groups cross-linked by a polyamine cross-linking agent.

26. A dressing according to claim 25, wherein the polyamine is selected from the group consisting of: diethylene triamine, bishexamethylene triamine, adipic acid dihydrazide, 1,6-diaminohexane and 1,12-diaminododecane, and mixtures thereof.

27. A dressing according to claim 25 or 26, wherein the dressing comprises between 10 and 300% oily ester, by weight of the adhesive.

28. A dressing according to claim 27, wherein the dressing comprises between 20 and 200% oily ester.

29. A dressing according to claim 27, wherein the dressing comprises between 40 and 160% oily ester.

30. A dressing according to claim 27, wherein the dressing comprises between 60 and 120% oily ester.

31. A dressing according to claim 27, wherein the dressing comprises about 100% oily ester.

32. A dressing according to any preceding claim, wherein the adhesive further comprises a permeation agent.

33. A dressing according to claim 32, wherein the permeation agent is selected from the group consisting of: compounds containing at least one amide bond, esters of lactic acid, lactic acid, salts of lactic acid, dicarboxylic acids, salts of dicarboxylic acids, citric acid, salts of citric acid, O-alkyl (polyoxyethyl)phosphates, esters of higher fatty acids, terpenes, carboxylic acids of glycerin, ethers of polyoxyethylene and monoalcohols, and mixtures thereof.

34. A dressing according to claim 32, wherein the permeation agent is selected from the group consisting of: lauryl di-methanol amide, polyoxyethylene lauryl ether, PEG (polyethylene glycol), liquid paraffin, Azone and vitamin E.

35. A dressing according to claim 32, wherein the permeation agent is N,N-bis(2-hydroxyethyl)dodecanamide.

36. A dressing according to any preceding claim, wherein the 5-HT_3 antagonist is in the form of a salt.

37. A dressing according to claim 36, wherein the salt is a simple mineral salt.

38. A dressing according to claim 36, wherein the salt is a hydrochloride.

39. A dressing according to claim 36, wherein the salt is ondansetron hydrochloride.

40. A dressing according to claim 36, wherein the salt is granisetron hydrochloride.

41. A dressing according to any preceding claim, which has an adhesive area of between 1 and 100 cm^2.

42. A dressing according to claim 41, which has an adhesive area of between 10 cm^2 and 50 cm^2.

43. A dressing according to any preceding claim, wherein the adhesive is a layer laminated onto a backing.

44. A dressing according to any preceding claim, comprising a semi-occlusive backing.

45. A dressing according to any preceding claim, capable of delivering effective amounts of drug for a continuous period of 5 days.

46. A method for the treatment of emesis in a patient in need thereof, comprising applying a dressing according to any preceding claim to the skin of the patient.

47. A method according to claim 46, wherein the dressing is applied prior to administering emetigenic therapy.

48. A method according to claim 46, wherein the dressing is applied after administering emetigenic therapy.

49. A method according to any of claims 46 to 48, wherein the medication is selected from the group consisting of: chemotherapy, fractionated chemotherapy, surgery and radiotherapy.

50. A method for the treatment of emesis in a patient in need thereof, comprising applying a dressing according to any of claims 1 to 45 to the skin of the patient, the patient being selected from the group consisting of: terminal cancer patients and bone marrow transplant patients.

51. The method of claim 47, wherein the dressing is applied the night before administration of the emetigenic therapy.

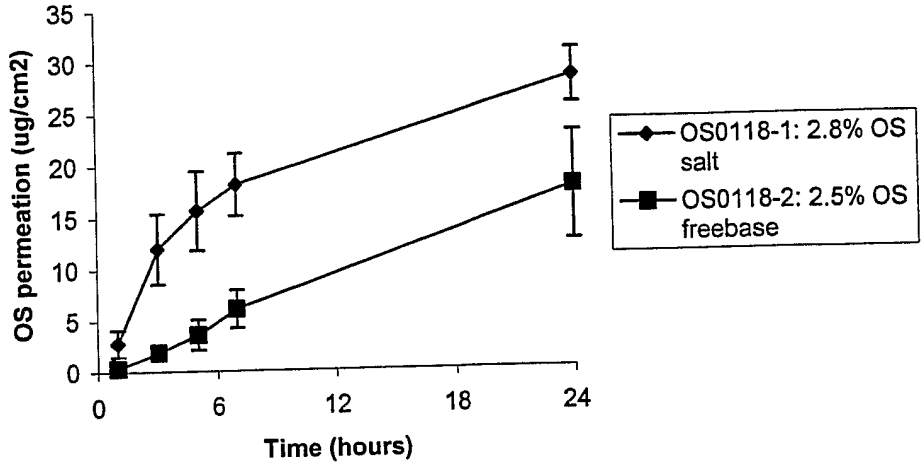
OS permeation (ug/cm2)
35
30
25
20
15
10
5
0
0
6
12
18
24
Time (hours)
OS0118-1: 2.8% OS salt
OS0118-2: 2.5% OS freebase

Fig. 1

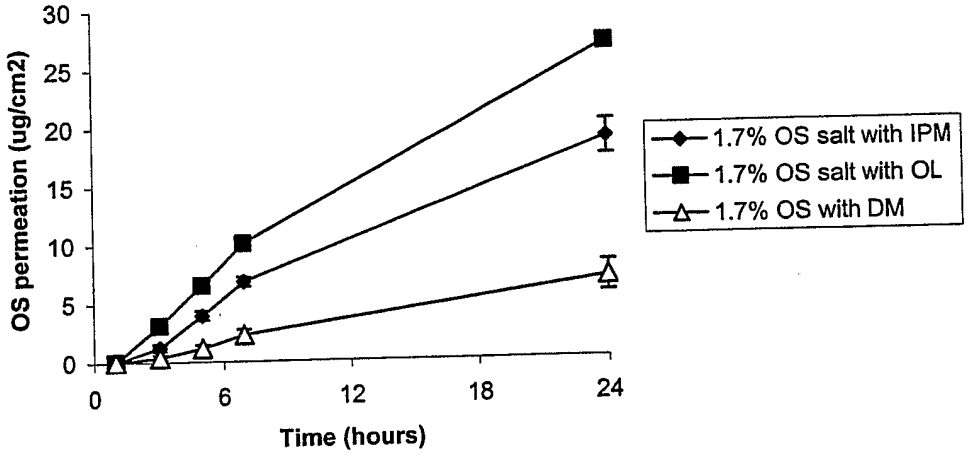
OS permeation (ug/cm2)
30
25
20
15
10
5
0
0
6
12
18
24
Time (hours)
1.7% OS salt with IPM
1.7% OS salt with OL
1.7% OS with DM

Fig. 2

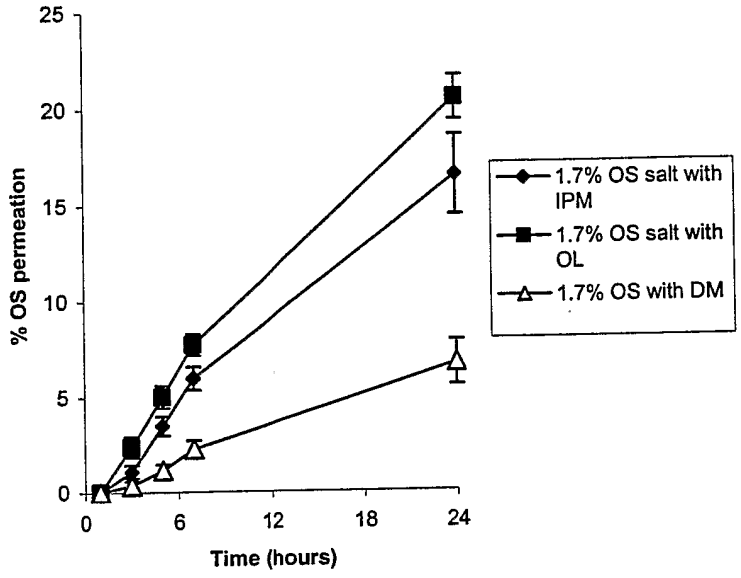
25
20
15
10
5
0
% OS permeation
0
6
12
18
24
Time (hours)
1.7% OS salt with IPM
1.7% OS salt with OL
1.7% OS with DM

Fig. 3

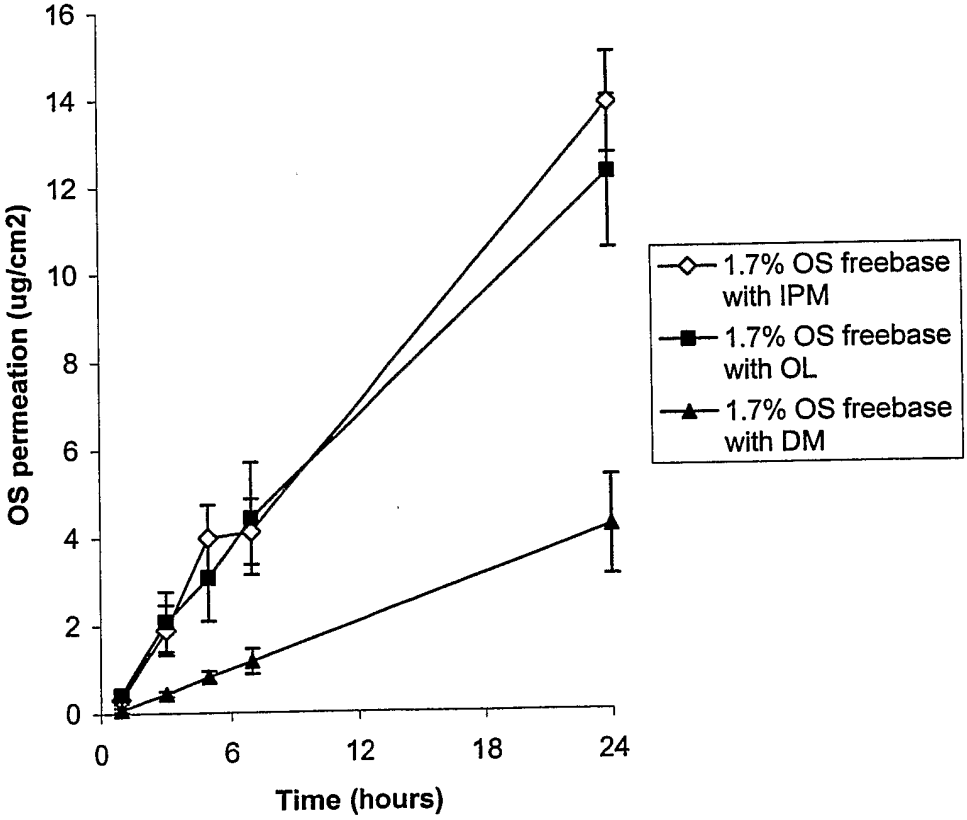
16
14
12
10
8
6
4
2
0
OS permeation (ug/cm2)
0
6
12
18
24
Time (hours)
1.7% OS freebase with IPM
1.7% OS freebase with OL
1.7% OS freebase with DM

Fig. 4

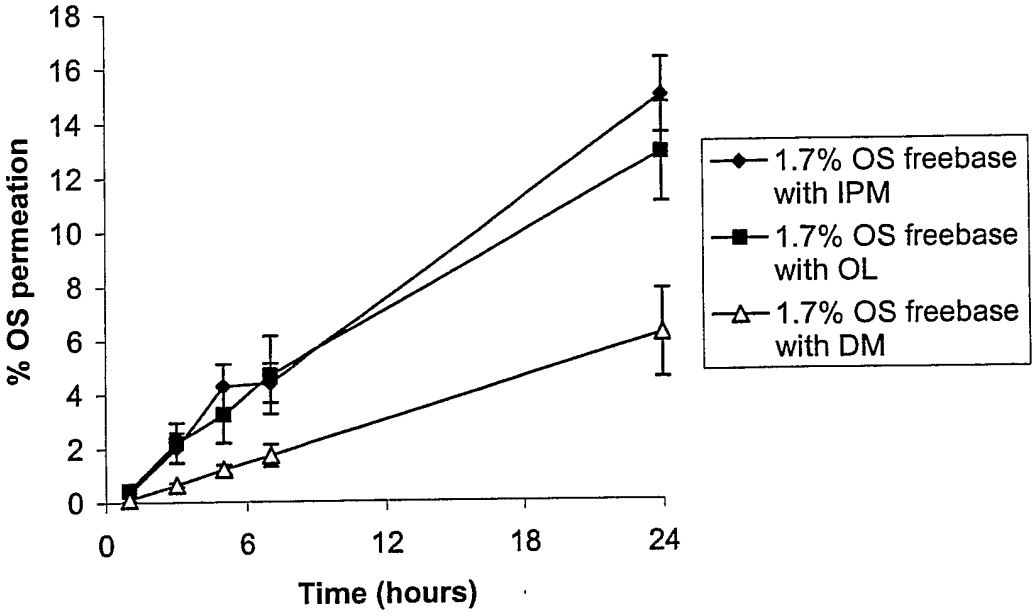
% OS permeation
Time (hours)
1.7% OS freebase with IPM
1.7% OS freebase with OL
1.7% OS freebase with DM

Fig. 5

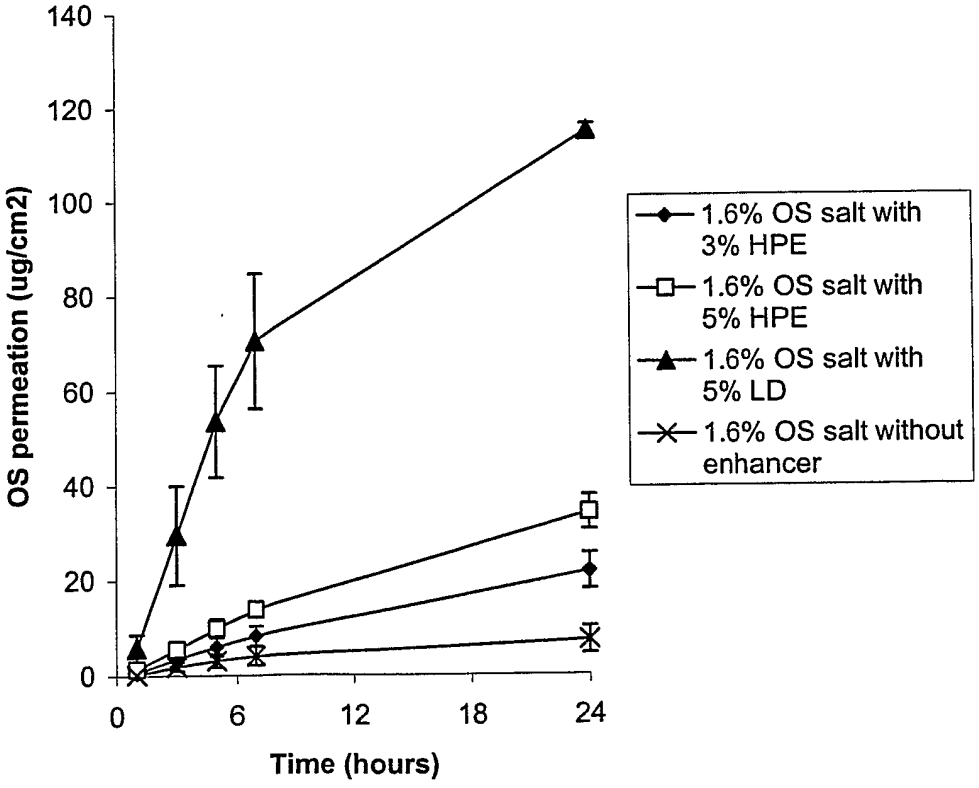
OS permeation (ug/cm2)
Time (hours)
1.6% OS salt with 3% HPE
1.6% OS salt with 5% HPE
1.6% OS salt with 5% LD
1.6% OS salt without enhancer

Fig. 6

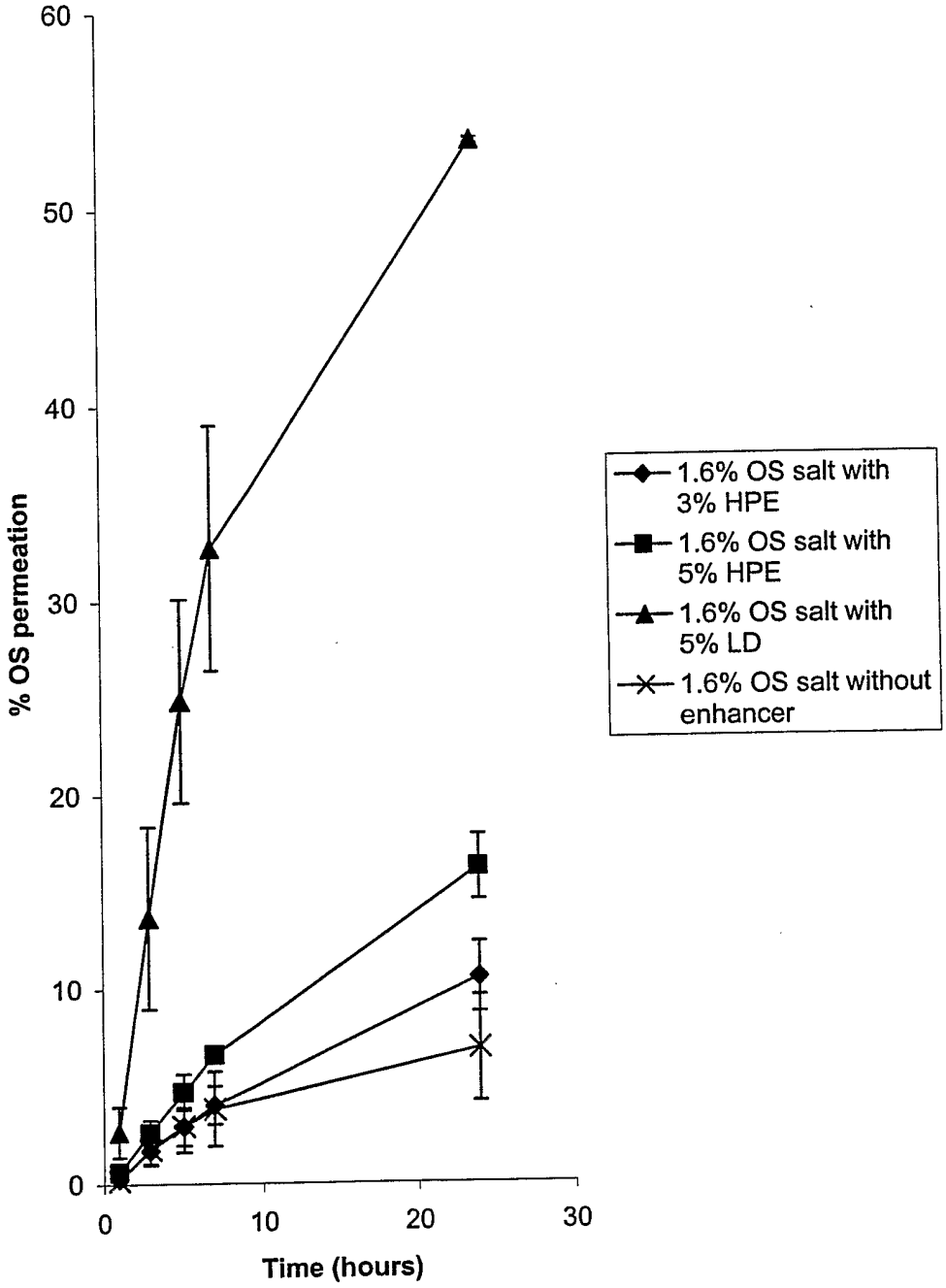
60
50
40
30
20
10
0
% OS permeation
0
10
20
30
Time (hours)
1.6% OS salt with 3% HPE
1.6% OS salt with 5% HPE
1.6% OS salt with 5% LD
1.6% OS salt without enhancer

Fig. 7

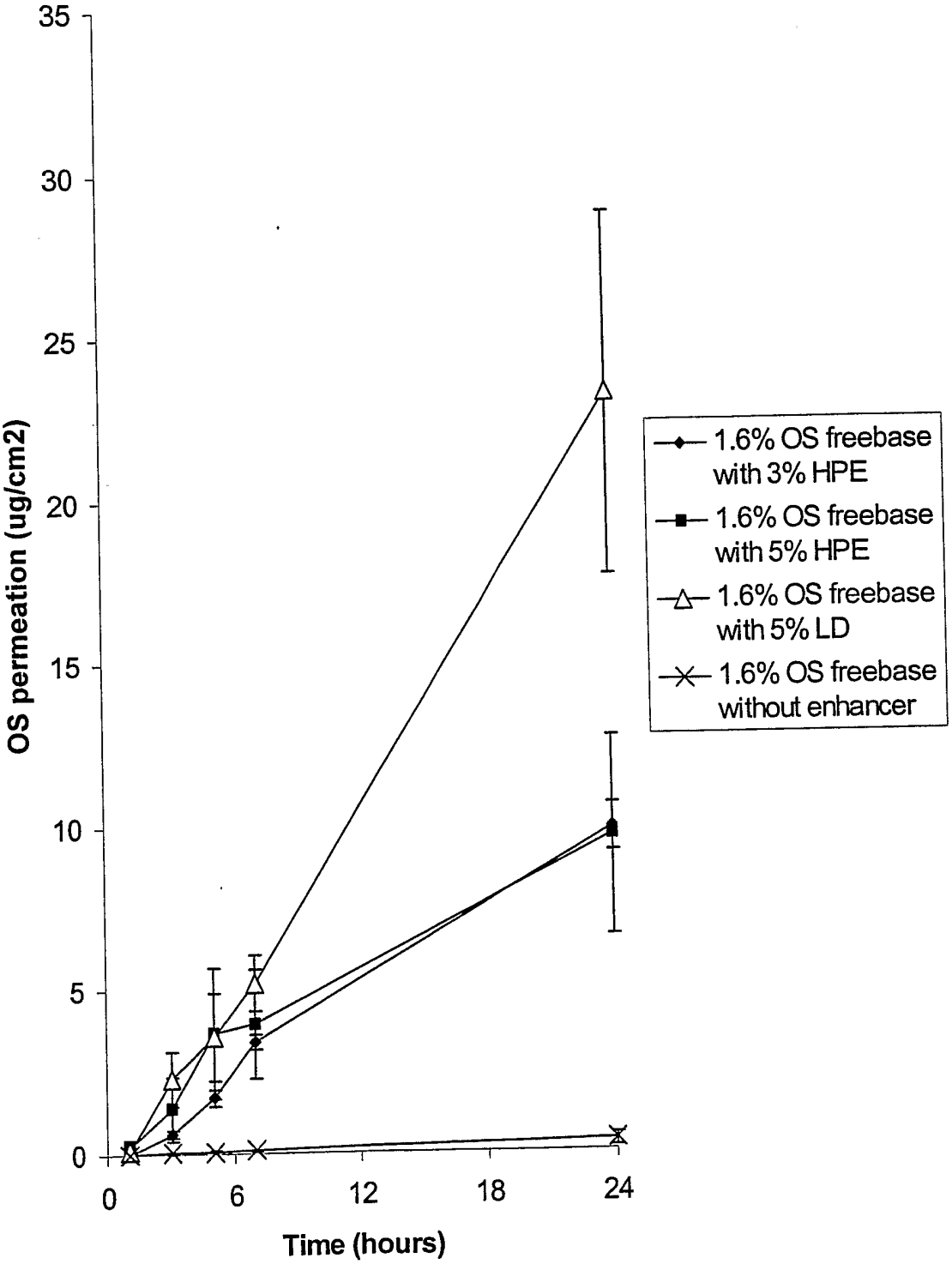
35
30
25
20
15
10
5
0
OS permeation (ug/cm2)
0
6
12
18
24
Time (hours)
1.6% OS freebase with 3% HPE
1.6% OS freebase with 5% HPE
1.6% OS freebase with 5% LD
1.6% OS freebase without enhancer

Fig. 8

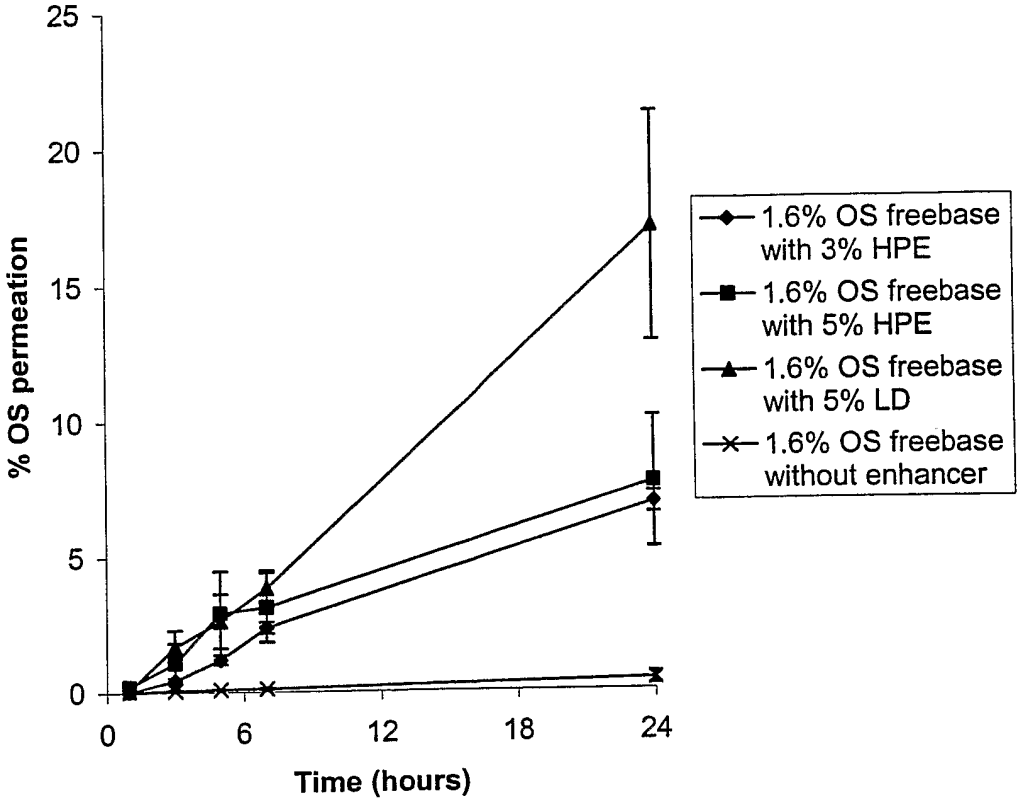
25
20
15
10
5
0
% OS permeation
0
6
12
18
24
Time (hours)
1.6% OS freebase with 3% HPE
1.6% OS freebase with 5% HPE
1.6% OS freebase with 5% LD
1.6% OS freebase without enhancer

Fig. 9

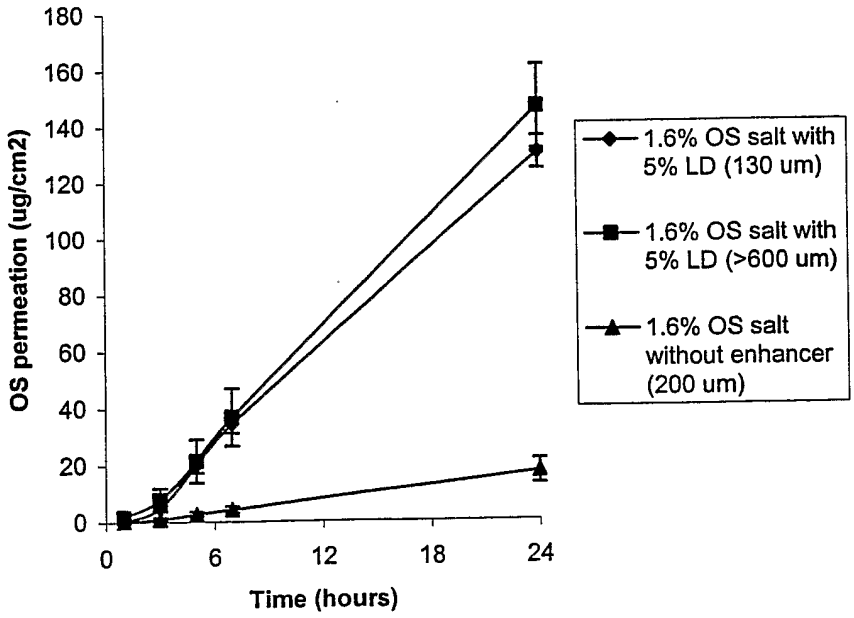
180
160
140
120
100
80
60
40
20
0
OS permeation (ug/cm2)
0
6
12
18
24
Time (hours)
1.6% OS salt with 5% LD (130 um)
1.6% OS salt with 5% LD (>600 um)
1.6% OS salt without enhancer (200 um)

Fig. 10

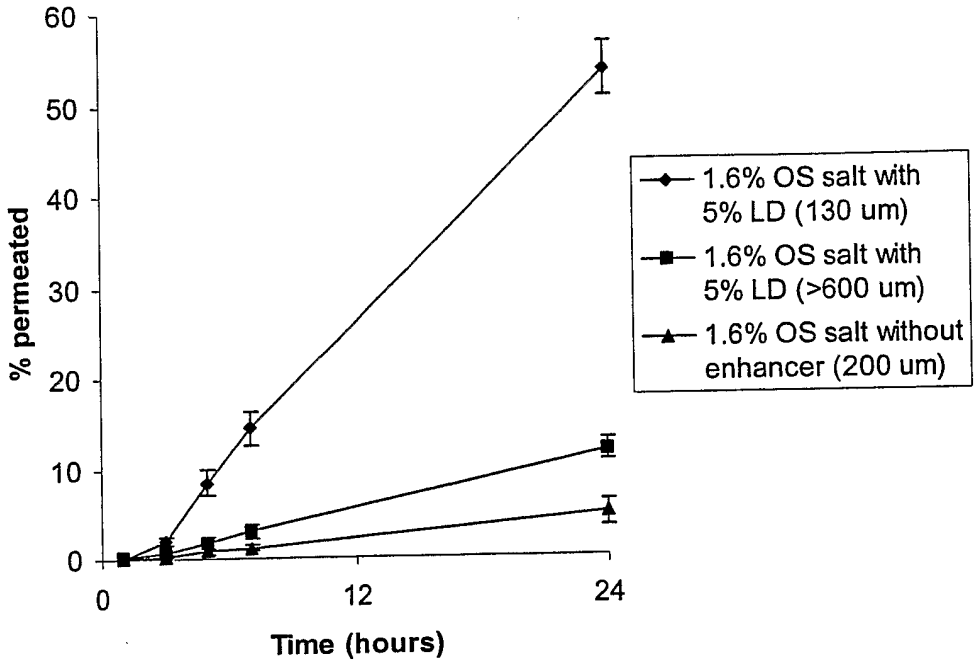
60
50
40
30
20
10
0
% permeated
0
12
24
Time (hours)
1.6% OS salt with 5% LD (130 um)
1.6% OS salt with 5% LD (>600 um)
1.6% OS salt without enhancer (200 um)

Fig. 11

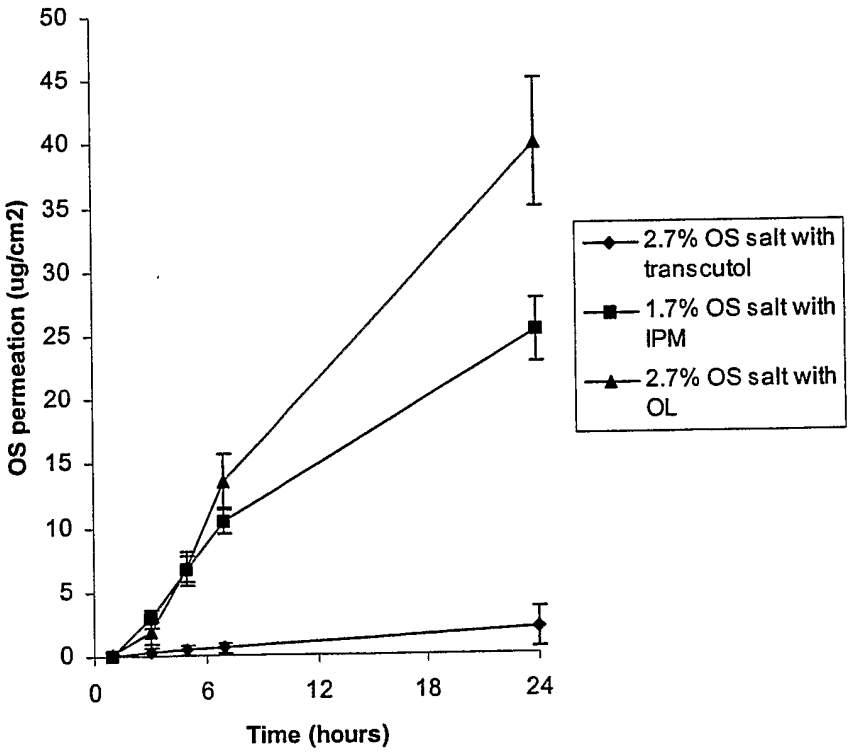
50
45
40
35
30
25
20
15
10
5
0
OS permeation (ug/cm2)
0
6
12
18
24
Time (hours)
2.7% OS salt with transcutol
1.7% OS salt with IPM
2.7% OS salt with OL

Fig. 12

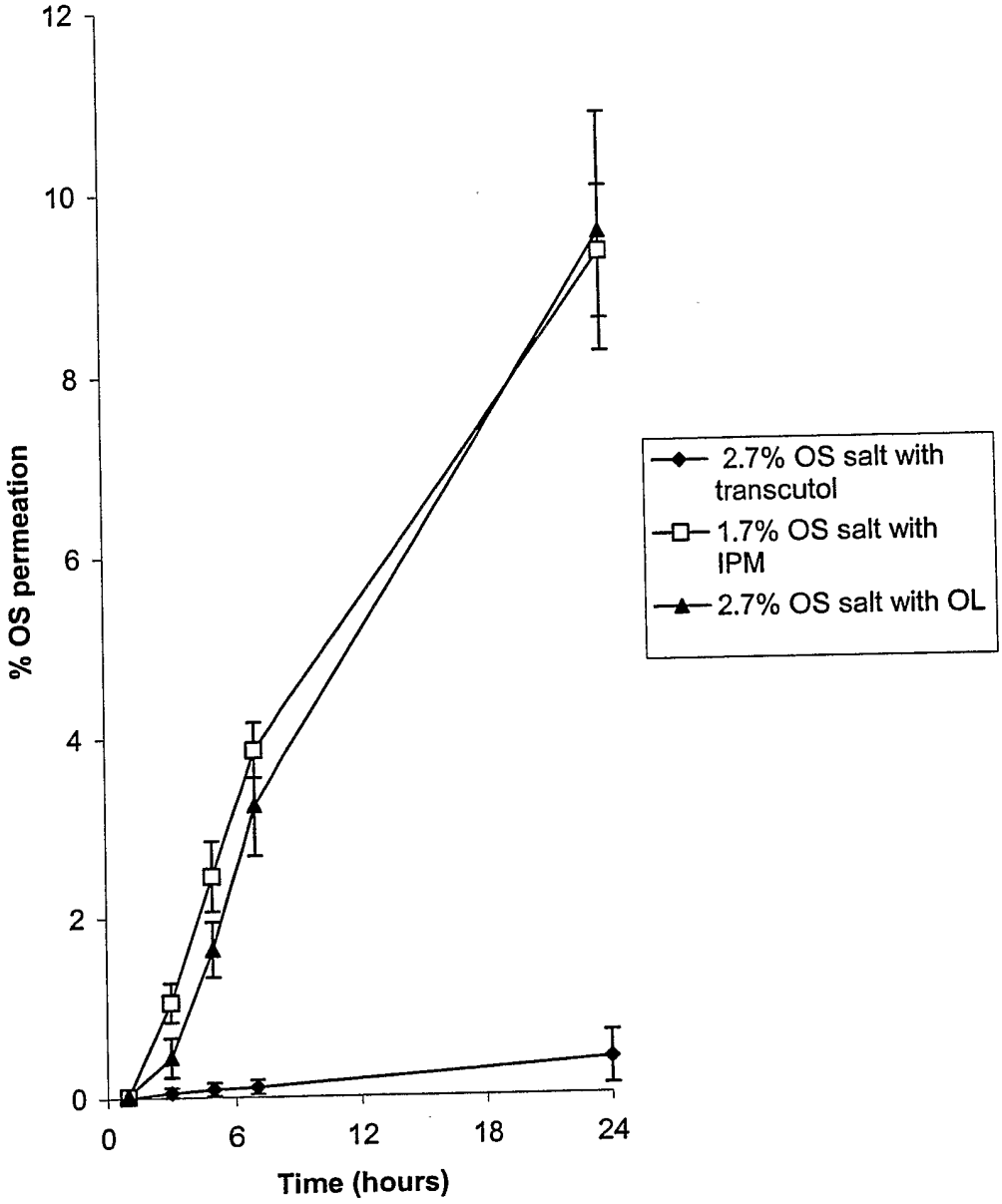
12
10
8
6
4
2
0
% OS permeation
0
6
12
18
24
Time (hours)
2.7% OS salt with transcutol
1.7% OS salt with IPM
2.7% OS salt with OL

Fig. 13

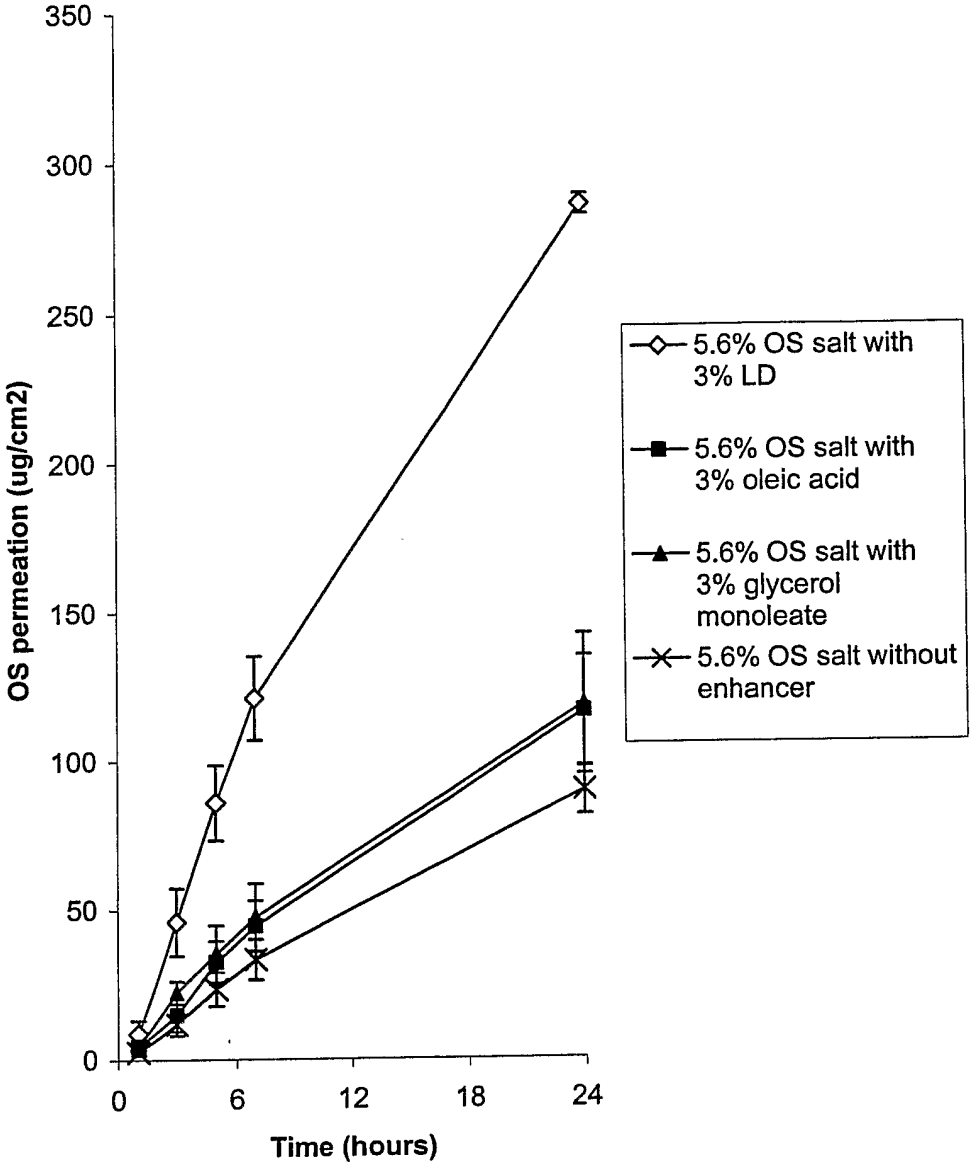
350
300
250
200
150
100
50
0
OS permeation (ug/cm2)
0
6
12
18
24
Time (hours)
5.6% OS salt with 3% LD
5.6% OS salt with 3% oleic acid
5.6% OS salt with 3% glycerol monoleate
5.6% OS salt without enhancer

Fig. 14

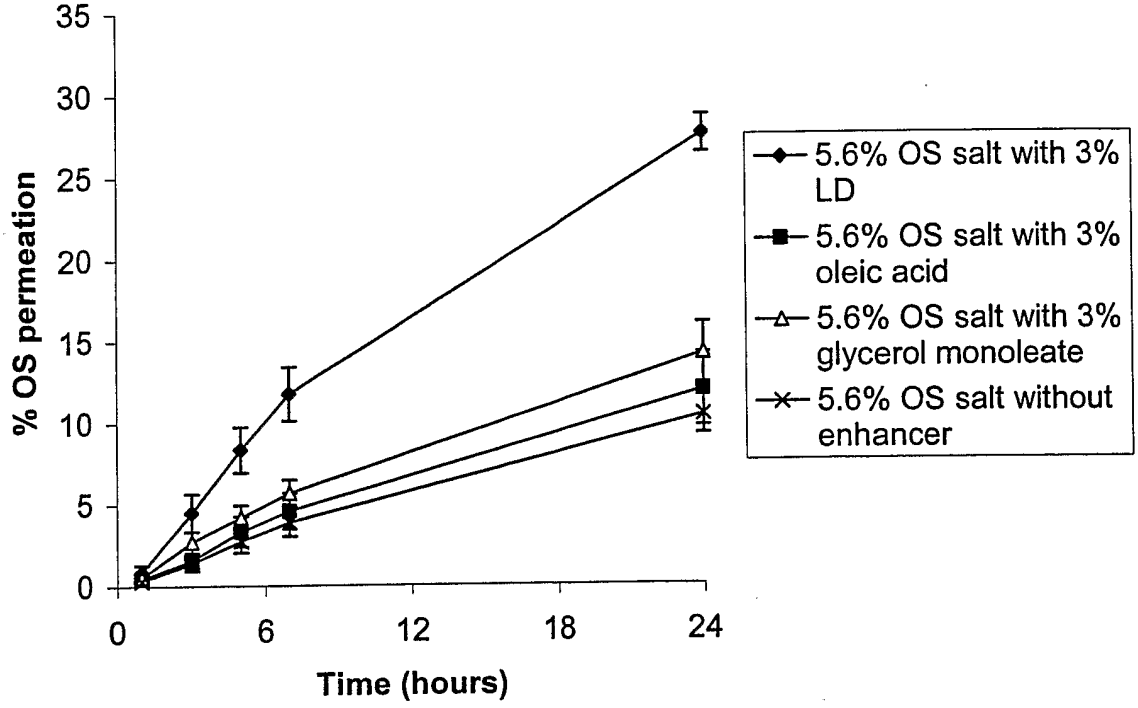
35
30
25
20
15
10
5
0
% OS permeation
0
6
12
18
24
Time (hours)
5.6% OS salt with 3% LD
5.6% OS salt with 3% oleic acid
5.6% OS salt with 3% glycerol monoleate
5.6% OS salt without enhancer

Fig. 15

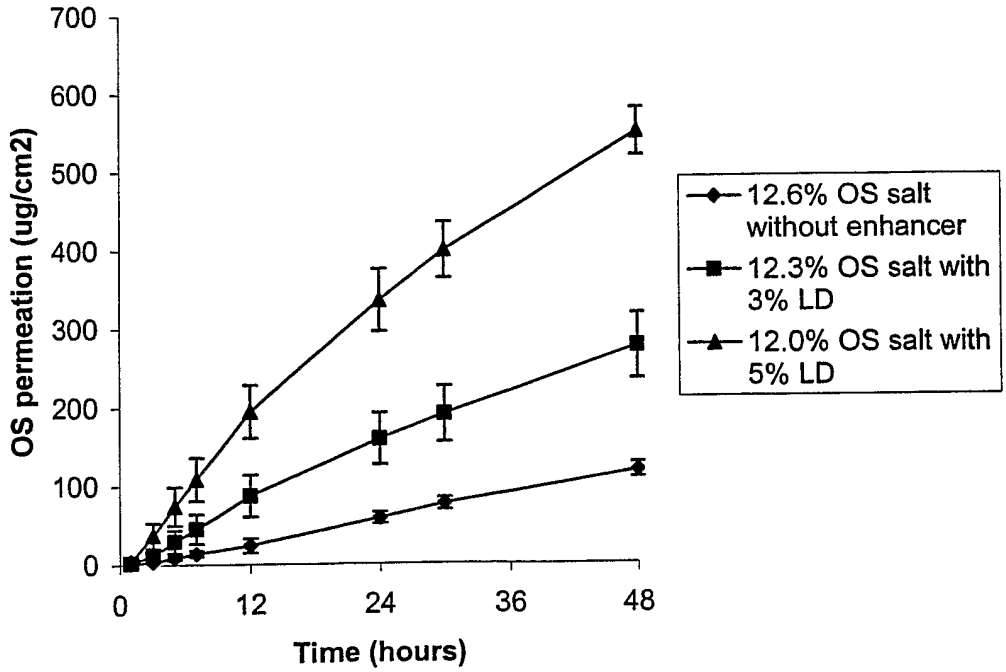
700
600
500
400
300
200
100
0
OS permeation (ug/cm2)
0
12
24
36
48
Time (hours)
12.6% OS salt without enhancer
12.3% OS salt with 3% LD
12.0% OS salt with 5% LD

Fig. 16

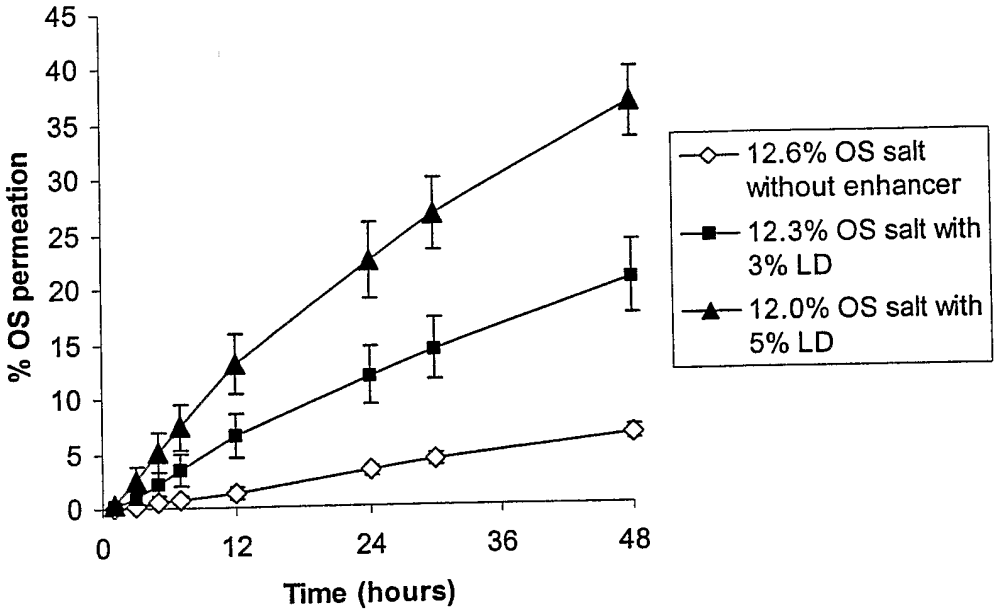
% OS permeation
45
40
35
30
25
20
15
10
5
0
0
12
24
36
48
Time (hours)
12.6% OS salt without enhancer
12.3% OS salt with 3% LD
12.0% OS salt with 5% LD

Fig. 17

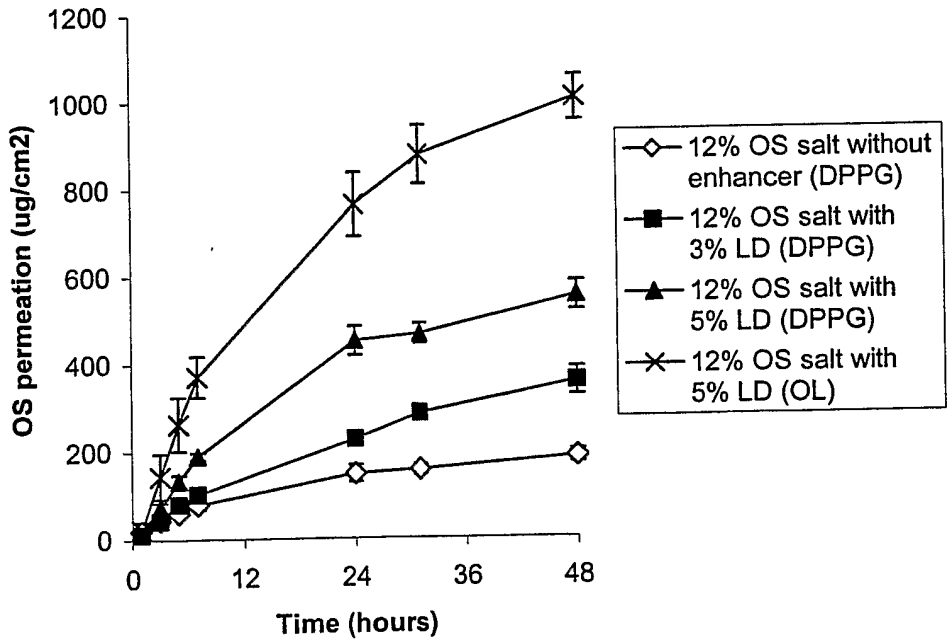
OS permeation (ug/cm2)
1200
1000
800
600
400
200
0
0
12
24
36
48
Time (hours)
12% OS salt without enhancer (DPPG)
12% OS salt with 3% LD (DPPG)
12% OS salt with 5% LD (DPPG)
12% OS salt with 5% LD (OL)

Fig. 18

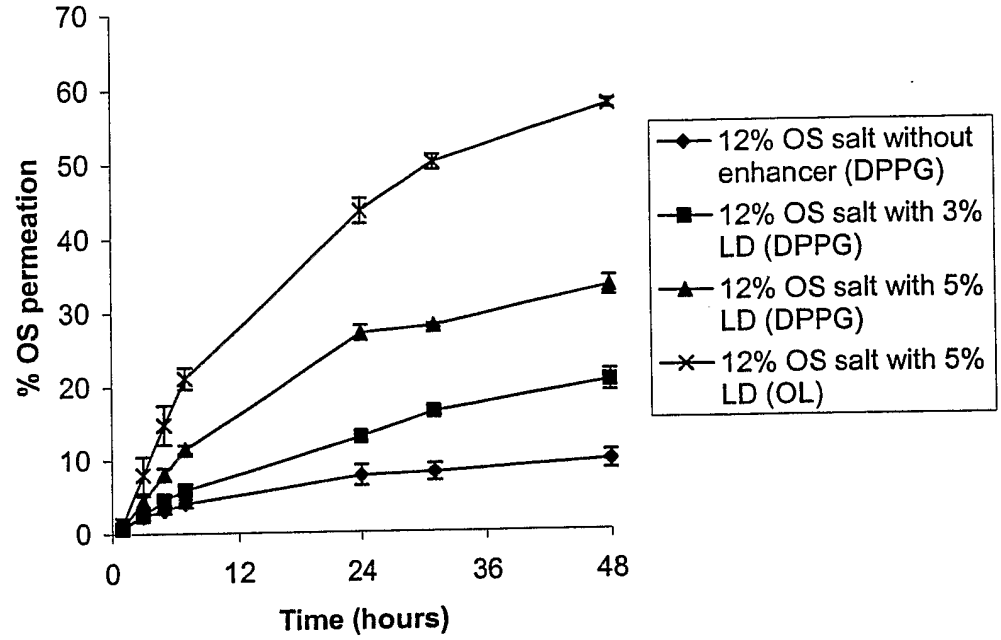
70
60
50
40
30
20
10
0
% OS permeation
0
12
24
36
48
Time (hours)
12% OS salt without enhancer (DPPG)
12% OS salt with 3% LD (DPPG)
12% OS salt with 5% LD (DPPG)
12% OS salt with 5% LD (OL)

Fig. 19

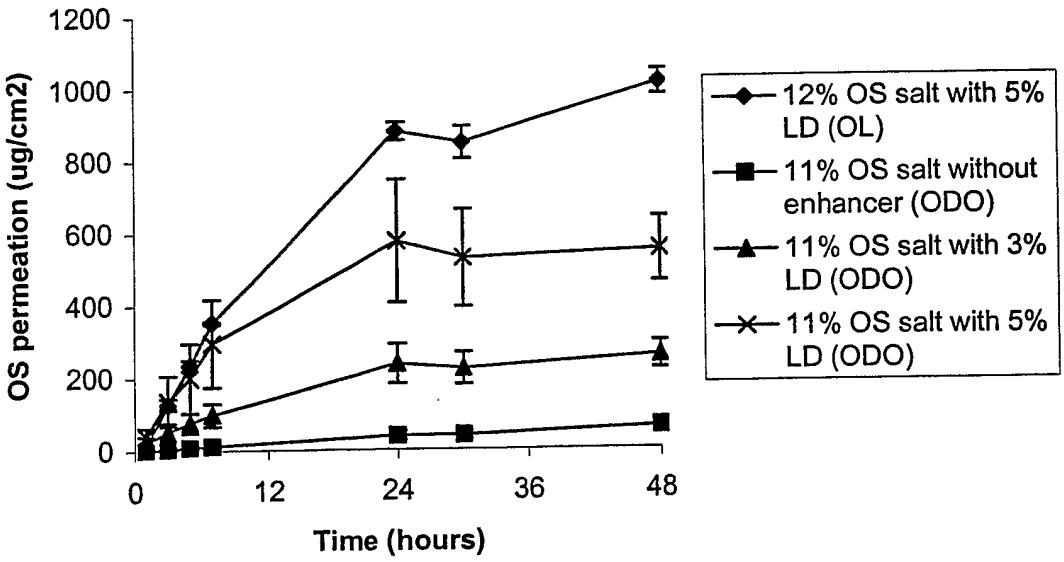
1200
1000
800
600
400
200
0
OS permeation (ug/cm2)
0
12
24
36
48
Time (hours)
12% OS salt with 5% LD (OL)
11% OS salt without enhancer (ODO)
11% OS salt with 3% LD (ODO)
11% OS salt with 5% LD (ODO)

Fig. 20

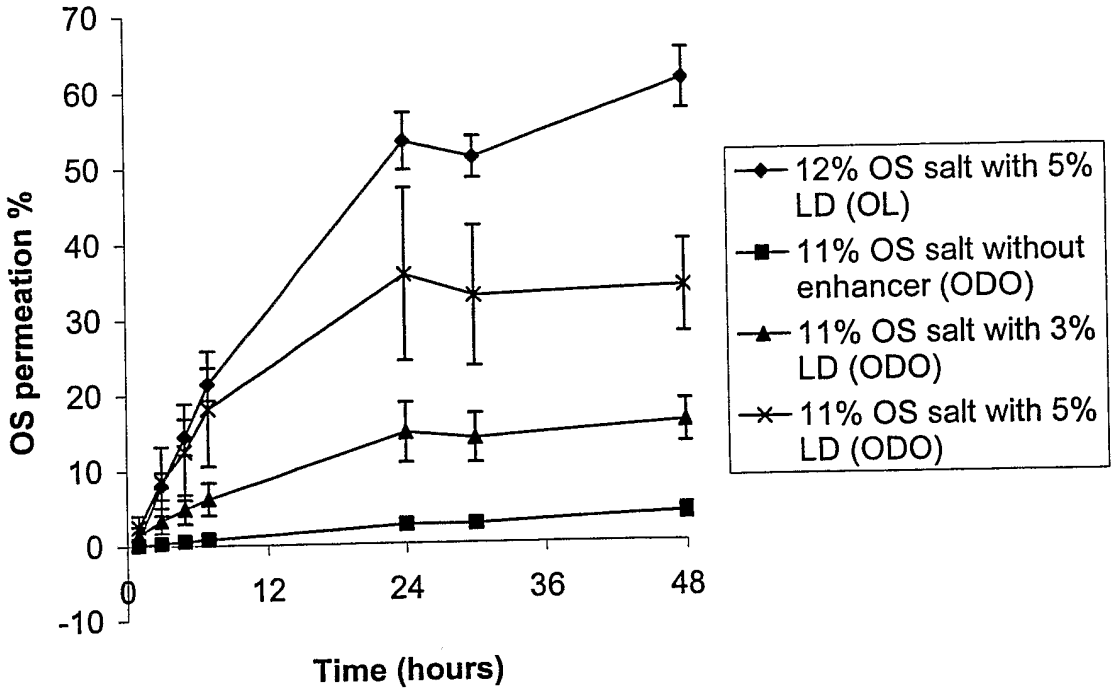
70
60
50
40
30
20
10
0
-10
0
12
24
36
48
OS permeation %
Time (hours)
12% OS salt with 5% LD (OL)
11% OS salt without enhancer (ODO)
11% OS salt with 3% LD (ODO)
11% OS salt with 5% LD (ODO)

Fig. 21

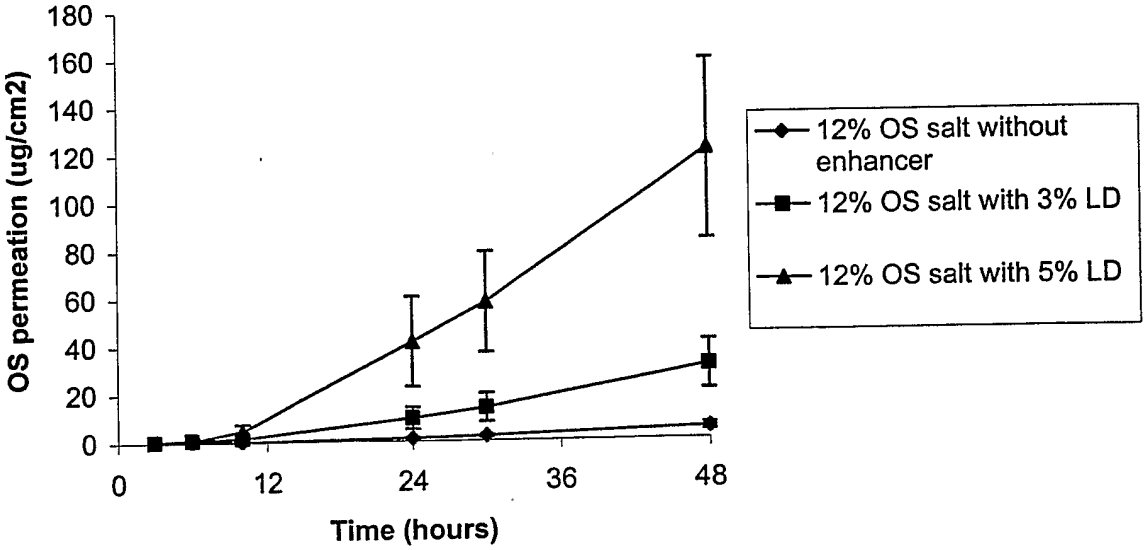
180
160
140
120
100
80
60
40
20
0
0
12
24
36
48
OS permeation (ug/cm2)
Time (hours)
12% OS salt without enhancer
12% OS salt with 3% LD
12% OS salt with 5% LD

Fig. 22

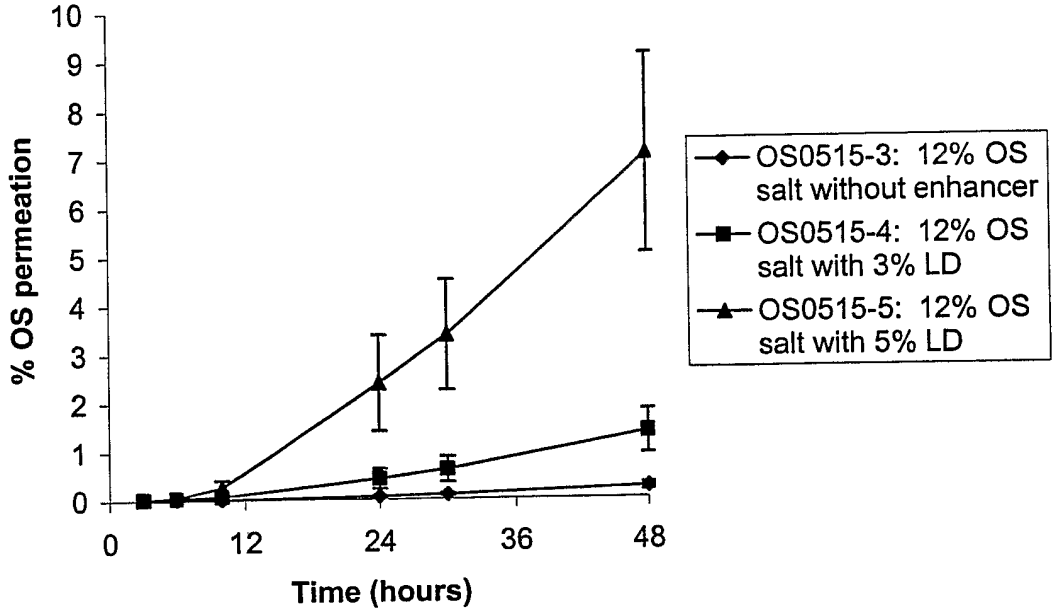
10
9
8
7
6
5
4
3
2
1
0
% OS permeation
0
12
24
36
48
Time (hours)
OS0515-3: 12% OS salt without enhancer
OS0515-4: 12% OS salt with 3% LD
OS0515-5: 12% OS salt with 5% LD

Fig. 23

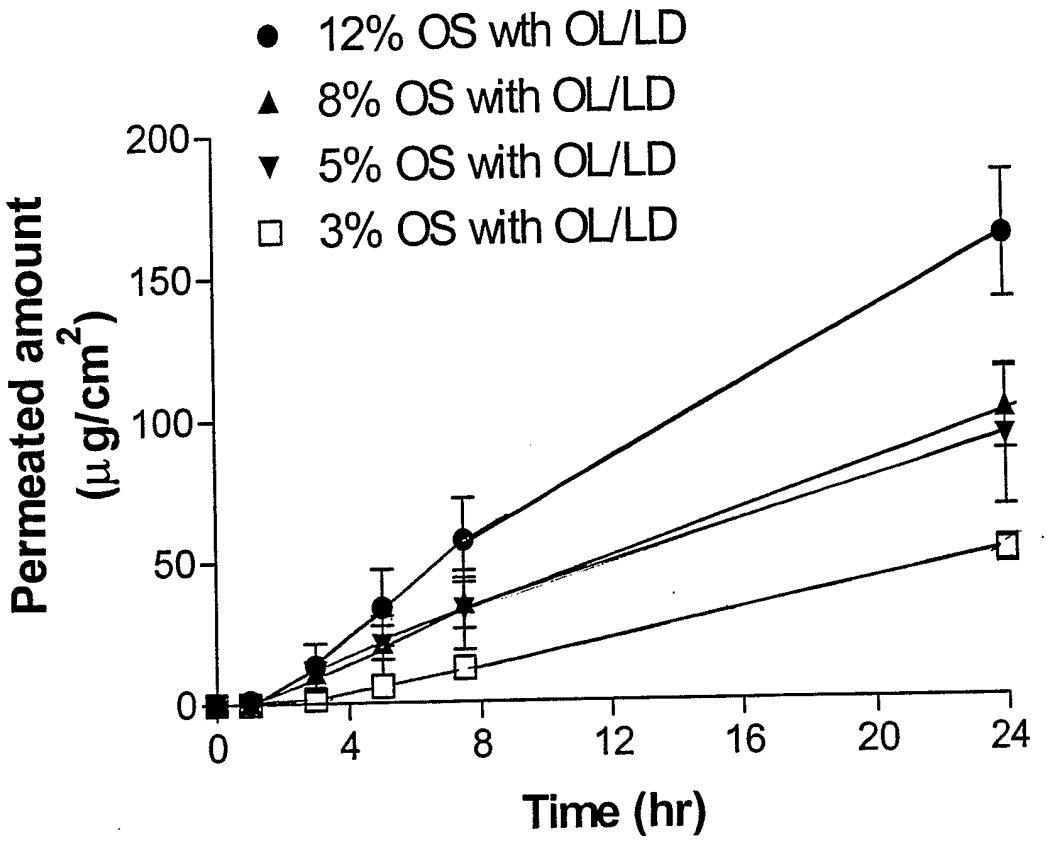
12% OS wth OL/LD
8% OS with OL/LD
5% OS with OL/LD
3% OS with OL/LD
Permeated amount
(μg/cm²)
200
150
100
50
0
0
4
8
12
16
20
24
Time (hr)

Fig. 24

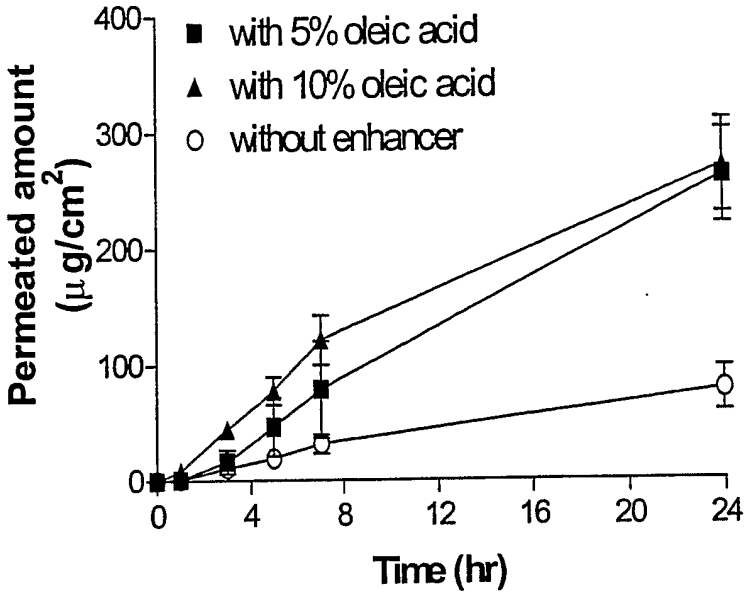
400
300
200
100
0
Permeated amount
(μg/cm²)
with 5% oleic acid
with 10% oleic acid
without enhancer
0
4
8
12
16
20
24
Time (hr)

Fig. 25

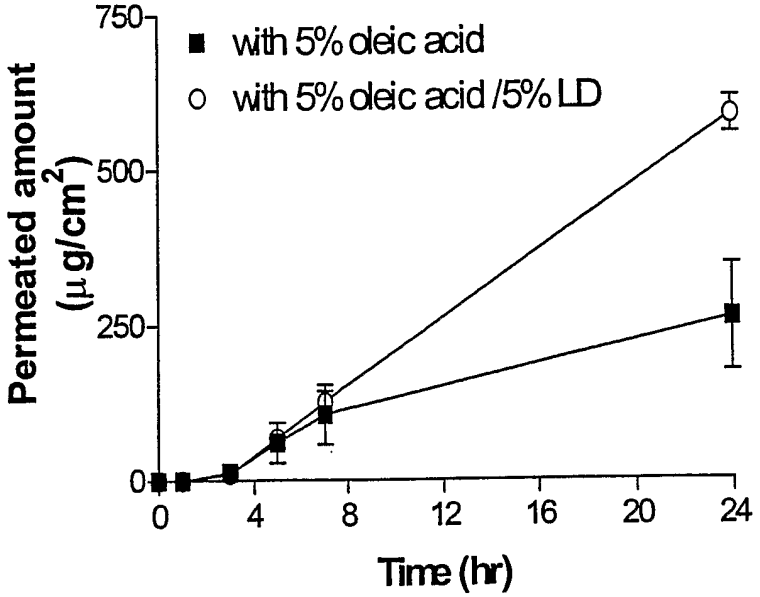
750
500
250
0
Permeated amount
(μg/cm²)
with 5% oleic acid
with 5% oleic acid /5% LD
0
4
8
12
16
20
24
Time (hr)

Fig. 26

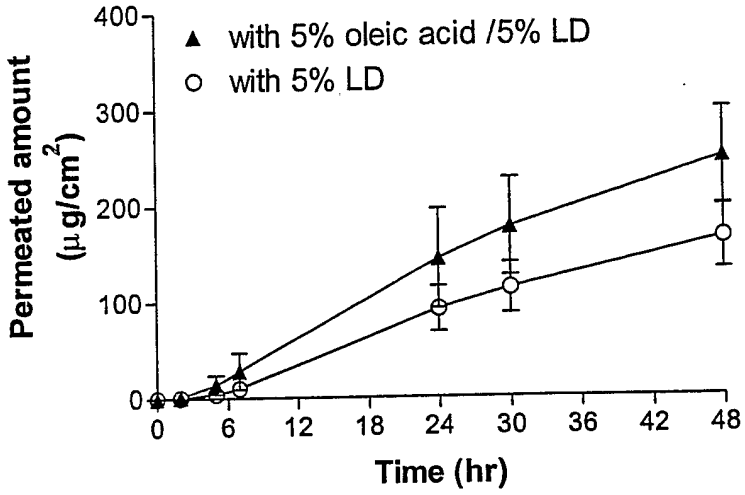
400
300
200
100
0
▲ with 5% oleic acid /5% LD
○ with 5% LD
Permeated amount
(μg/cm²)
0
6
12
18
24
30
36
42
48
Time (hr)

Fig. 27

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K31/4178 A61K31/46

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)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 53815 A (EFFING JOCHEM ;MINNESOTA MINING & MFG (US)) 3 December 1998 (1998-12-03) page 1, line 5,6 page 2, line 11 -page 3, line 28 page 6, line 4 - line 21 page 7, line 7 - line 22	1-10, 13-15, 17-24, 32-34, 41-51
Y	---	1-10, 13-51
Y	WO 00 44846 A (STRAKAN LIMITED ;KAMIYAMA FUMIO (JP)) 3 August 2000 (2000-08-03) cited in the application page 3, line 1 - line 24 page 10, line 3 -page 13, line 8 page 22; example 4	1-10, 13-51

	-/--	

[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
31 October 2002	12/11/2002

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	VON EGGELKRAUT, S

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 10420 A (STRAKAN GROUP PLC ;VICKERS JANE ANN (GB))--- 15 February 2001 (2001-02-15) page 6, last paragraph - last paragraph page 12, last paragraph - paragraph 1 ---	
A	WO 92 13529 A (STIEFEL LABORATORIES) 20 August 1992 (1992-08-20) page 9, paragraph 3 -----	11

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03571

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 46-51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box I.2

The terms "hard and soft segments" and "high molecular weight oily ester" are not generally accepted terms. The term "5-HT3 antagonist" tries to functionally define a group of compounds that can not be clearly defined. Therefore, present claims 1-51 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely the concepts of "hard and soft segments", "high molecular weight oily ester" and "5-HT3 antagonist", the compounds as specified in claims 11, 15, on page 15, line 4 - page 16, third paragraph, and page 20, last paragraph - page 21, first paragraph.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03571

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