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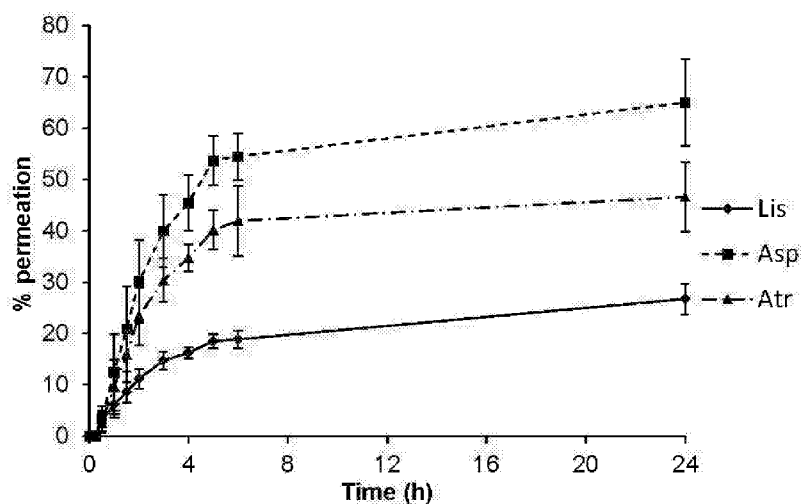


Figure 12C.

(57) Abstract: The invention is directed to a transdermal delivery device comprising a microneedle array and a reservoir portion, wherein said microneedles are composed of a swellable hydrogel polymer composition, the polymers being cross-linked polymers selected from at least one of the group consisting of poly(methylvinylether/maleic acid), esters thereof and poly(methyl/vinyl ether/maleic anhydride). The reservoir portion comprises at least one amphipathic component and at least one hydrophobic active agent, wherein in use, on insertion of the microneedles into the stratum corneum of skin, said microneedles swell and said amphipathic component and said at least one hydrophobic active agent diffuse down a concentration gradient from the reservoir layer via the microneedles into the skin.



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DRUG DELIVERY DEVICE

Field of the Invention

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The present invention relates to drug delivery devices. In particular, it relates to transdermal delivery devices, for example microneedle arrays, for the delivery of hydrophobic drugs.

10 Background to the Invention

Transdermal drug delivery offers certain advantages over conventional oral or parenteral administration, including prevention of drug degradation in the stomach, avoidance of first pass hepatic metabolism, possibility of improved bioavailability, maintenance of relatively constant blood concentrations and elimination of pain, discomfort, and poor compliance associated with injections [Williams AC, Transdermal and topical drug delivery. London, Pharmaceutical Press 2003; Barry BW, Eur J Pharm Sci 2001; 14: 101-14; Gozes et al., Endocrinology 1994; 134: 2121-5]. More than 35 transdermal products have been approved for sale in the US and approximately 16 active ingredients have been approved for use worldwide.

Permeation enhancement across skin can be achieved by a variety of techniques, such as laser or thermal ablation, iontophoresis, electroporation, radiofrequency, microneedles, ultrasound/phonophoresis or sonophoresis and high-pressure gas/powder or liquid microporation. However, controlled microporation of the stratum corneum (SC) has been found to be very beneficial in terms of both drug delivery of molecules across the skin and interstitial fluid monitoring.

Microporation of a biological membrane, to desired depths, can be effectively achieved by the use of microneedle/microporation arrays (microneedles). As previously reviewed by the inventors [Thakur et al., *Rec Pat Drug Deliv Form* 2010 4: 1-17; Donnelly et al., *Rec Pat Drug Deliv Form* 2007 1: 195-200; Donnelly et al., *Drug Delivery*. 2010 17: 1-24; Thakur et al., *Pharmaceutical Manufacturing and Packing Sourcer*. August 2010, Issue 48, 26-29], microfabrication technology, and enhancement in the delivery of

drugs and biomolecules of a wide variety of physicochemical properties, has been demonstrated in *in vitro*, *ex vivo* and *in vivo* experiments, with a number of microporation techniques used to bypass biological barriers, including different microneedle fabrication technologies known.

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A large proportion of candidate therapeutic compounds, identified by, for example, combinatorial chemistry and high throughput screening are molecules with relatively high lipophilicity. Most drug targets, such as enzyme active sites and membrane proteins, tend to be more accessible to lipophilic compounds. Indeed, an estimated 40% of currently-approved drugs are poorly water soluble and nearly 90% of the developmental pipe-line consists of molecules with poor water solubility. In fact, the average solubility of all drugs approved in 2012 was more than ten times less than those drugs approved in 1983. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profiles in humans are recognised today as major challenges in oral delivery of new drugs. Orally-administered drugs on the List of Essential Medicines of the World Health Organisation (WHO) are assigned Biopharmaceuticals Classification System (BCS) status on the basis of publically-available data. Of the 130 orally-administered drugs on the WHO List, 61 can be classified with certainty. Of these, 84% belong to Class I (highly soluble, highly permeable), 17% to Class II (poorly soluble, highly permeable), 39% to Class III (highly soluble, poorly permeable) and 10% to Class IV (poorly soluble, poorly permeable). The rate and extent of absorption of Class II and IV compounds govern bioavailability, which ultimately depends upon solubility in gastrointestinal fluid and intestinal permeability. The presence of food, particularly if high in fat, or alcohol in the gastrointestinal tract can enhance dissolution of poorly soluble drugs, thus leading to unpredictable absorption.

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Extensive research in both industry and academia continues to focus principally on strategies for enhancing drug solubility in gastrointestinal fluid. Use of enhancing molecules (surfactants, co-solvents, cyclodextrins, hydrotropes), particle size reduction techniques, co-crystals, solid lipid nanoparticles, mesoporous silica nanoparticles, solid dispersions and hot melt extrusion have all made significant contributions to improving aqueous solubility and, in turn, oral bioavailability of a wide range of poorly soluble drugs. However, hepatic first pass metabolism significantly reduces the proportion of

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the absorbed dose that reaches the systemic circulation for many drugs given orally. This often necessitates higher doses, which leads to side effects, due to hepatic production of toxic metabolites. Gastrointestinal transit also typically limits the duration of drug absorption to a window of no more than several hours, meaning even
5 controlled release oral dosage forms must be given at least every 24 hours.

In 2015, the worldwide transdermal patch market was estimated to approach \$31.5 billion, yet is based on less than 20 drugs. This rather limited number of transdermal drugs is attributed to the skin's excellent barrier function, which is accomplished
10 entirely by the outermost 10-15 μm of tissue, the *stratum corneum* (SC). Before being taken up by blood vessels in the upper papillary dermis, and prior to entering the systemic circulation, substances permeating the skin must cross the SC and the viable epidermis. Typically, the ideal properties of a molecule penetrating intact SC well are considered to be:

- 15 • Molecular mass less than 600 Da, when the diffusion coefficient in SC tends to be high
- Log *P* value between 1 and 3
- 20 • High, but balanced, SC:vehicle partition coefficient, such that the drug can diffuse out of the vehicle, partition into, and move across, the SC without becoming sequestered within it
- Low melting point, correlating with good solubility, as predicted by ideal solubility theory

25 Clearly, many drug substances do not do not satisfy these criteria. Those with Log *P* values below 1 are too hydrophilic to efficiently penetrate the SC by passive diffusion. Those with Log *P* values greater than 3 are so hydrophobic that they become entrapped within the intercellular lipids of the SC and partition into the essentially aqueous environment of the viable epidermis below at such low rates that therapeutic plasma
30 concentrations cannot be achieved. Chemical penetration enhancers have no appreciable value in increasing transdermal flux of such compounds. Alternative enhancement strategies have, to date, focussed strongly on increasing transdermal delivery of hydrophilic drugs. Accordingly, iontophoresis has been used to drive hydrophilic drugs through hair follicles and sweat glands, while electroporation,
35 sonophoresis and suction, laser and thermal ablation create transient aqueous pores in the SC. It is clear that none of these approaches represents a realistic strategy for successful transdermal delivery of hydrophobic drugs. Indeed, it would appear that

even the currently most promising transdermal enhancement strategies based on microneedle technology, which also create aqueous pathways in the *SC*, would be similarly limited.

5 Indeed, to date, microneedle based devices have been used almost exclusively to enhance delivery of substances traditionally regarded as relatively hydrophilic, with Log *P* values in the range -0.2 to 1.5. Crucially, this neglects the sizeable proportion of drug substances with higher log *P* values, such as log *P* values of 3 and above which cannot be delivered transdermally using traditional means.

10 Recently, drugs with poor aqueous solubility have been formulated into microneedles platforms. However, such platforms have relied on dip- and inkjet-coated microneedles and dissolving microneedles loaded with nanoparticles and have thus been limited to the delivery of very small drug doses, potentially suitable for local treatment of pain,
15 fungal skin infections or skin tumours only.

Summary of the Invention

20 The present invention addresses some of the problems of the prior art.

The present inventors have surprisingly shown that by employing a combination of at least one amphipathic agent (i.e. an agent having both hydrophobic and hydrophilic character) and at least one hydrophobic agent in a microneedle based transdermal
25 delivery device, hydrophobic active agents may be effectively delivered at clinically relevant doses across the stratum corneum. The amphipathic agent acts as a bridging agent, enabling solubilisation of the hydrophobic drug. Indeed, the invention, in one embodiment enables the microneedle-mediated transdermal administration of poorly soluble drug substances to the systemic circulation at therapeutic doses.

30 The invention thus opens up the many advantages of the transdermal route to a wide range of clinically-important compounds not previously considered deliverable transdermally, with ensuing benefits for patients.

According to a first aspect of the invention, there is provided a transdermal delivery device comprising a microneedle array and a reservoir portion, wherein said microneedles are composed of a swellable hydrogel polymer composition, said polymers being cross-linked polymers selected from at least one of the group consisting of poly(methylvinylether/maleic acid), esters thereof and poly(methylvinyl ether/maleic anhydride), wherein said reservoir portion comprises at least one amphipathic component and at least one hydrophobic active agent, wherein in use, on insertion of the microneedles into the *stratum corneum* of skin, said microneedles swell and said amphipathic component and said at least one hydrophobic active agent diffuse down a concentration gradient from the reservoir layer via the microneedles into the skin.

The reservoir may have any structure which enables the reservoir to maintain the hydrophobic active agent prior to its subsequent delivery with said amphipathic component via the microneedle.

In one embodiment, the reservoir portion comprises at least a first chamber external to the microneedles of the microneedle array but in fluid communication with the microneedles. Optionally, the transdermal delivery device may comprise an additional reservoir portion comprised within the bores of the microneedles themselves.

In one embodiment, the amphipathic component and/or the hydrophobic active agent is a liquid at room temperature.

In another embodiment, the amphipathic component and/or the hydrophobic active agent is a solid at room temperature. In such embodiments, the amphipathic component may be comprised within or be a component of a matrix within the reservoir.

The amphipathic component which is used in the invention may be any biocompatible amphipathic component with suitable solubility properties which, in use in a microneedle array inserted into the stratum corneum, will be diffused through the microneedles into the skin together with the hydrophobic active agent.

For example, in a particular embodiment of the invention, the amphipathic component comprises polyethylene glycol, propylene glycol, or a surfactant, such as a polysorbate.

In particular embodiments, the amphipathic component has a molecular weight in the range 0.1-60 kDa, for example 0.2-50 kDa. In one preferred embodiment, the at least one amphipathic component has a molecular weight which is no greater than 60kDa.

5 Amphipathic components of 60kDa or less may be eliminated from the body by glomerular filtration.

Optionally, the amphipathic component has a hydrophilic-lipophilic balance (HLB) value in the range 7.0-18.0, for example, 7.0-16.0, such as 8.0 -15.0, such as 8.0- 14.0.

10 The microneedle array of the transdermal delivery device may be composed of any suitable material. In a particular embodiment, said microneedle array consists of a biodegradable polymer-based array.

15 As disclosed herein, the invention enables the effective transdermal delivery of hydrophobic agents such as hydrophobic pharmaceuticals. Optionally, the hydrophobic active agent is a member of the Biopharmaceuticals Classification System Class II. In another embodiment, the hydrophobic active agent is a member of the Biopharmaceuticals Classification System Class IV.

20 Optionally, the hydrophobic active agent has a Log *P* value of greater than 2.0, for example greater than 3.0, 4.0, or 5.0.

In the transdermal delivery device of the invention, the microneedles are composed of a

25 swellable polymer composition, wherein, upon insertion into the skin, said microneedles swell. In one embodiment, said swellable polymer is a hydrogel. For example, the microneedles may be fabricated from cross-linked polymers. The polymers are chemically or physically crosslinked. The polymers are selected from at least one of the group consisting of poly(methylvinylether/maleic acid), esters thereof and

30 poly(methyl vinyl ether/maleic anhydride). In such embodiments, any suitable cross-linking agent may be used. For example, the cross-linked polymers may be crosslinked by a polyhydric alcohol or a polyamine.

The transdermal delivery device of the present invention enables control of the rate of

35 delivery of particular hydrophobic drugs across the stratum corneum and into, for example, the systemic circulation. For example the rate of delivery can be modulated by

one or more of selection of reservoir amphipathic agents, selection of reservoir matrix materials, the composition of the microneedles etc. The degree of cross linking will modulate the rate of delivery of the active agent(s). For example, lightly cross-linked microneedles will typically enable rapid delivery of active agent, whereas more
5 extensively cross-linked microneedles typically allow slower sustained drug delivery and thus may be used to deliver drug for maintaining desired plasma levels. Thus lightly cross-linked microneedles may be useful in a microneedle device for the rapid delivery of a bolus of active agent, such as a hydrophobic antibiotic or antifungal agent. Delivery over several days is possible, as with commercially-available transdermal patches

10 In embodiments of the transdermal delivery device of the invention, said microneedles are substantially insoluble in interstitial fluid. In the context of the invention, microneedles, may be considered to be substantially insoluble in interstitial fluid if, in use, less than 10% by weight, such as less than 5% by weight or less than 2% by weight,
15 for example less than 1% by weight of said polymer composition of said microneedles in contact with the skin dissolves in interstitial fluid during a predetermined e.g. 12 hour or 24hour period of use of said transdermal delivery device.

By varying, for example, the degree of cross linking of the polymers, the solubility of the
20 microneedles in interstitial fluid may be varied, with for example, greater cross linking associated with reduced solubility.

In one embodiment, the transdermal delivery device of the invention may comprise microneedle arrays of different compositions, for example with different degrees of
25 cross linking, thus allowing the transdermal delivery device to give a rapid bolus dose, achieving a therapeutic plasma level, followed by controlled delivery to maintain this level.

Moreover, as well as being able to provide the same drug at different rates of delivery in
30 this way, the transdermal delivery device of the invention may alternatively, or indeed additionally be used to deliver two or more active agents by, for example, use of different arrays of microneedles having different release characteristics for delivery of the two or more active agents. The two or more active agents may be comprised in different reservoirs or different compartments of the same reservoir.

Such an arrangement may be used to deliver two or more hydrophobic drugs using the same transdermal delivery device. However, it may also be used to deliver at least one hydrophobic drug and at least one amphipathic or hydrophilic drug, at different controllable rates.

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However, the present invention may also be used to deliver a plurality of active agents, such as drugs, of different water and lipid solubilities from a single reservoir. As demonstrated in the Examples, the inventors have surprisingly shown that a transdermal delivery device of the invention may be successfully used to co-deliver a combination of drugs of very different solubilities, e.g. a hydrophobic drug and a hydrophilic drug, from the same reservoir portion.

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Accordingly, in embodiments of the invention, said reservoir portion may comprise, in addition to at least one hydrophobic active agent, at least one hydrophilic active agent and/or at least one amphipathic active agent, wherein in use, on insertion of the microneedles into the stratum corneum of skin, said at least one hydrophilic active agent and/or at least one amphipathic active agent diffuses from the reservoir layer via the microneedles into the skin.

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For example, the reservoir portion comprises, in addition to said at least one hydrophobic active agent, at least one hydrophilic active agent having a Log *P* value of less than 0.5, such as less than 0, for example less than -1.0.

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In an embodiment in which said reservoir portion comprises both an hydrophobic active agent and a hydrophilic active agent, said at least one hydrophobic active agent may have a Log *P* value of greater than 3.0, and said at least one hydrophilic active agent may have Log *P* value of less than 0, for example less than -1.0.

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Additionally, at least some of one or more active agents may be comprised within the polymer composition of the microneedle array. This has the distinct advantage over conventional microneedle arrays in which drugs are delivered via a channel in the microneedle that, on insertion into the skin, drug delivery may be initiated almost immediately.

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In particular embodiments, one or more active agent(s) can be chemically bonded to the

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polymer(s) making up the microneedles and/or base elements. In this case, the active agent can be released upon insertion into the skin by one or more of; hydrolysis, enzymatic or spontaneous non-catalysed breakage of the bonds holding it to the polymer(s). The rate of drug release can thus be at least partially determined by the rate of reaction/bond breakage.

The microneedle arrays of the invention may be used for many different purposes. In one embodiment, they are for use in the transdermal delivery of an active agent, for example a beneficial substance, such as a drug, to the skin.

In such transdermal delivery devices, an active agent is comprised within a reservoir or matrix with which the microneedle array is in communication. In use, on insertion of the microneedle array into skin, the active agent moves from the reservoir or matrix through the microneedles to the skin.

In a second aspect of the present invention, there is provided a method of delivering a hydrophobic active agent through or into the skin, said method comprising the steps:

- providing a transdermal delivery device according to the first aspect of the invention, wherein the transdermal therapeutic device comprises said hydrophobic active agent;
- applying the microneedle array to the skin such that the microneedles protrude through or into the stratum corneum; and
- allowing the hydrophobic active agent and the amphipathic component to flow through the microneedles into the skin.

The transdermal delivery device of the present invention has a number of significant advantages over prior art means of delivering hydrophobic drugs or other hydrophobic active agents. Advantages over existing delivery strategies for poorly soluble drugs may include:

- Avoidance of hepatic and gut wall first pass metabolism
- Predictable drug delivery rate
- Easy administration as in a conventional transdermal patch, improving convenience, reproducibility and patient compliance.

Detailed Description of the Invention

The transdermal delivery device of the invention may comprise a base element and plurality of microneedles formed thereon. In particular embodiments said base element can have a first side and a second side; and said plurality of microneedles comprise a plurality of elements which project from the second side of said base element at an angle. In one embodiment with respect to said base element said angle is in the range 45° to 90°, for example in the range 70° to 90°. In a particular embodiment, said angle is about 90°.

Said base element and plurality of microneedles can be formed of polymeric materials known to form hydrogels upon absorption of moisture. Suitably, in such embodiments, in use, upon insertion into skin the polymeric materials of said microneedles and base element can absorb moisture and increase in size to form swollen hydrogels; wherein therapeutic active agents can diffuse through said swollen base element and swollen hydrogel microneedles. In particular embodiments, the hydrophobic active agent can be provided from a reservoir; wherein said reservoir can be attached to the first side of the base element. In particular embodiments of the device, the reservoir can be a drug dispersed in a suitable matrix material, for example a suitable adhesive or non-adhesive polymer matrix, a fluid-containing reservoir or a dry reservoir or depot containing solid therapeutic active agent(s) for reconstitution by a liquid injected into said reservoir.

In an alternative embodiment of a transdermal delivery device of the invention, an attached reservoir is not present. In such embodiments, one or more hydrophobic drug substances or other hydrophobic beneficial substances may be contained within the base element. In addition to the one or more hydrophobic drug substances being provided in a reservoir and/or base element, one or more of the active agents may also be present in the microneedles themselves. Said substances can be either dissolved in a swellable polymer composition or suspended in particulate form. In embodiments in which the microneedles are composed of a swellable polymer, upon insertion into skin and swelling of the microneedles, the therapeutic active agents can be released into the skin at a rate determined by the degree of crosslinking of the microneedles and the water solubilities of the therapeutic active agents themselves.

A backing layer with an adhesive border extending beyond the area of the base element

of the microneedles may be used to keep microneedle-based devices in place on the skin surface for protracted periods of time, for example up to or greater than 72 hours. The surface of a base element of and, optionally, the microneedles themselves, may be coated with an adhesive material, so as to promote retention at the site of application.

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In particular embodiments, the one or more active agent(s) can be chemically bonded to polymer(s) making up the microneedles and base elements. In this case, the drug can be released upon insertion into the skin by, for example, hydrolysis, enzymatic or spontaneous non-catalysed breakage of the bonds holding it to the polymer(s). The rate of drug release can thus also be determined by the rate of reaction/bond breakage.

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Optionally, the polymeric composition of a polymeric-based microneedle array and/or base element can be adjusted such that it can be stimulus-responsive. For example, local changes in pH or temperature can alter the properties (eg ability to swell upon imbibing moisture) of the microneedles and base elements, such that a change in the rate of delivery of therapeutic active agent(s) occurs. Alternatively, an external stimulus, such as light illumination, can be used to affect a change in the properties of the microneedles and base elements, such that a change in the rate of delivery of therapeutic active agent(s) occurs.

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The polymeric composition of microneedles and base elements can be adjusted such that the surface properties of the device are altered, becoming more hydrophilic, lipophilic, anionic or cationic in character.

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Microneedle Arrays

Microneedles which may be used in the invention may be constructed from any suitable material. The microneedle device comprises microneedles composed of biocompatible polymers. For example, the polymers may be composed of swellable hydrogels, such as those described in WO 2009/040548.

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Microneedle arrays are prepared from hydrogel-forming materials and combined with drug reservoirs designed to enhance aqueous solubility of poorly soluble drugs. In such an embodiment, the microneedles puncture the skin and drugs are delivered as the

microneedles swell. In such an embodiment, the nominally-hydrophobic drugs are delivered through aqueous pores created by the swelling microneedles, with the rate of delivery controllable by selection of polymer and/or reservoir composition. Co-delivery of the reservoir amphipathic components maintain solubility of the hydrophobic active agent in the swollen hydrogel and skin interstitial fluid, enabling enhanced permeation into the vessels of the rich dermal microcirculation, thus facilitating absorption.

Such microneedles can be fabricated from any suitable swellable polymer, which in its dry state is hard and sharp to allow penetration of the stratum corneum, but then which, upon taking up moisture, swells to allow diffusion of therapeutic active agents. Microneedles for use in the invention may be composed of polymers of poly(methylvinylether/maleic acid) or poly(methylvinylether/, maleic anhydride) and derivatives thereof.

Suitable such polymers include Gantrez -S ® polymers, for example Gantrez S-97 polymers, or Gantrez -AN polymers (Ashland, USA).

The polymers of such microneedles are crosslinked, either physically, chemically or both. The degree of cross-linking is sufficient to prevent substantial dissolution of the microneedles in interstitial fluid but not so much to prevent swelling of the microneedles. The microneedle array can comprise groups of microneedles wherein a first group comprises at least one different cross-linker to at least a second group.

Further, to modulate the rate of delivery of a drug through the skin, an agent deliverable by a microneedle device of the invention, for example a hydrophobic drug, can be encapsulated within polymeric nanoparticles to further modulate their release from microneedles. The amphipathic agent could also be in the nanoparticles. In an alternative embodiment, the nanoparticles could be dispersed in a solid or liquid reservoir containing the amphipathic agent.

Combinations of lightly crosslinked and/or extensively crosslinked microneedles can be combined in a single device so as to deliver a bolus dose of an active agent e.g. or therapeutic substance(s), achieving a therapeutic plasma level, followed by controlled delivery to maintain this level.

Optionally, the base element and microneedles may contain defined quantities of one or more water soluble excipients in their matrix. Upon insertion into skin these excipients will dissolve leaving pores behind in the matrix of the base element and microneedles.

5 This can enhance the rate of release, which can be further controlled by changing the excipient, its concentration and/or its particle size. Suitable excipients include, but are not limited to glucose, dextrose, dextran sulfate, sodium chloride and potassium chloride or other water soluble excipients known in the art.

10 In order to be of use in transdermal delivery, arrays of microneedles must be capable of creating openings in the stratum corneum barrier through which beneficial substances can move. Thus, the force of insertion is less than the force required to fracture the microneedles. Suitably, the microneedles do not fracture when a pressure of insertion of less than 50 N cm⁻², for example less than 30 N cm⁻², such as less than 10 N cm⁻² is
15 exerted on the microneedles along their length.

A microneedle can be any suitable size and shape for use in an array to puncture the stratum corneum. The microneedles of the array of the first aspect of the present invention are designed to pierce and optionally cross the stratum corneum. Suitably,
20 the length of the microneedles can be altered so as to allow penetration into the upper epidermis, as far as the deep epidermis or even the upper dermis, but not allowing penetration deep enough into the skin to cause bleeding.

The choice of microneedle structure and size may thus depend on the site of utilisation.
25 For example, where the microneedle device is envisaged for use in skin of the arm, shoulder, hip or chest regions, the physician may employ a microneedle device with longer microneedles than for use in skin of the face, for example the periorbital area. Application to the face, in particular the periorbital area, may be of particular use in cosmetic applications.

30 In one embodiment, the microneedle device comprises microneedles of length in the range 50-4000 µm, such as 350-1200 µm for example 400-1000 µm. In another embodiment, for example for use on skin of the face, the microneedle device may comprise microneedles of length in the range 80-600 µm, for example 100-300 µm.

Suitably, in embodiments of the microneedle device of the invention, microneedles can have a width, e.g. diameter in the case of microneedles of circular cross-section, of 1 - 500 μm at their base. Optionally microneedles of and for use in the invention can have a diameter in the range 50-300 μm , for example 100-200 μm . In another embodiment, microneedles for use in the invention may be of a diameter in the range of 1 μm to 50 μm , for example in the range 20-50 μm .

The apical separation distance between each of the individual microneedles in an array can be modified to ensure penetration of the skin while having a sufficiently small separation distance to provide high transdermal transport rates. Optionally the range of apical separation distances between microneedles can be in the range 50 -1000 μm , such as 100-300 μm , for example 100-200 μm . This allows a compromise to be achieved between efficient penetration of the stratum corneum and enhanced delivery of therapeutic active agents or passage of interstitial fluid or components thereof.

It will be apparent to those skilled in the art that the microneedles for use in devices of the invention can take any reasonable shape, including, but not limited to, microneedles, cones, rods and/or pillars. As such, the microneedles may have the same diameter at the tip as at the base or may taper in diameter in the direction base to tip. The microneedles may have at least one sharp edge and may be sharp at the tips. In embodiments of the transdermal delivery device of the invention, the microneedles may optionally have a hollow bore down at least one longitudinal axis at an angle to the base element and extending to the first side of the base element or they may be porous. In one embodiment, the microneedles are conical in shape with a circular base which tapers to a point at a height of the microneedle above the base.

In use, the microneedles may be inserted into the skin by gentle applied pressure or by using a mechanical applicator suitable for applying the required pre-defined force. An additional device may be used to reduce the elasticity of skin by stretching, pinching or pulling the surface of the skin so as to facilitate insertion of the microneedles. This latter function could be usefully combined with the function of the applicator to produce a single integrated device for insertion of a microneedle array.

Transdermal delivery devices of and for use in the invention can be affixed to the skin or other tissue to deliver active agents continuously or intermittently, for example for durations ranging from a few seconds to several hours or days.

5 Transdermal delivery devices of the invention may comprise groups of microneedles having different characteristics from each other, for example having different shapes, polymer compositions, crosslinkers or degrees of crosslinking, thus enabling a single microneedle array to have regions which can deliver active agents, e.g. drugs at different rates. This would enable, for example, a rapid bolus to be delivered to a patient on
10 positioning of the microneedle array followed by a slower sustained release of the same active agent. Indeed, in one embodiment, the microneedle devices of the invention may be used to deliver more than one active agent, for example two or more hydrophobic drugs, or at least one hydrophobic drug and at least one hydrophilic drug, or at least one hydrophobic drug and at least one amphipathic drug from the same transdermal
15 therapeutic device. For example, a first active agent could be comprised within a polymer of which swellable microneedles are composed with a second active agent stored in the reservoir. On positioning on the skin and puncturing of the stratum corneum, the microneedles will swell and the active agent will be released from the microneedles. Subsequently, the second active agent may be released from the reservoir
20 and enter the skin via the microneedles.

In such embodiments, drug contained in the microneedles themselves will be rapidly released upon swelling, initially as a burst release due to drug at the surface of the microneedles. The subsequent extent of release will be determined by one or more of
25 the crosslink density, the physicochemical properties of the drug, and the physicochemical properties of the amphipathic agent. Release of hydrophobic drug from the drug reservoir will occur more slowly at first as a result of the time required to swell the microneedles up as far as the drug reservoir, subsequent partitioning of the drug into the swollen microneedles and diffusion of the drug through the swollen matrix.
30 The microneedles of the microneedle devices of the invention may thus be adapted to deliver two active agents in succession, with the composition adapted, e.g. by crosslinking of the composition of the microneedles, to vary delivery times of one or both active agents.

Microneedles composed of polymers known to form hydrogels can be manufactured by any such methods known in the art. For example, they can be prepared by a micromoulding technique using a master template, such as a microneedle array made from one or more of a wide variety of materials, including for example, but not limited to; silicon, metal polymeric material. Master templates can be prepared by a number of methods, including, but not limited to, electrochemical etching, deep plasma etching of silicon, electroplating, wet etch processes, micromoulding, microembossing, drawing lithography /“thread-forming” methods and by the use of repetitive sequential deposition and selective x-ray irradiation of radiosensitive polymers to yield solid microneedle arrays.

Micromoulds can be prepared by coating the master template with a liquid monomer or polymer which is then cured and the master template removed to leave a mould containing the detail of the master template. In the micromoulding technique, a liquid monomer, with or without initiator and/or crosslinking agent is placed in the mould, which is filled by means of gravitational flow, application of vacuum or centrifugal forces, by application of pressure or by injection moulding. The monomer may then be cured in the mould by means of heat or application of irradiation (for example, light, UV radiation, x-rays) and the formed microneedle array, which is an exact replicate of the master template is removed. Alternatively, a solution of a polymer with or without crosslinking agent can be placed in the mould, which is filled by means of gravitational flow, application of vacuum or centrifugal forces, by application of pressure or by injection moulding. The solvent can then be evaporated to leave behind a dried microneedle array, which is an exact replicate of the master template, and can then be removed from the mould. The solvents that can be used include, but are not limited to, water, acetone, dichloromethane, ether, diethylether, ethyl acetate. Other suitable solvents will be obvious to one skilled in the art. Micromoulds can also be produced without the need for master templates by, for example, micromachining methods and also other methods that will be obvious to those skilled in the art.

Microneedles composed of polymers known to form hydrogels can also be manufactured using a “self-moulding” method. In this method, the polymeric material is first made into a thin film using techniques well known in the art, including for example, but not limited to, casting, extrusion and moulding. The material may, or may not be

crosslinked before the “self moulding” process. In this process, the thin film is placed on a previously-prepared microneedle array and heated. Plastic deformation due to gravity causes the polymeric film to deform and, upon hardening, create the desired microprojection structure.

5

Microneedles composed of polymers known to form hydrogels can also be manufactured using a “thread forming” method whereby a polymer solution spread on a flat surface has its surface contacted by a projection which is then moved upwards quickly forming a series of polymer “threads”, which then dry to form microneedles.

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Microneedles with a hollow bore can be manufactured by using moulds prepared from hollow master templates or suitably altering the micromachining methods or other methods used to prepare solid microneedles. Hollow bores can also be drilled mechanically or by laser into formed microneedles

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In such methods, substances to be incorporated into the microneedles themselves (e.g., active therapeutic agents, pore forming agents, enzymes etc.) can be added into the liquid monomer or polymer solution during the manufacturing process. Alternatively, such substances can be imbibed from their solution state in a solution used to swell the formed microneedle arrays and dried thereafter or the formed arrays can be dipped into a solution containing the agent of interest or sprayed with a solution containing the agent of interest. Solvents used to make these solutions include water, acetone, dichloromethane, ether, diethylether, ethyl acetate. Other suitable solvents will be obvious to those skilled in the art, as will the processes used to dry the microneedle arrays. If the microneedles and/or base elements are to be made adhesive, the formed arrays can be dipped into a solution containing an adhesive agent or sprayed with a solution containing an adhesive agent. The adhesive agents used can be a pressure sensitive adhesive or a bioadhesive. These substances are well known and will be obvious to those skilled in the art.

25

The base element on which the microneedles are formed can be varied in thickness by suitable modification of the method of manufacture, including, for example, but not limited to, increasing the quantity of a liquid monomer or polymer solution used in the manufacturing process. In this way the barrier to diffusion/transport of therapeutic

active agents and/or analytes of interest can be controlled so as to achieve, for example rapid delivery or sampling or sustained release. Where therapeutic active agent(s) is/are to be contained within the matrix of the microneedles and/or the base element, the thickness of the base element can usefully be increased so as it functions as a fully integrated reservoir portion.

Cross Linking

Crosslinks may be physical or chemical and intermolecular or intramolecular. Methods for crosslinking polymers are well known in the art. Crosslinking is the process whereby adjacent polymer chains, or adjacent sections of the same polymer chain, are linked together, preventing movement away from each other. Physical crosslinking occurs due to entanglements or other physical interaction. With chemical crosslinking, functional groups are reacted to yield chemical bonds. Such bonds can be directly between functional groups on the polymer chains or a crosslinking agent can be used to link the chains together. Such an agent must possess at least two functional groups capable of reacting with groups on the polymer chains. Crosslinking prevents polymer dissolution, but may allow a polymer system to imbibe fluid and swell to many times its original size.

Hydrophilicity and Hydrophobicity

The degree to which a compound is hydrophilic or lipophilic may be categorised according to the hydrophilic-lipophilic balance (HLB) value of the compound. The HLB value of a compound may be calculated according to the method of Griffin ((1949), *"Classification of Surface-Active Agents by 'HLB', Journal of the Society of Cosmetic Chemists*, 1 (5): 311-26 and *"Calculation of HLB Values of Non-Ionic Surfactants" Journal of the Society of Cosmetic Chemists*, 5 (4): 249-56), according to the formula

$$HLB=20 M_h/M$$

where M_h is the molecular mass of the hydrophilic portion of the molecule and M is the molecular mass of the whole molecule, giving a scale of 0 to 20. A compound having an HLB value of 0 is completely lipophilic/hydrophobic, whereas a compound having an HLB value of 20 is completely hydrophilic/lipophobic. Recently, ionic surfactants have been assigned relative HLB values, extending the range of HLB values to 60.

The relative hydrophilicity /hydrophobicity of a drug may be expressed in terms of the logarithm of its partition coefficient, P , which is defined as the ratio of concentrations of the drug between water and a non-polar solvent (typically octanol):

$$\text{Log } P_{\text{octanol/water}} = \log ([\text{drug}]_{\text{octanol}} / [\text{drug}]_{\text{water}})$$

Amphipathic Component

Amphipathic agents are chemical compounds which comprise both hydrophilic and hydrophobic properties. Amphipathic components used in the invention act to bridge the solubility gap. They essentially act as co-solvents to firstly keep the hydrophobic drug in solution (liquid solution or solid solution, depending on the nature of the reservoir) and then to stop it from coming out of solution as it diffuses through the hydrophilic matrix of the swollen microneedles during delivery. By delivering the amphipathic agent along with the drug, the drug will also not come out of solution when it reaches the aqueous environment of the viable epidermis/dermis after being released from the microneedles. Suitable amphipathic components which may be used in the invention include but are not limited to, poly(ethyleneglycol), propyleneglycol, glycerol, tripropyleneglycolmonomethylether, surfactants, block copolymers, biocompatible oils, waxes or synthetic tri- or poly-glycerides.

In particular embodiments of the invention, the at least one amphipathic component comprises a polymer of polyethylene glycol, propylene glycol, or polysorbate. In certain embodiments two or more amphipathic components are used. For example, in order to obtain the solubilisation conditions required for a certain drug, PEG 10,000 may be mixed with PEG 300 and polyoxyethylensorbitan mono-oleate (also known as Tween 80 or polysorbate 80). The choice of amphipathic agents and combinations of amphipathic agents will depend on the choice of hydrophobic drug to be delivered, the desired rate of delivery, the matrix components etc.

In particular embodiments, the at least one amphipathic component has a molecular weight in the range 0.1-60 kDa, for example 0.2-50 kDa.

Optionally, the amphipathic component has a hydrophilic-lipophilic balance (HLB) value in the range 7.0-18.0, for example, 7.0-16.0, such as 8.0 -15.0, such as 8.0- 14.0.

Where the transdermal delivery device comprises both a hydrophobic active agent and an amphipathic active agent, for example an amphipathic drug, the amphipathic active agent may act as the amphipathic component which enables co-delivery of the hydrophobic active agent. In an alternative embodiment in which the transdermal delivery device is used for delivery of both a hydrophobic active agent and an amphipathic active agent, the amphipathic component which enables co-delivery of the hydrophobic active agent may be a different amphipathic component from the amphipathic active agent and thus need not be an active, for example therapeutically active, agent.

Optionally, the rate of delivery of the hydrophobic active agent or agents is enhanced by the amphipathic components(s) of the matrix or reservoir by a factor of at least 10, such as at least 20, 30, 50, 75, 100, 125, 150 or 200 compared to a corresponding transdermal delivery device in which the amphipathic component (s) is/are not present.

Optionally, the aqueous solubility of the hydrophobic active agent or agents is enhanced by the presence of the amphipathic components(s) of the matrix or reservoir by a factor of at least 20, 30, 50, 75, 100, 125, 150 or 200 compared to a corresponding transdermal delivery device in which the amphipathic component (s) is/are not present.

Optionally, the total dose of hydrophobic active agent or agents which may be delivered using the transdermal delivery device of the invention is at least 10 fold, such as at least 20 fold, 30 fold, 50 fold, 75 fold, 100 fold, 125 fold, 150 fold or 200 fold that of a corresponding transdermal delivery device in which the amphipathic component (s) is/are not present.

Active Agents

The transdermal delivery devices of the invention may be used to deliver any suitable hydrophobic active agent. For example, the active agent may be a drug, a vaccine, a nutrient or a cosmetic agent. The term drug includes 'beneficial substances' for the treatment or prophylaxis of disease, for example, drug substances, substances that may

improve the general health of the skin, for example, vitamins and minerals, and substances that may improve the aesthetic appearance of the skin, for example, by reducing the appearance of wrinkles or improving the degree of hydration of the skin.

5 Non-limiting examples of drugs suitable for delivery using such a device include oligonucleotides, proteins, enzymes, antigens, nucleic acids, growth factors, and polysaccharides, as well as smaller molecules, synthetic organic and inorganic compounds such as antibiotics, anti-infectives, hormones, drugs relating to cardiac action and blood flow, drugs for pain control, steroids, sedatives, anxiolytics, 10 neuroleptics, anti-depressants, anti-neoplastics, drugs used to control disease (eg HIV), lipid-lowering agents etc.

The invention will be particularly useful for the delivery of drugs having a Log *P* value of greater than 1.5, for example greater than 2.0, 3.0, 4.0, or 5.0.

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The British Pharmacopoeia defines a substance which requires more than 10000 parts of solvent by volume to dissolve one part of the substance by weight to be practically insoluble. In certain embodiments of the invention, the hydrophobic active agent is practically insoluble in water i.e. , less than 0.1g of the active agent is soluble in 1 litre of 20 water.

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The transdermal delivery device of the invention is particularly suitable to the delivery of hydrophobic active agents which are otherwise difficult to deliver by passive transdermal means. Such molecules include ionic molecules such as bisphosphonates 25 etc.

25

In one embodiment, the drug can be for local treatment or regional therapy.

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Optionally, the transdermal delivery device of the invention may be used for the co-delivery of two or more active agents. In one such embodiment, the two or more active agents are hydrophobic agents. In another embodiment, at least one active agent is a hydrophobic agent and at least one other active agent is either an amphipathic active agent or a hydrophilic active agent. In another embodiment, the transdermal delivery device of the invention may be used for the simultaneous delivery of (i) one or more

hydrophobic agents and (ii) one or more amphipathic active agents and/or one or more hydrophilic active agents.

A particular advantage of the present invention is that by co-delivery of the amphipathic component with the hydrophobic active agent, doses of hydrophobic agent suitable for systemic therapy may be delivered. Thus in one embodiment of the invention, the transdermal delivery device is for delivery of therapeutically-active doses of the hydrophobic agent suitable for systemic treatment. For example, the reservoir portion may comprise per cm² of area at least 7mg, for example at least 10mg, at least 20mg, at least 30mg, at least 40mg, at least 50mg, at least 75 mg or at least 100mg of the hydrophobic agent. Optionally in use, at least 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the hydrophobic agent in the reservoir portion is delivered via the microneedles into the skin over a period of treatment. For example, in an embodiment wherein per cm² said reservoir comprises at least 10mg of said at least one hydrophobic agent, in use, at least 50% of the total volume of hydrophobic agent in the reservoir may be delivered via the microneedles into the skin over a treatment period. Suitable periods of treatment may be, for example, 1-4 hours, 4-6 hours, 6-12 hours 12-24 hours, or 24-72 hours. The precise volume of hydrophobic drug comprised in the reservoir portion and the treatment period duration will of course depend on a number of factors within the knowledge of the physician treating a patient and include the nature of the drug, the condition being treated and the patient being treated.

The transdermal delivery devices of the invention may be of any suitable size for delivery of drugs. For example, the devices may have an area in the range 5-50cm², for example 20 -40cm². Typically the reservoir portion of the device will have an area the same or at least 90% of the total area of the device.

In embodiments of the transdermal delivery device, the transdermal delivery device can comprise a reservoir or matrix upon which microneedles can be attached. In particular embodiments, in use, the reservoir or matrix can comprise the hydrophobic agent to be delivered, for example a drug which, together with the amphipathic component, on insertion of the microneedle into the skin, flows from the reservoir or matrix through the microneedle to the delivery site.

In particular embodiments, prior to flowing through the microneedles, an agent to be delivered can be stored in a reservoir or matrix. The reservoirs can be deformable. In particular embodiments, the reservoirs can be sub- divided into a number of chambers wherein each chamber supplies different agents simultaneously or sequentially into the delivery site.

In particular embodiments, a device of the invention and optionally a reservoir or matrix can be incorporated into a wrist band or conveniently worn by a patient.

Sensors

The transdermal delivery devices of the invention may optionally comprise at least one pressure indicator. The pressure indicator provides a detectable signal when pressure exceeding a predetermined minimal level is applied to the device. For example, the predetermined minimal level may be greater than 5 Ncm⁻², for example in the range 10 Ncm⁻² to 40 Ncm⁻², such as 15 Ncm⁻² to 30 Ncm⁻². The user can thus determine when sufficient pressure has been applied for insertion of the microneedle array.

Optionally, the transdermal delivery devices of the invention may also comprise a second pressure indicator which provides a detectable signal when pressure exceeding a predetermined maximal level is applied to the microneedle device. Such a second pressure indicator thus enables the user to determine when more than optimal pressure or too much pressure is being applied.

In the invention, any suitable means of detecting and indicating pressure applied to the transdermal delivery device may be used. In one embodiment, the pressure indicator is a pressure sensitive film, which, for example, provides a visual signal when pressure exceeding a predetermined minimal level is applied.

In one embodiment, the pressure sensitive film comprises a layer in which a colour indicator is comprised within, for example, micro bubbles. Application of pressure greater than a predetermined minimal level results in bursting of the micro bubbles, thus releasing the colour indicator within the indicator layer, with the greater the pressure applied, the more bubbles being burst and the more intense the colour.

In an alternative embodiment, the pressure sensitive film may comprise two layers, the first of which is an adhesive receiver layer and the second of which is a layer impregnated with coloured microparticles. Once a pressure greater than a predetermined minimum is applied, the coloured microparticles are transferred to the receiver layer, providing a visual indication that a predetermined minimal pressure has been applied. For example, a suitable pressure sensitive film which may be used in the present invention is the Pressurex® Microgreen PMG2 (Sensor Products Inc, Madison, NJ, USA).

In embodiments which comprise a first pressure indicator for indicating the application of pressure beyond a predetermined minimal level and a second pressure indicator for indicating the application of pressure beyond a predetermined maximal level, the pressure sensitive film may comprise, for example, two layers, the first layer comprising microbubbles which release a colour indicator when a predetermined minimal level of pressure is applied and the second layer comprising microbubbles which release a different colour indicator when a predetermined maximal level of pressure is applied.

As well as colour indicators, any other suitable type of indicator may be used. For example, other types of indicators which may be used include pressure sensitive electrical conductors, conductive pressure sensitive textiles, strain gauge type sensing elements or tactile sensors/indicators.

For example, the pressure indicator may comprise a pressure sensitive electrical conductor, such as a strip of conducting material. For example, in such an embodiment on application of pressure exceeding a predetermined minimal level or a predetermined maximal level, the change in conductivity of the material results in activation of a visual indicator, such as an LED.

In another embodiment, the pressure indicator may comprise a conductive pressure sensitive textile. For example, such a conductive pressure sensitive textile may comprise a first plurality of elongated electrical conductors crossed by a second plurality of elongated electrical conductors, the conductors being separated at crossover points, such that, on application of a predetermined minimal pressure, the conductors make

contact, enabling activation of a switch operating a visual indicator such as an LED. An example of such material is described, for example, in US2003/0119391.

In an alternative embodiment, the pressure sensitive electrical conductor may be comprised in a strain gauge type sensing element. Such a sensing element may comprise a resistive foil mounted on a backing material, wherein when the foil is subjected to a predetermined minimal pressure, the resistance of the foil changes and via a detector mechanism such as a Wheatstone bridge circuit, a signal output is generated which may activate a visual indicator.

In a further embodiment, the pressure indicator may comprise a tactile sensor. Such a sensor may comprise a layer having one or more textural elements, such as an array of tactile pins, for example Braille like characters covered with at least one covering layer. The covering layer may comprise compressible material. The tactile sensor may be arranged such that when applying pressure to the pressure indicator at a pressure below a predetermined minimal level, the textural elements are not detectable through the covering layer by the finger(s) of the user applying the pressure. However, when a pressure at or above the predetermined minimal level, for example 15 N cm^{-2} , is applied, the textural elements are detectable through the covering layer by the user.

The invention will now be described further in the following non-limiting examples with reference made to the accompanying drawings in which:

Figure 1 shows dissolution curves for: (A) pure PEG 3000/6000/8000, (B) 50% PEG 3000/6000/8000 + 50% PEG 400 and (C) 25% PEG 3000/6000/8000 + 75% PEG 400.

Figure 2 shows dissolution curves for different formulations containing PEG 6000 and another compound: (A) formulations containing 50% of PEG 6000 and (B) formulations containing 25% of PEG 6000. The only exception are formulations called PEG 6000 that are composed of 100% of this polymer.

Figure 3 illustrates tablet dissolution kinetics: A (F1 – F4), B (F5 – F8), C (F9 – F12). Mean $\pm$ SD, $n = 5$.

Figure 4 illustrates FTIR spectra of pure PEG 6000, PEG 400 and carvedilol. Also included are representative FTIR spectra of physical mixtures (PM)s and solid

dispersions (SD)s formulated as a binary component system (A) and a tenary component system (B).

Figure 5 illustrates DSC thermograms of pure PEG 6000, PEG 400 and carvedilol. Also included are representative FTIR spectra of physical mixtures (PM)s and solid
5 dispersions (SD)s formulated as a binary component system (A) and a tenary component system (B).

Figure 6 illustrates in vitro cumulative permeation profile of Nile Red from (a) PEG 400:PEG 6000 75:25 tablets and, (b) Tween 80:PEG 6000 50:50 tablets.

Figure 7 illustrates in vitro permeation profile for the first 4 hours of atorvastatin calcium trihydrate permeation across dermatomed 350 μ m neonatal porcine skin when
10 delivered using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from different ratios of PEG 400 and PEG 6000 (means $\pm$ S.D., n = 3).

Figure 8 illustrates an in vitro permeation profile of atorvastatin calcium trihydrate
15 across dermatomed 350 μ m neonatal porcine skin over 24 h when delivered using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from different ratios of PEG 400 and PEG 6000 (means $\pm$ S.D., n = 3).

Figure 9 illustrates an in vitro permeation profile of atorvastatin calcium trihydrate across dermatomed 350 μ m neonatal porcine skin over 24 h when delivered using
20 hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from 50% propylene glycol and 50% PEG 10,000 (means $\pm$ S.D., n = 4).

Figure 10 illustrates an in vitro permeation profile of aspirin across dermatomed (350 μ m) neonatal porcine skin when delivered using hydrogel-forming Gantrez® S-97 MN arrays with drug reservoirs prepared from 50:50 ratios of PEG 400:PEG 6000
25 and propylene glycol:PEG 10,000 (means $\pm$ S.D., n = 4).

Figure 11 illustrates an in vitro permeation profile of lisinopril dihydrate across dermatomed (350 μ m) neonatal porcine skin when delivered using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from 50:50 ratio of propylene glycol:PEG 10,000 (means $\pm$ S.D., n = 4).

Figure 12 illustrates an *in vitro* cumulative permeation profile of carvedilol across 350 μm thick dermatomed porcine skin when delivered from PEG tablets containing 5 %w/w carvedilol using in-swelling 'regular' (A) and 'super-swelling' (B) hydrogel microneedle arrays to act as a conduit through porcine skin at 37°C. In both cases values are expressed as mean $\pm$ SD, n = 3.

Figure 12C illustrates an *in vitro* percentage permeation profile of lisinopril dihydrate (Lis), aspirin (Asp) and atorvastatin calcium trihydrate (Atr) across dermatomed 350 μm neonatal porcine skin over 24 h when delivered simultaneously using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoir prepared from 50% w/w propylene glycol and 50%

Figure 13 illustrates Franz cell set-up for evaluating delivery from liquid reservoirs in conjunction with hydrogel-forming microneedle arrays.

Figure 14 illustrates an *in vitro* cumulative permeation profile of Nile Red dissolved in PEG 400 (350 $\mu\text{g/mL}$) in a liquid reservoir across dermatomed neonatal skin using hydrogel-forming Gantrez® S-97 microneedles (means $\pm$ S.D., n = 4).

Figure 15 illustrates an *in vitro* permeation profile of atorvastatin calcium trihydrate across dermatomed 350 μm neonatal porcine skin over 24 h when delivered using hydrogel-forming Gantrez® S-97 MN arrays with a liquid drug reservoir of either propylene glycol or PEG 400 (means $\pm$ S.D., n = 4).

Examples

FORMULATION

EXAMPLE 1

Method

Empty hydrophobic drug reservoirs were formulated using different compounds. The selected compounds were weighed in a beaker. The mixture always contained at least one solid product. Subsequently, this beaker was placed inside a convection oven to melt the solid compound. Once all products were melted, the mixture was stirred,
5 placed in moulds and cooled at ambient temperature until a solid drug reservoir was obtained.

Results

The compounds used were: polyethylene glycols (PEG) with molecular weight ranging from 400 to 35,000; Propyleneglycol; Surfactants such as Tween 80 and Pluronic F127
10 (F127). Table 1 contains all different combinations of these compounds that were used to obtain solid tablets.

Table 1. Formulations used to prepare solid tablets following the method previously described

	Composition (%)									
	PEG 200	PEG 400	Tween 80	Prop. Glycol	PEG 3000	PEG 6000	PEG 8000	PEG 10000	PEG 35000	F127
F1	25	-	-	-	-	-	-	75	-	-
F2	50	-	-	-	-	-	-	50	-	-
F3	75	-	-	-	-	-	-	25	-	-
F4	80	-	-	-	-	-	-	20	-	-
F5	85	-	-	-	-	-	-	15	-	-
F6	87.5	-	-	-	-	-	-	12.5	-	-
F7	-	50	-	-	50	-	-	-	-	-
F8	-	75	-	-	25	-	-	-	-	-
F9	-	85	-	-	15	-	-	-	-	-
F10	-	50	-	-	-	50	-	-	-	-
F11	-	75	-	-	-	25	-	-	-	-
F12	-	85	-	-	-	15	-	-	-	-
F13	-	90	-	-	-	10	-	-	-	-
F14	-	50	-	-	-	-	50	-	-	-
F15	-	75	-	-	-	-	25	-	-	-
F16	-	85	-	-	-	-	15	-	-	-
F17	-	90	-	-	-	-	10	-	-	-
F18	-	25	-	-	-	-	-	75	-	-
F19	-	50	-	-	-	-	-	50	-	-
F20	-	75	-	-	-	-	-	25	-	-
F21	-	80	-	-	-	-	-	20	-	-
F22	-	85	-	-	-	-	-	15	-	-
F23	-	87.5	-	-	-	-	-	12.5	-	-
F24	-	85	-	-	-	-	-	-	15	-
F25	-	90	-	-	-	-	-	-	10	-
F26	-	95	-	-	-	-	-	-	5	-
F27	-	-	50	-	50	-	-	-	-	-
F28	-	-	75	-	25	-	-	-	-	-
F29	-	-	50	-	-	50	-	-	-	-
F30	-	-	75	-	-	25	-	-	-	-
F31	-	-	50	-	-	-	50	-	-	-
F32	-	-	75	-	-	-	25	-	-	-
F33	-	-	50	-	-	-	-	50	-	-
F34	-	-	75	-	-	-	-	25	-	-
F35	-	-	-	50	50	-	-	-	-	-
F36	-	-	-	75	25	-	-	-	-	-
F37	-	-	-	50	-	50	-	-	-	-
F38	-	-	-	75	-	25	-	-	-	-
F39	-	-	-	75	-	-	25	-	-	-
F40	-	-	-	50	-	-	-	50	-	-

DISSOLUTION STUDIES

EXAMPLE 2

Method

5 The dissolution kinetics of different tablet formulations were tested. For this purpose, one tablet (0.33 g) was placed in a test tube containing 15 mL of PBS (pH 7.4). The test tubes were placed in a shaking water bath at 37°C. Tubes were shaken during all the process at 80 strokes per minute. At different time intervals tablets were removed from the tube, dried with tissue paper and weighted. The weight loss was evaluated using the
10 following equation:

$$\% \text{ Weight loss} = 100 \times \frac{w_0 - w_t}{w_0}$$

Where w_0 is the initial weight of the tablet and w_t is the weight of the tablet at time t .

Results

15 Figure 1A shows the dissolution curves of tablets prepared using molten solid polyethylene oxide (PEG) polymers of different molecular weights (3000, 6000 and 8000). As can be seen the dissolution profile of PEG 3000 tablets is faster than those of PEG 6000 and PEG 8000. Additionally the dissolution profile of PEG 6000 and PEG 8000 can be considered equivalent.

20 These types of formulations can be prepared mixing a high molecular weight PEG with a lower molecular weight molecule. If PEG 400 is added to the formulation (50% of solid PEG and 50% of PEG 400) the dissolution kinetic is accelerated in all cases (Figure 1B). Besides, if the amount of PEG 400 is increased (up to 75%) the observed dissolution process was even faster (Figure 1C). However, the slower dissolution can be obtained
25 for the formulations containing PEG 8000 (Figure 1B and 1C), followed by those containing PEG 6000.

As alternatives to PEG 400 different molecules were used such as propylene glycol and Tween 80. Figure 2 shows the influence of these molecules in the dissolution of PEG 6000 based formulations. Formulations containing propylene glycol showed the fastest dissolution profile followed by those containing PEG 400 and finally those containing Tween 80. In all cases the pure PEG 6000 formulation showed the slowest dissolution profile.

MECHANICAL CHARACTERIZATION TABLETS

EXAMPLE 3

Methods

Tablet formulation

Tablets were formulated as described in EXAMPLE 1. The different formulations are described in Table 2.

Table 2: Table of investigated formulations.

Formulation composition	Formulation code
PEG 3000	F1
PEG 3000: PEG 400 (3:1)	F2
PEG 3000: PEG 400 (1:1)	F3
PEG 3000: PEG 400 (1:3)	F4
PEG 6000	F5
PEG 6000: PEG 400 (3:1)	F6
PEG 6000: PEG 400 (1:1)	F7
PEG 6000: PEG 400 (1:3)	F8
PEG 8000	F9
PEG 8000: PEG 400 (3:1)	F10
PEG 8000: PEG 400 (1:1)	F11
PEG 8000: PEG 400 (1:3)	F12

Mass and thickness uniformity

Twenty tablets were randomly selected, weighed individually and their average mass calculated to determine mass uniformity. The percentage deviation of each tablet's mass

from the average mass was determined. A digital micrometre (Digital Calliper, 0-150mm, Jade Produces Rugby Limited, Warwickshire, UK) was used to determine the individual thicknesses of twenty randomly selected tablets, from which the average thickness was calculated. Percentage deviation of each tablet's thickness from the average value was then computed.

Friability

Prior to testing, a sample of tablets with a total mass (W_0) approaching 6.5 g were weighed (i.e. 44 for tablets of 2 mm thickness and 22 for tablets of 4 mm thickness). Friability of tablets was carried out as per British Pharmacopoeial guidelines (BP 2015, Volume 5) in a friability tester (uncoated) (Copley Scientific, Nottingham, UK). The drum was operated at 25 rpm for 4 min (i.e. 100 rotations). The tablets were then weighed again (W). The % friability was then calculated using the following equation.

$$\% \text{ Friability} = \left[\frac{(W - W_0)}{W_0} \right] \times 100$$

Diametrical compression test

Tablets of a predefined mass and thickness were placed onto the platform of a TA-TX2 Texture Analyser (Stable Micro Systems, Surrey, UK) (50 kg load cell) under distance mode so that a force was applied by a cylindrical probe (length 150 mm, diameter 35 mm) along a tablet's longest axis. Test parameters were as follows; pre-test speed 5 mm/s, test speed 1 mm/s, post-test speed 4.5 mm/s, distance 5 mm, hold time 15 sec, trigger force 50 grams. Ten measurements were made for each formulation at ambient temperature. The maximum force and work done to along the loaded diameter was derived from force-distance plots produced by the Exponent software (v6.0.2.0, Stable Micro Systems, Surrey, UK).

Tablet dissolution kinetics

To gain an understanding on the dissolution kinetics of the tablets in an aqueous medium pre-weighed tablets were placed into 10ml of PBS pH 7.4. At pre-defined times tablets and any visible fragments of tablets were carefully removed and blotted dry with filter paper before weighing again. Measurement was halted once the tablet had completely dissolved. Percentage mass change was then calculated using the following equation, where M_0 = initial mass and M = mass at a given time.

$$\% \text{ Mass change} = \left[\frac{(M - M_0)}{M_0} \right] \times 100$$

Results

All tablets produced were of a consistent mass, thickness and diameter (Table 3). There was no significance difference between these parameters for any given formulation and all complied with the BP Pharmacopoeial standard for tablet friability. The molecular weight (MW) of solid PEG used (PEG 3000/ 6000/ 8000) and the proportion of PEG 400 employed both had a significant effect on the maximum force and work done to break/deform tablets.

Table 3: Mechanical properties of blank tablets (F1 – F12) and carvedilol-containing tablets (FC1 – FC12). Mean $\pm$ SD, $n = 10$ (except for friability as described in 3.2.4.2.).

Formulation	Mass (mg)	Thickness (mm)	Diameter (mm)	Friability (%)	Maximum force (N)	Mean work done (mJ)
F1	296.2 $\pm$ 7.5	3.90 $\pm$ 0.07	9.96 $\pm$ 0.10	-0.76	24.04 $\pm$ 1.76	23.28 $\pm$ 1.65
F2	298.3 $\pm$ 8.0	3.94 $\pm$ 0.09	9.97 $\pm$ 0.09	-1.01	8.07 $\pm$ 1.13	7.29 $\pm$ 0.47
F3	294.3 $\pm$ 6.1	3.97 $\pm$ 0.09	10.00 $\pm$ 0.12	-0.50	3.84 $\pm$ 0.71	6.21 $\pm$ 0.59
F4	296.3 $\pm$ 9.1	3.94 $\pm$ 0.09	10.00 $\pm$ 0.09	-0.95	2.88 $\pm$ 0.55	3.97 $\pm$ 0.54
F5	300.2 $\pm$ 8.8	3.91 $\pm$ 0.07	9.96 $\pm$ 0.07	-0.79	29.77 $\pm$ 1.36	28.12 $\pm$ 3.24
F6	298.0 $\pm$ 7.7	3.94 $\pm$ 0.08	9.92 $\pm$ 0.06	-0.43	13.93 $\pm$ 1.71	12.43 $\pm$ 1.56
F7	296.7 $\pm$ 8.0	3.98 $\pm$ 0.10	9.95 $\pm$ 0.09	-0.99	12.19 $\pm$ 1.79	10.16 $\pm$ 1.08
F8	300.8 $\pm$ 6.8	3.94 $\pm$ 0.10	10.03 $\pm$ 0.11	-0.83	3.93 $\pm$ 0.34	5.45 $\pm$ 0.25
F9	301.1 $\pm$ 6.4	3.98 $\pm$ 0.04	9.97 $\pm$ 0.06	-0.18	36.87 $\pm$ 1.95	35.34 $\pm$ 2.18
F10	298.7 $\pm$ 5.4	3.97 $\pm$ 0.06	9.96 $\pm$ 0.10	-0.69	20.34 $\pm$ 1.90	17.29 $\pm$ 1.71
F11	295.2 $\pm$ 7.8	3.97 $\pm$ 0.08	9.96 $\pm$ 0.08	-0.91	15.28 $\pm$ 1.08	12.31 $\pm$ 0.89
F12	296.1 $\pm$ 5.7	3.91 $\pm$ 0.09	9.93 $\pm$ 0.10	-0.25	5.16 $\pm$ 0.52	7.40 $\pm$ 0.42

- 5 When placed into PBS pH 7.4 tablets started to dissolve instantly. Every formulation dissolved completely within 35 mins (Figures 3A/B/C). Similarly to what was found during diametrical compression there is a significant difference between the time for complete dissolution and the MW of solid PEG and mass of liquid PEG 400 used.

10 CHARACTERIZATION OF TABLETS CONTAINING A HYDROPHOBIC DRUG (CARVEDILOL)

EXAMPLE 4

Methods

Tablet formulation

Tablets were formulated as described in EXAMPLE 1. The different formulations are described in Table 4.

Table 4: Table of investigated formulations.

Formulation composition	Formulation code
PEG 3000: CAR (19:1)	FC1
PEG 3000: PEG 400: CAR (29:9:2)	FC2
PEG 3000: PEG 400: CAR (19:19:2)	FC3
PEG 3000: PEG 400: CAR (9:29:2)	FC4
PEG 6000: CAR (19:1)	FC5
PEG 6000: PEG 400: CAR (29:9:2)	FC6
PEG 6000: PEG 400: CAR (19:19:2)	FC7
PEG 6000: PEG 400: CAR (9:29:2)	FC8
PEG 8000: CAR (19:1)	FC9
PEG 8000: PEG 400: CAR (29:9:2)	FC10
PEG 8000: PEG 400: CAR (19:19:2)	FC11
PEG 8000: PEG 400: CAR (9:29:2)	FC12

(CAR-carvedilol)

Mechanical characterization

Performed as described in EXAMPLE 3.

ATR-FTIR spectral studies

Attenuated total reflectance (ATR)-Fourier transform infrared (FTIR) spectroscopy was used to study potential interactions between PEG and CAR. A FTIR Accutrac FT/IR-4100 Series (Jasco, Essex, UK) equipped with MIRacle™ diamond ATR accessory (Pike Technologies, Madison, Wisconsin) was used at room temperature. Pure samples of PEG 400, 3000, 6000 and 8000 Da and CAR, physical mixtures of PEG and CAR and blank PEG and CAR-containing PEG tablets were investigated. Samples were clamped between the stage of the sample holder and a digital torque controller. The digital display of the inbuilt force gauge allowed constant monitoring of the pressure applied to the sample.

The samples were scanned and recorded in the region of 4000–400 cm⁻¹ at a resolution of 4.0 cm⁻¹ and a gain of 8.

Differential scanning calorimetry (DSC)

- 5 DSC scans were performed with a DSC Q100 (TA instruments Ltd, Herts, UK) at a heating rate of 10°C/min over a temperature range of 20 – 150°C/min under nitrogen purge gas at a rate of 50 mL/min. Masses of samples were accurately weighed (5.0 - 10.0 mg of pure materials and PEG tablets) and sealed in crimped aluminium pans). The DSC machine was calibrated with the melting temperature of indium (156.6°C).
- 10 Endothermic peaks attributable to the melting of PEG and CAR were determined for all samples using TA Instruments Universal Analysis 200 software, version 4.4A (TA instruments, Elstree, Herts, UK)

Thermogravimetric analysis (TGA)

- 15 Percentage water content of the tablets was investigated using a Q500 Thermogravimetric Analyser (TA Instruments, Elstree, Herts, UK). Samples of 5.0 –10.0 mg were heated from 20°C to 300 °C at a heating rate of 10 °C/min. Nitrogen flow rates of 40 ml/min (balance purge gas) and 60 ml/min (sample purge gas) were maintained for all samples. TA Instruments Universal Analysis 200 software, version 4.4A (TA instruments, Elstree, Herts, UK) was then used to determine % water content from TGA traces.
- 20

Results

- 25 *Mechanical characterization*

Table 5 shows the results of the mechanical characterization of the tablets. No significant difference on the maximum force and work done was observed due to incorporation of CAR 5 %w/w into a tablet relative to its equivalent blank formulation (EXAMPLE 3) e.g. F1 and FC1 or F6 and FC6.

Table 5: Mechanical properties of blank tablets (F1 – F12) and carvedilol-containing tablets (FC1 – FC12). Mean $\pm$ SD, $n = 10$ (except for friability as described in 3.2.4.2.).

Formulation	Mass (mg)	Thickness (mm)	Diameter (mm)	Friability (%)	Maximum force (N)	Mean work done (mJ)
FC1	298.0 $\pm$ 5.0	3.96 $\pm$ 0.06	10.02 $\pm$ 0.05	-0.01	23.12 $\pm$ 1.75	22.48 $\pm$ 1.44
FC2	299.2 $\pm$ 4.1	3.97 $\pm$ 0.06	10.00 $\pm$ 0.09	-0.59	7.77 $\pm$ 0.64	6.92 $\pm$ 0.39
FC3	299.1 $\pm$ 3.6	3.99 $\pm$ 0.06	10.01 $\pm$ 0.07	-0.24	3.65 $\pm$ 0.55	5.99 $\pm$ 0.64
FC4	300.0 $\pm$ 5.6	3.97 $\pm$ 0.08	9.98 $\pm$ 0.09	-0.59	2.84 $\pm$ 0.37	3.91 $\pm$ 0.40
FC5	301.2 $\pm$ 5.7	3.99 $\pm$ 0.06	9.97 $\pm$ 0.04	-0.22	28.39 $\pm$ 1.43	26.43 $\pm$ 2.42
FC6	299.0 $\pm$ 4.9	3.94 $\pm$ 0.07	9.99 $\pm$ 0.04	-0.29	13.32 $\pm$ 1.22	12.21 $\pm$ 1.55
FC7	298.5 $\pm$ 4.1	3.99 $\pm$ 0.04	10.02 $\pm$ 0.07	-0.88	11.81 $\pm$ 1.32	9.89 $\pm$ 0.49
FC8	299.0 $\pm$ 7.2	3.95 $\pm$ 0.08	9.97 $\pm$ 0.07	-0.23	3.74 $\pm$ 0.48	5.22 $\pm$ 0.27
FC9	296.1 $\pm$ 7.7	3.99 $\pm$ 0.05	9.97 $\pm$ 0.05	-0.33	35.70 $\pm$ 1.87	34.52 $\pm$ 1.69
FC10	299.5 $\pm$ 3.5	3.97 $\pm$ 0.06	9.93 $\pm$ 0.07	-0.34	19.85 $\pm$ 1.87	16.80 $\pm$ 1.38
FC11	295.6 $\pm$ 7.8	3.97 $\pm$ 0.08	9.96 $\pm$ 0.08	-0.83	14.76 $\pm$ 1.09	11.52 $\pm$ 0.82
FC12	296.2 $\pm$ 6.1	3.95 $\pm$ 0.08	9.99 $\pm$ 0.06	-0.95	4.87 $\pm$ 0.43	7.15 $\pm$ 0.42

ATR-FTIR spectral studies

- 5 As PEGs are a family of polymers with a generalised chemical structure, every PEG IR spectra displayed a broad peak between 3100-3500 cm⁻¹ (O-H stretch), a strong, sharp peak at 2900 cm⁻¹ (C-H stretch) and a peak at 1109 cm⁻¹ (C-O stretching vibrations). Pure CAR IR spectra showed a peak at 3346 cm⁻¹ (O-H and N-H stretching merged together), 2925 cm⁻¹ (C-H stretching), 1599 cm⁻¹ (N-H bending) and at 1254 cm⁻¹ (O-H bending and C-O stretching vibrations).
- 10

In the IR spectra of a physical mixture comprised of two components (a solid PEG and CAR) (e.g. FC5) (Figure 4A) peaks attributable to CAR are present (most prominently the peak due to O-H and N-H stretching), yet, not when this system is formed via the melt-fusion method, highlighting molecular dispersion of CAR in the PEG matrix and

hence SD formation. Moreover in the IR spectra of a ternary component system (solid PEG, PEG 400 and CAR) (e.g. FC7) (Figure 4B) the absence of CAR peaks in the PM suggests that PEG 400 is a highly efficient cosolvent for solubilising CAR. These patterns were observed were all formulations studied.

5

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is a thermoanalytical technique, the theory of which is based upon the observation that a change in a compound's physical state is accompanied by the liberation (exothermic process) or absorption of heat (endothermic process). In practice it is used to measure the thermal energy necessary to establish a near zero temperature differential between a material and a reference analyte, as the two samples are exposed to identical temperature methods in an environment where they are heated or cooled at a controlled rate. For SDs it can be used to determine a number of thermal events. These include the glass transition of a crystalline to an amorphous material, the detection of melting and recrystallisation of different polymorphic forms and potential interactions between polymers and drugs.

All solid PEGs displayed melting points (MPs) in the range of 55 - 65°C. PEG 400 does not show an endothermic peak in its DSC thermogram under the temperature range investigated as it is already a liquid under ambient conditions (not shown in Figure 5). No peak attributable to a glass transition was noted in pure CAR samples and CAR melted with a sharp endothermic peak at 119.19°C, showing that supplied CAR was in the crystalline state. The DSC thermograms of both a PM and SD made of solid PEG-CAR showed only a PEG melting peak (e.g. FC5), with the absence of a CAR melting peak. This suggests that in both scenarios CAR is fully dispersed and present in an amorphous form (which would be in disagreement of IR spectra for a binary PM) or that the ability of the DSC instrument to resolve a separate CAR melting peak in the PM is not high enough.

The DSC thermograms of a ternary component system (Figure 5B) were in agreement with the IR spectra as only a PEG melting peak was present. To definitively establish the physical state of CAR, X-ray diffraction (XRD) will be carried out subsequently.

Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) is a technique used to measure the change in mass of a sample as a function of temperature, providing information on the composition of the sample. The sample is loaded into an inert pan (usually platinum) which is placed onto a balance and the sample mass recorded accurately. The pan is then heated in a temperature-controlled furnace within an inert nitrogen atmosphere (which is at a given flow rate) until vaporisation of one of the sample's components occurs, causing it to leave the pan with the mass being recorded throughout. A graph of % mass versus temperature is created, where the % mass loss can be used to infer information on processes that have taken place. A derivative weight loss curve can also be produced to aid interpretation, emphasising areas where weight loss is more pronounced. The technique is often used to assess sample purity, as well as investigate the decomposition/stability of samples.

The combined bound and free water of the raw materials employed and blank tablets and CAR-containing tablets were investigated via TGA. The PEG tablets contained a greater % water content relative to the raw materials; this may have been due to the uptake of water under exposed, ambient conditions because of the hygroscopic nature of PEG (Table 5). This is in contrast to the tightly sealed (lidded) and more water-impermeable packaging that the raw materials are stored in. The amount of PEG 400 within the tablets significantly affected the % water content, whereas there was no significant difference between the water content between blank and CAR-containing tablets. The extent of water uptake under long term storage may be tested in the form of accelerated stability tests as outlined in International Committee of Harmonisation guidelines: QA1 - Q1F Stability. The long-term exposure may be evaluated in terms of the effects on the tablets' physical integrity and physiochemical properties.

Table 6: Percentage water content of raw materials and blank tablets (F1 – F12) and carvedilol-containing tablets (FC1 – FC12). Mean $\pm$ SD, n = 3.

Raw material/ formulation	Water content (% w/w)
Carvedilol	0.64 $\pm$ 0.22
PEG 400	0.86 $\pm$ 0.26
PEG 3000	0.74 $\pm$ 0.07
PEG 6000	0.40 $\pm$ 0.25
PEG 8000	0.16 $\pm$ 0.13

F1	0.74 ± 0.07
F2	0.96 ± 0.09
F3	1.60 ± 0.06
F4	2.36 ± 0.09
F5	0.40 ± 0.25
F6	0.93 ± 0.06
F7	1.53 ± 0.09
F8	2.29 ± 0.14
F9	0.16 ± 0.13
F10	0.90 ± 0.11
F11	1.56 ± 0.11
F12	2.35 ± 0.20
FC1	0.75 ± 0.08
FC2	0.89 ± 0.19
FC3	1.49 ± 0.17
FC4	2.26 ± 0.18
FC5	0.47 ± 0.11
FC6	0.91 ± 0.14
FC7	1.44 ± 0.09
FC8	2.45 ± 0.15
FC9	0.31 ± 0.05
FC10	0.81 ± 0.08
FC11	1.62 ± 0.20
FC12	2.11 ± 0.13

TRANSDERMAL DRUG RELEASE STUDIES USING PEG BASED TABLETS IN COMBINATION WITH MICRONEEDLE ARRAYS

5 EXAMPLE 5 (NILE RED)

Method

Nile Red dye was dissolved in PEG 400 with PEG 6000 added in a 75:25 ratio at a loading of $74.35 \mu\text{g} \pm 6.45 \mu\text{g}$. The mixture was stirred and heated at 80°C until a homogenous liquid was obtained. The solution was dispensed into aluminium-foil lined silicone moulds with a volume of 314.16 mm^3 . This was left at room temperature until tablets solidified. The same process was repeated to produce 50:50 Tween 80: PEG 6000 tablets containing Nile Red at a loading of $470.67 \mu\text{g} \pm 24.59 \mu\text{g}$. In vitro

transdermal delivery of Nile Red was investigated across dermatomed neonatal porcine skin (approximately 350 μm thickness) mounted on Franz cell apparatus. Briefly, porcine skin was attached to Franz cell donor compartments using cyanoacrylate glue, hydrogel-forming microneedle arrays 11 x 11 (600 μm height, 300 μm width at base and 150 μm interspacing) were inserted using manual pressure with 20 μL PBS placed on the array to promote adhesion of the tablets containing 400 μg Nile Red. 200 μL samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 20 % PEG 400) Samples were analysed using UV-vis spectroscopy at a wavelength of 570 nm. Hydrogel-forming microneedles were prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array.

Results

Nile Red containing tablets were formed to address the complexities of delivering a poorly soluble drug substance across the skin. At the highest Nile Red loading possible in PEG 400:PEG 6000 less than 60 μg Nile Red was delivered (Figure 6a). The replacement of PEG 400 with Tween 80 enabled a higher drug loading with increased mass delivered over 24 hours (Figure 6b).

EXAMPLE 6 (ATORVASTATIN)

Method

Atorvastatin calcium trihydrate was dissolved in PEG 400 with PEG 6000 added in three different ratios of 75:25, 50:50 and 25:75, with a final drug loading of 0.8%. The mixture was stirred and heated at 80°C until a homogenous liquid was obtained. The solution was dispensed into a polystyrene square weigh boat and left at ambient temperature until the mixture solidified. A scalpel was then used to cut the solidified mass into 1 cm^2 tablets, weighing approximately 0.25 g each. The same process was repeated to produce 50:50 propylene glycol and PEG 10,000 tablets containing the same atorvastatin calcium trihydrate loading of 0.8%. In vitro transdermal delivery of atorvastatin calcium trihydrate was investigated across dermatomed neonatal porcine skin (approximately

350 µm thickness) mounted on Franz cell apparatus. Briefly, porcine skin was attached to Franz cell donor compartments using cyanoacrylate glue, microneedle arrays 11 x 11 (700 µm height, 300 µm width at base and 150 µm interspacing) were inserted using manual pressure with 10 µL PBS placed on the array to promote adhesion of the tablets, each containing 2 mg atorvastatin calcium trihydrate. 200 µl samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 5% v/v PEG 400) Samples were analysed using reversed phase HPLC.

HPLC analysis was carried out using an Agilent 1200 series system (Agilent Technologies UK Ltd, Stockport, UK). Chromatographic separation was achieved using reversed phase chromatography with gradient elution. The column used was a Luna® C18 (ODS1) column (150 mm x 4.6 mm i.d. with 5 µm packing; Phenomenex, Macclesfield, UK). The mobile phase was a mixture of 25 mM potassium dihydrogen phosphate buffer, pH 2.5, (A) and methanol/acetonitrile (50:50, v/v) (B), adjusted in composition from 60% A to 50% A after 5 minutes, with a total run time of 20 minutes and post-time set at 2 minutes. The column temperature was 20°C and injection volume 20 µl. The chromatograms obtained were analysed using Agilent ChemStation® Software B.02.01 (Agilent Technologies UK Ltd, Stockport, UK).

Hydrogel-forming microneedles were prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array.

Results

Atorvastatin is very hydrophobic, and has a high Log *P* value (greater than 6.0). Atorvastatin containing tablets were formed to address the complexities of delivering a very poorly soluble drug substance across the skin. Using PEG 400:PEG 6000 Atorvastatin can be delivered across neonatal porcine skin (Figure 7, Figure 8 and Table 7). If the composition of the drug reservoir is modified the final amount of drug released remains the same (Figure 8 and Table 7). However, the permeation kinetic during the first 4 hours is affected (Figure 7). The faster initial permeation profiles were obtained when the drug reservoirs contained lower amounts of PEG 6000.

Similar results can be obtained when the drug reservoir is formulated using PEG 10,000 and propyleneglycol (Figure 9 and Table 7).

Table 7. In vitro permeation amounts of atorvastatin calcium trihydrate across dermatomed 350 μ m neonatal porcine skin after 24 h, when delivered using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from different compositions of PEG of various molecular weights and propylene glycol (means $\pm$ S.D., n $\geq$ 3).

Tablet composition	Cumulative atorvastatin permeation $\pm$ S.D. (μ g)	Percentage atorvastatin permeation $\pm$ S.D. (%)
75% PEG 400 25% PEG 6000	1082.1 $\pm$ 119.9	54.4 $\pm$ 7.23
50% PEG 400 50% PEG 6000	1033.6 $\pm$ 35.6	53.3 $\pm$ 2.08
25% PEG 400 75% PEG 6000	1106.9 $\pm$ 194.4	54.80 $\pm$ 10.5
50% propylene glycol 50% PEG 10,000	958.6 $\pm$ 132.2	48.8 $\pm$ 6.68

EXAMPLE 7 (ASPIRIN)

Method

Aspirin was dissolved in PEG 400 with PEG 6000 added in a ratio of 50:50, with a final drug loading of 6%. The mixture was stirred and heated at 80°C until a homogenous liquid was obtained. The solution was dispensed into a polystyrene square weigh boat and left at ambient temperature until the mixture solidified. A scalpel was then used to cut the solidified mass into 1 cm² tablets, weighing approximately 0.25 g each. The same process was repeated to produce 50:50 propylene glycol and PEG 10,000 tablets containing the same aspirin loading of 6%. In vitro transdermal delivery of aspirin was investigated across dermatomed neonatal porcine skin (approximately 350 µm thickness) mounted on Franz cell apparatus. Briefly, porcine skin was attached to Franz cell donor compartments using cyanoacrylate glue, microneedle arrays 11 x 11 (700 µm height, 300 µm width at base and 150 µm interspacing) were inserted using manual pressure with 10 µL PBS placed on the array to promote adhesion of the tablets, each containing 15 mg aspirin. 200 µl samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 5% v/v PEG 400). Samples were analysed using reversed phase HPLC.

HPLC analysis was carried out using an Agilent 1200 series system (Agilent Technologies UK Ltd, Stockport, UK). Chromatographic separation was achieved using reversed phase chromatography with gradient elution. The column used was a Luna® C18 (ODS1) column (150 mm x 4.6 mm i.d. with 5 µm packing; Phenomenex, Macclesfield, UK). The mobile phase was a mixture of 25 mM potassium dihydrogen phosphate buffer, pH 2.5, (A) and methanol/acetonitrile (50:50, v/v) (B), adjusted in composition from 60% A to 50% A after 5 minutes, with a total run time of 20 minutes and post-time set at 2 minutes. The column temperature was 20°C and injection volume 20 µl. The chromatograms obtained were analysed using Agilent ChemStation® Software B.02.01 (Agilent Technologies UK Ltd, Stockport, UK).

Hydrogel-forming microneedles were prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array.

Results

Aspirin containing tablets were formulated using PEG 400:PEG 6000 and Propyleneglycol:PEG10,000. Aspirin can be delivered across neonatal porcine skin

using both formulations (Figure 10). However, when the drug reservoir is formulated using propyleneglycol and PEG 10,000 the aspirin permeation was slightly higher (Figure 10 and Table 8)

- 5 **Table 8.** *In vitro* permeation amounts of aspirin across dermatomed 350 μm neonatal porcine skin after 24 h, when delivered using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from different compositions of PEG of various molecular weights and propylene glycol (means $\pm$ S.D., n = 4).

Tablet composition	Cumulative aspirin permeation $\pm$ S.D. (μg)	Percentage aspirin permeation $\pm$ S.D. (%)
• 50% PEG 400 • 50% PEG 6000	6930 $\pm$ 841.2	45.0 $\pm$ 5.89
• 50% propylene glycol • 50% PEG 10,000	8040 $\pm$ 987.0	57.1 $\pm$ 7.28

10 EXAMPLE 8 (LISINOPRIL)

Method

Lisinopril dihydrate is a very hydrophilic drug. Lisinopril dihydrate was dissolved in propylene glycol with PEG 10,000 added in a ratio of 50:50, with a final drug loading of 0.8%. The mixture was stirred and heated at 80°C until a homogenous liquid was obtained. The solution was dispensed into a polystyrene square weigh boat and left at ambient temperature until the mixture solidified. A scalpel was then used to cut the solidified mass into 1 cm^2 tablets, weighing approximately 0.25 g each. In vitro transdermal delivery of lisinopril was investigated across dermatomed neonatal porcine skin (approximately 350 μm thickness) mounted on Franz cell apparatus. Briefly, porcine skin was attached to Franz cell donor compartments using cyanoacrylate glue, microneedle arrays 11 x 11 (700 μm height, 300 μm width at base and 150 μm interspacing) were inserted using manual pressure with 10 μL PBS placed on the array to promote adhesion of the tablets, each containing 2 mg lisinopril dihydrate. 200 μL

samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 5% v/v PEG 400) Samples were analysed using reversed phase HPLC.

HPLC analysis was carried out using an Agilent 1200 series system (Agilent Technologies UK Ltd, Stockport, UK). Chromatographic separation was achieved using reversed phase chromatography with gradient elution. The column used was a Luna® C18 (ODS1) column (150 mm x 4.6 mm i.d. with 5 µm packing; Phenomenex, Macclesfield, UK). The mobile phase was a mixture of 25 mM potassium dihydrogen phosphate buffer, pH 2.5, (A) and methanol/acetonitrile (50:50, v/v) (B), adjusted in composition from 60% A to 50% A after 5 minutes, with a total run time of 20 minutes and post-time set at 2 minutes. The column temperature was 20°C and injection volume 20 µl. The chromatograms obtained were analysed using Agilent ChemStation® Software B.02.01 (Agilent Technologies UK Ltd, Stockport, UK).

Hydrogel-forming microneedles were prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array.

Results

Lisinopril containing tablets were formulated using PEG 400:PEG 6000. This drug can be delivered successfully across neonatal porcine skin (Figure 11 and Table 9)

Table 9. In vitro permeation amounts of lisinopril dihydrate across dermatomed 350 µm neonatal porcine skin after 24 h, when delivered using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from different compositions of PEG of various molecular weights and propylene glycol (means ± S.D., n = 4).

Tablet composition	Cumulative lisinopril permeation ± S.D. (µg)	Percentage lisinopril permeation ± S.D. (%)
50% propylene glycol 50% PEG 10,000	931.6 ± 246.7	46.6 ± 12.0

EXAMPLE 9 (CARVEDILOL)

Methods

The release of Carvedilol (CAR) from PEG tablets through hydrogel microneedle arrays across dermatomed (350 μm thick) neonatal porcine skin was investigated in vitro using Franz diffusion cells, as described previously. Neonatal porcine skin samples were shaved carefully so as not to damage the skin and pre-equilibrated in PBS pH 7.4 for one hour before beginning experiments. A circular section of the skin was secured to the donor compartment of the diffusion cell using cyanoacrylate glue with the *stratum corneum* side facing the donor compartment. This was then placed on a piece of dental wax to support the skin and microneedle arrays as they were inserted into the centre of the skin section using a custom-made applicator which provides a consistent force of 11 N. A 300 mg PEG tablet (4 mm thickness) containing CAR 5% w/w was then placed carefully onto the centre of each microneedle array. To ensure the tablet and microneedle array remained in place a circular steel weight (diameter 11.0 mm, 5.0 g mass) was placed on top of the tablet.

Donor compartments were then mounted onto the receptor compartments of the Franz cells. The donor compartment and sampling arm were sealed using Parafilm®. The receiver compartment contained a solution of 5% v/v PEG 400 and 95% v/v PBS pH 7.4 with the PEG 400 acting as a co-solvent to enhance solubility of CAR in the receiver medium and maintain sink conditions. The receiver solution was thermostatically maintained at $37 \pm 0.1^\circ\text{C}$ and stirred at 600 rpm via magnetic stirrers. 1.0 mL syringes with attached needles were used to remove 200 μL of the contents of the receiver compartments at pre-defined time intervals and 200 μL of pre-warmed PBS was subsequently added to replace this. Samples were centrifuged for 5 min at 14,000 g using an Eppendorf Minispin centrifuge (Eppendorf UK Limited, Stevenage, UK). CAR content in the receptor compartment was then determined by RP-HPLC as described above.

Results

CAR exhibited a biphasic release profile across dermatomed neonatal porcine in vitro irrespective of the microneedles composition, comprised of an initial burst release

which lasted for 6 h for regular microneedles and 4 h for super-swelling microneedles after which the rate of release slows dramatically (Figure 12). The slower rate of release through regular microneedles resulted in a significantly higher mass of CAR released after 24 h. As the drug reservoir (tablets) were known to contain on average 15 mg of CAR, the percentage of CAR delivered through regular microneedles ranged from 42.40 – 47.7% and 25.39 – 28.09% for super-swelling microneedles. It is suspected that the faster rate of swelling of the super-swelling microneedles may have caused the array to be pushed out of the skin, even under the force of the cylindrical weight pressing down on the tablet and microneedles. The proportion of PEG 400 in the drug reservoir (tablet) did not significantly affect the mass of drug released after 24 h for either microneedles formulation.

As soon as the donor compartment assembly is placed on top of the receptor compartment, the dry hydrogel microneedles start to imbibe water causing swelling of the microneedles and the formation of porous aqueous channels within the microneedles through which drug may diffuse. As the microneedles swell, water will contact the tablet and start to dissolve, liberating CAR and with the combined solubility enhancement of the two PEGs, CAR is soluble in the aqueous phase and can travel through the microneedles into the receptor compartment. Due to the relatively low loading (5 %w/w) of CAR in the tablets it can be reasonably assumed that the mechanism of release is carrier-mediated.

Upon disassembly the donor compartment of the Franz cells it was noticed in the majority of cases the tablet had completely or almost completely dissolved. The microneedles appeared to contain large patches of white material, which is likely contributable to a large deposition of dissolved PEG 3000 within the hydrogel matrix. It may be the case that a large proportion of CAR is trapped within the hydrogel network which now has a much higher viscosity due to the entrapped PEG 3000 and thus is acting as a retardant to drug diffusion. However this would be counter-intuitive to the observation that drug release was not dependent on liquid PEG 400 and thus solid PEG 3000 content. Another possible explanation is that an equilibrium has been reached, regarding the partitioning of CAR between the hydrogel microneedles and receptor compartment medium. To test the validity of these potential explanations the proportion of PEG 400 in the receptor compartment could be increased to encourage further partitioning of CAR into the receptor medium or following 24 h of drug release

the microneedles employed could be placed into a bottle containing a volume of the receptor medium and left in an orbital incubator for 24 or 48 h, after which the mass of CAR in the solvent can be quantified.

5 **EXAMPLE 10 (Multiple drugs in same solid reservoir)**

Table 10 and Figure 12C summarise the results of an experiment in which lisinopril dehydrate, aspirin and atorvastatin calcium trihydrate were delivered using a microneedle array with a single reservoir.

10 **Method**

Lisinopril dehydrate, aspirin and atorvastatin calcium trihydrate were dissolved in propylene glycol with PEG 10,000 added in a ratio of 50:50, with a final drug loading of 0.8% lisinopril, 6% aspirin and 0.8% atorvastatin. The mixture was stirred and heated at 80°C until a homogenous liquid was obtained. The solution was dispensed into a polystyrene square weigh boat and left at ambient temperature until the mixture solidified. A scalpel was then used to cut the solidified mass into 1 cm² tablets, weighing approximately 0.25 g each. In vitro transdermal delivery of lisinopril was investigated across dermatomed neonatal porcine skin (approximately 350 µm thickness) mounted on Franz cell apparatus. Briefly, porcine skin was attached to Franz cell donor compartments using cyanoacrylate glue, microneedle arrays 11 x 11 (700 µm height, 300 µm width at base and 150 µm interspacing) were inserted using manual pressure with 10 µL PBS placed on the array to promote adhesion of the tablets, each containing 2 mg lisinopril dihydrate. 200 µl samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 5% v/v PEG 400) Samples were analysed using reversed phase HPLC.

HPLC analysis was carried out using an Agilent 1200 series system (Agilent Technologies UK Ltd, Stockport, UK). Chromatographic separation was achieved using reversed phase chromatography with gradient elution. The column used was a Luna® C18 (ODS1) column (150 mm x 4.6 mm i.d. with 5 µm packing; Phenomenex, Macclesfield, UK). The mobile phase was a mixture of 25 mM potassium dihydrogen phosphate buffer, pH 2.5, (A) and methanol/acetonitrile (50:50, v/v) (B), adjusted in

composition from 60% A to 50% A after 5 minutes, with a total run time of 20 minutes and post-time set at 2 minutes. The column temperature was 20°C and injection volume 20 µl. The chromatograms obtained were analysed using Agilent ChemStation® Software B.02.01 (Agilent Technologies UK Ltd, Stockport, UK).

- 5 Hydrogel-forming microneedles were prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array.

Results

- 10 Tablets containing a combination of three drugs were formulated using propylene glycol and PEG 10,000. The results show that a plurality of drugs having different physicochemical properties, can be successfully delivered together from the same reservoir at high doses across skin (Table 10, Figure 12C).
- 15 Table 10 *in vitro* permeation amounts of the three different drugs when delivered simultaneously across dermatomed 350 µm neonatal porcine skin after 24 h, using hydrogel-forming Gantrez® S-97 microneedle arrays with drug reservoirs prepared from 50% w/w propylene glycol and 50% w/w PEG 10,000 (means ± S.D., n = 4).

20 **Table 10**

Drug	Cumulative permeation ± S.D. (µg)	Percentage permeation ± S.D. (%)
Lisinopril dihydrate	494.9 ± 47.7	26.7 ± 3.06
Aspirin	9039 ± 987	65.0 ± 8.50
Atorvastatin calcium trihydrate	868.6 ± 137	46.6 ± 6.70

TRANSDERMAL DRUG RELEASE STUDIES USING PEG CONTAINING LIQUID RESERVOIRS IN COMBINATION WITH MICRONEEDLE ARRAYS

EXAMPLE 11 Nile Red

The delivery of hydrophobic agents from amphipathic agent containing liquid reservoirs via microneedle arrays was tested, using Nile Red and atorvastatin as examples of hydrophobic agents. Liquid reservoir designs were evaluated *in vitro* using the set-up shown in Figure 13.

Briefly, Nile Red dye was dissolved in liquid PEG 400 (350 µg/mL). In vitro transdermal delivery of the Nile Red dissolved in the PEG400 was tested across dermatomed neonatal porcine skin (approximately 350 µm thickness) mounted on Franz cell apparatus as shown in Figure 13. Briefly, porcine skin was attached to Franz cell donor compartments using cyanoacrylate glue, and hydrogel-forming microneedle arrays 11 x 11 (600 µm height, 300 µm width at base and 150 µm interspacing) were inserted using manual pressure. 200 µL samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 20 % PEG 400). Samples were analysed using UV-vis spectroscopy at a wavelength of 570 nm. Hydrogel-forming microneedles were prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array. Control preparations did not employ the microneedles.

Results

Figure 14 illustrates an *in vitro* cumulative permeation profile of Nile Red dissolved in PEG 400 (350 µg/mL) in a liquid reservoir across dermatomed neonatal skin using hydrogel-forming Gantrez® S-97 microneedles (means ± S.D., n = 4). The results show that Nile Red was successfully delivered.

EXAMPLE 12 Atorvastatin

The delivery of atorvastatin from amphipathic agent containing liquid reservoirs via microneedle arrays was tested, using two examples of amphipathic agent, propylene glycol and PEG400. Liquid reservoir designs were evaluated *in vitro* using the set-up shown in Figure 13.

5 Briefly, atorvastatin was dissolved in either propylene glycol (2 mg/mL) or PEG 400 (2 mg/mL).

In vitro transdermal delivery of atorvastatin was investigated across dermatomed neonatal porcine skin (approximately 350 μ m thickness) mounted on Franz cell apparatus as shown in Figure 13. Briefly, porcine skin was attached to Franz cell donor
10 compartments using cyanoacrylate glue, and hydrogel-forming microneedle arrays 11 x 11 (600 μ m height, 300 μ m width at base and 150 μ m interspacing) were inserted using manual pressure. 200 μ L samples were removed at regular intervals and replaced with fresh receiver media (PBS containing 20 % PEG 400) Samples were analysed using UV-vis spectroscopy at a wavelength of 570 nm. Hydrogel-forming microneedles were
15 prepared as described previously, with a formulation of 20% Gantrez® S-97, 7.5% PEG 10,000 and the addition of 3% sodium bicarbonate to facilitate enhanced swelling of the microneedle array.

Results

20 Figure 15 illustrates an *in vitro* permeation profile of atorvastatin calcium trihydrate across dermatomed 350 μ m neonatal porcine skin over 24 h when delivered using hydrogel-forming Gantrez® S-97 MN arrays with a liquid drug reservoir of either propylene glycol or PEG 400 (means $\pm$ S.D., n = 4). The results show that atorvastatin was successfully delivered from the liquid reservoir.

25

All documents referred to in this specification are herein incorporated by reference. Various modifications and variations to the described embodiments of the inventions will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific
30 preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of

the described modes of carrying out the invention which are obvious to those skilled in the art are intended to be covered by the present invention.

Claims

- 5 1. A transdermal delivery device comprising a microneedle array and a reservoir portion, wherein said microneedles are composed of a swellable hydrogel polymer composition, said polymers being cross-linked polymers selected from at least one of the group consisting of poly(methylvinylether/maleic acid), esters thereof and poly(methyl vinyl ether/maleic anhydride), wherein said reservoir portion comprises at least
10 one amphipathic component and at least one hydrophobic active agent, wherein in use, on insertion of the microneedles into the *stratum corneum* of skin, said microneedles swell and said amphipathic component and said at least one hydrophobic active agent diffuse down a concentration gradient from the reservoir layer via the microneedles into the skin.
15
2. The transdermal delivery device according to claim 1, wherein said cross-linked polymers are crosslinked by a polyhydric alcohol or a polyamine.
3. The transdermal delivery device according to claim 1 or claim 2, wherein
20 said microneedles are substantially insoluble in interstitial fluid.
4. The transdermal delivery device as claimed in any one of the preceding claims wherein, in use, less than 2% by weight of said polymer composition of said microneedles in contact with the skin dissolves in interstitial fluid
25 during a 12 hour period of use of said transdermal delivery device.
5. The transdermal delivery device as claimed in any one of the preceding claims, wherein said at least one amphipathic component is a liquid at room
30 temperature.

6. The transdermal delivery device as claimed in any one of claims 1 to 4, wherein said at least one amphipathic component is a solid at room temperature.
- 5 7. The transdermal delivery device as claimed in any one of the preceding claims, wherein said at least one amphipathic component comprises at least one of poly(ethyleneglycol), propylene glycol, glycerol, tripropyleneglycolmonomethylether, a surfactant, a block copolymer, a biocompatible oil, a wax or a synthetic tri- or poly-glyceride.
- 10 8. The transdermal delivery device as claimed in any one of the preceding claims wherein said amphipathic component comprises a polymer of polyethylene glycol, propylene glycol or polysorbate.
- 15 9. The transdermal delivery device as claimed in any one of the preceding claims wherein said amphipathic component has a molecular weight in the range 0.2-60 kDa.
- 20 10. The transdermal delivery device as claimed in any one of the preceding claims wherein said amphipathic component has a hydrophilic-lipophilic balance (HLB) value in the range 8.0-14.0.
- 25 11. The transdermal delivery device as claimed in any one of the preceding claims wherein said at least one hydrophobic active agent is a member of the Biopharmaceuticals Classification System Class II or IV.
- 30 12. The transdermal delivery device as claimed in any one of the preceding claims wherein said hydrophobic active agent has a log *P* value of greater than 2.0.
13. The transdermal delivery device as claimed in any one of the preceding claims, wherein the aqueous solubility of said at least one hydrophobic

active agent is enhanced at least 20-fold by the material(s) of the matrix or reservoir.

5 14. The transdermal delivery device as claimed any one of the preceding claims, wherein the transdermal or intradermal delivery of an at least one hydrophobic active agent is enhanced at least 20-fold relative to passive permeation.

10 15. The transdermal delivery device according to any one of the preceding claims, wherein said array comprises microneedles of length in the range 400-3000 μ m.

15 16. The transdermal delivery device according to any one of the preceding claims, wherein said reservoir portion comprises, in addition to at least one hydrophobic active agent, at least one hydrophilic active agent and/or at least one amphipathic active agent, wherein in use, on insertion of the microneedles into the *stratum corneum* of skin, said at least one hydrophilic active agent and/or at least one amphipathic active agent diffuses from the reservoir layer via the microneedles into the skin.

20 17. The transdermal delivery device according to claim 16, wherein said reservoir portion comprises, in addition to said at least one hydrophobic active agent, at least one hydrophilic active agent having a log *P* value of less than 0.0, such as less than -1.0.

25 18. The transdermal delivery device according to claim 17, wherein said at least one hydrophobic active agent has a log *P* value of greater than 3.0, and said at least one hydrophilic active agent has a log *P* value of less than 0.5.

30 19. The transdermal delivery device according to any one of the preceding claims, wherein per cm² said reservoir comprises at least 10mg of said at least one hydrophobic agent and, in use, at least 50% of the total volume of

hydrophobic agent in the reservoir is delivered via the microneedles into the skin.

- 5 20. The transdermal delivery device according to any one of the preceding claims, wherein said device comprises at least one pressure indicator which provides a detectable signal when pressure exceeding a predetermined minimal level is applied to the device.
- 10 21. The transdermal delivery device according to claim 20, wherein said device comprises a second pressure indicator which provides a detectable signal when pressure exceeding a predetermined maximal level is applied to the device.

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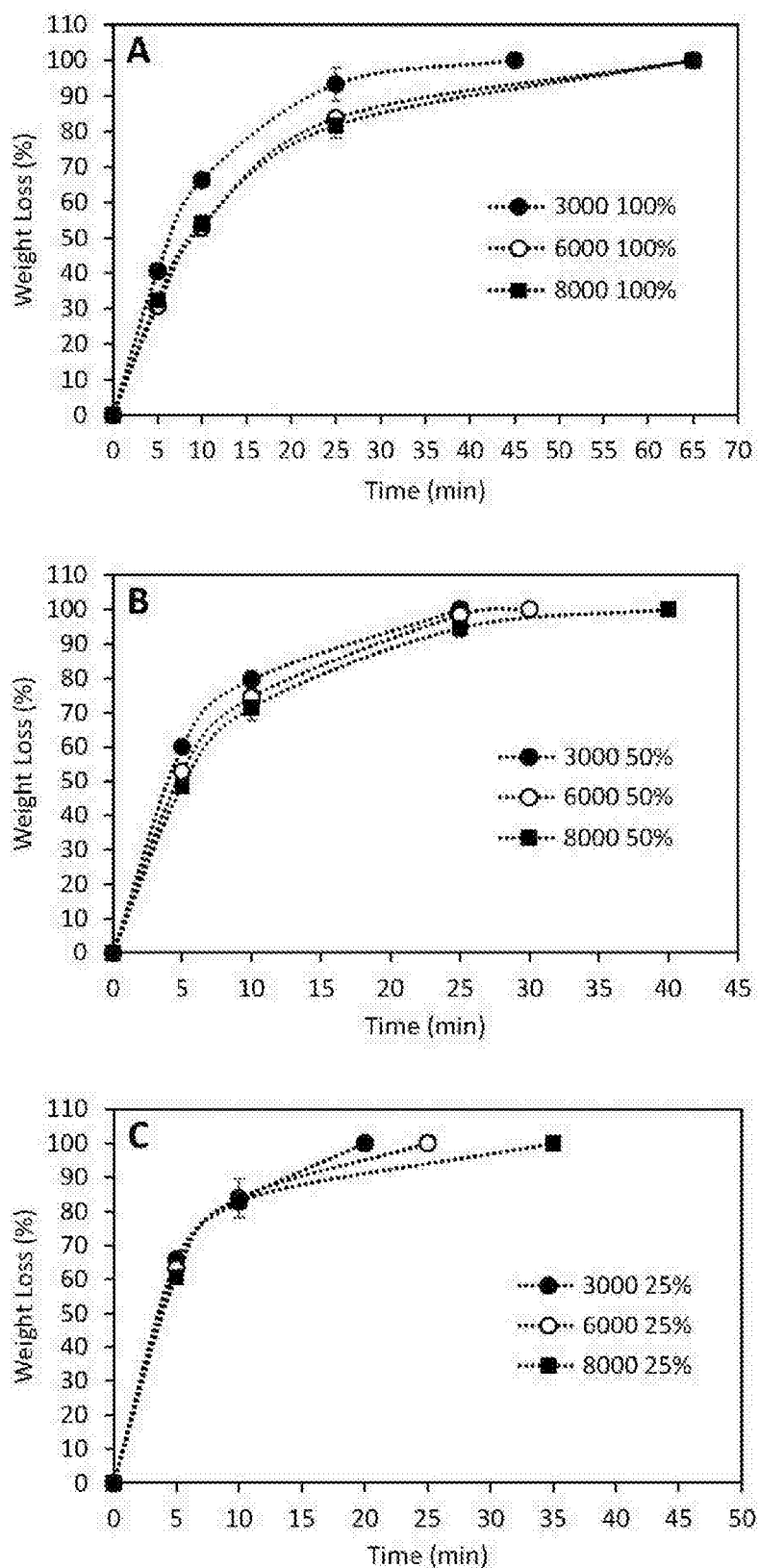


Figure 1.

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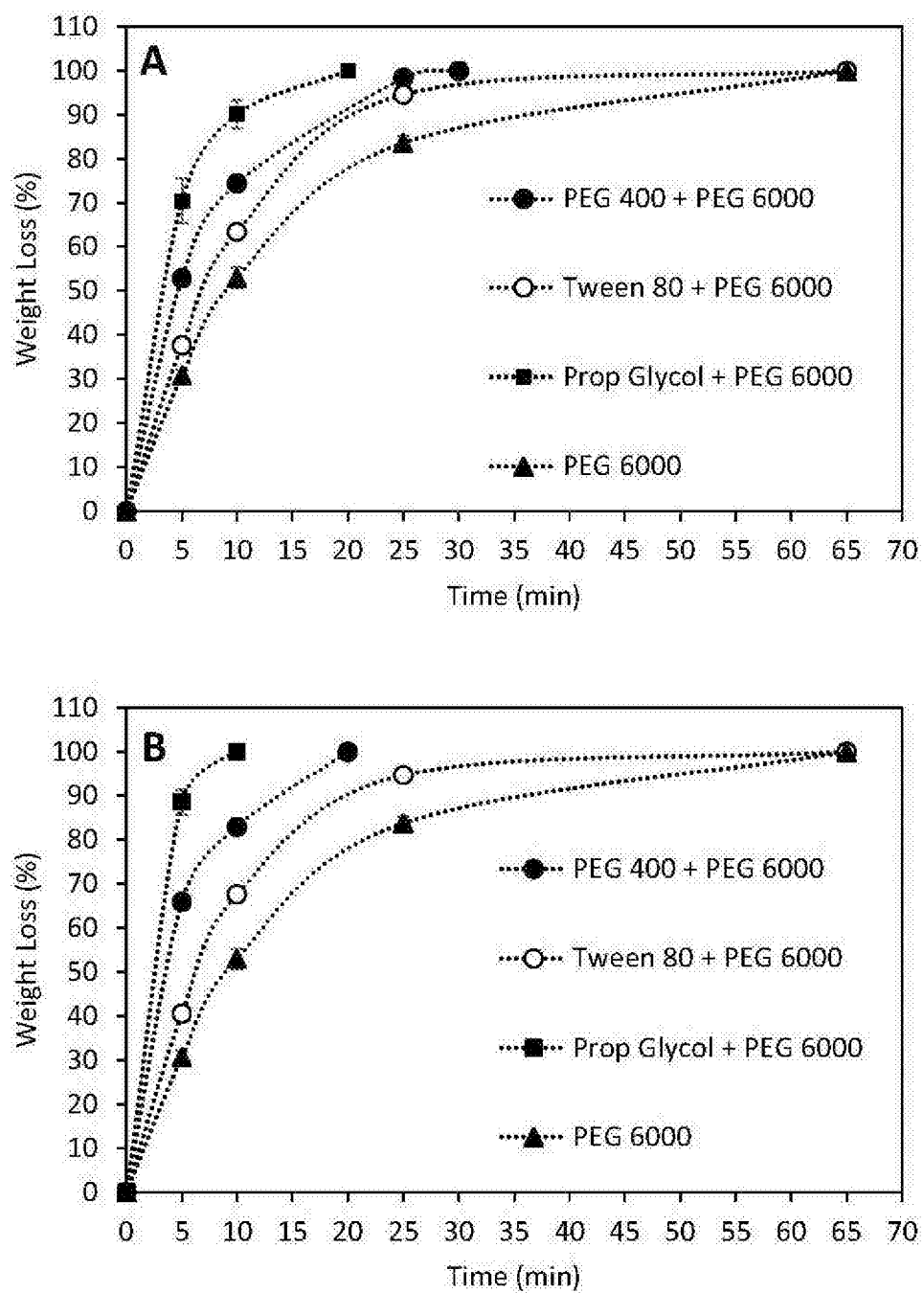


Figure 2.

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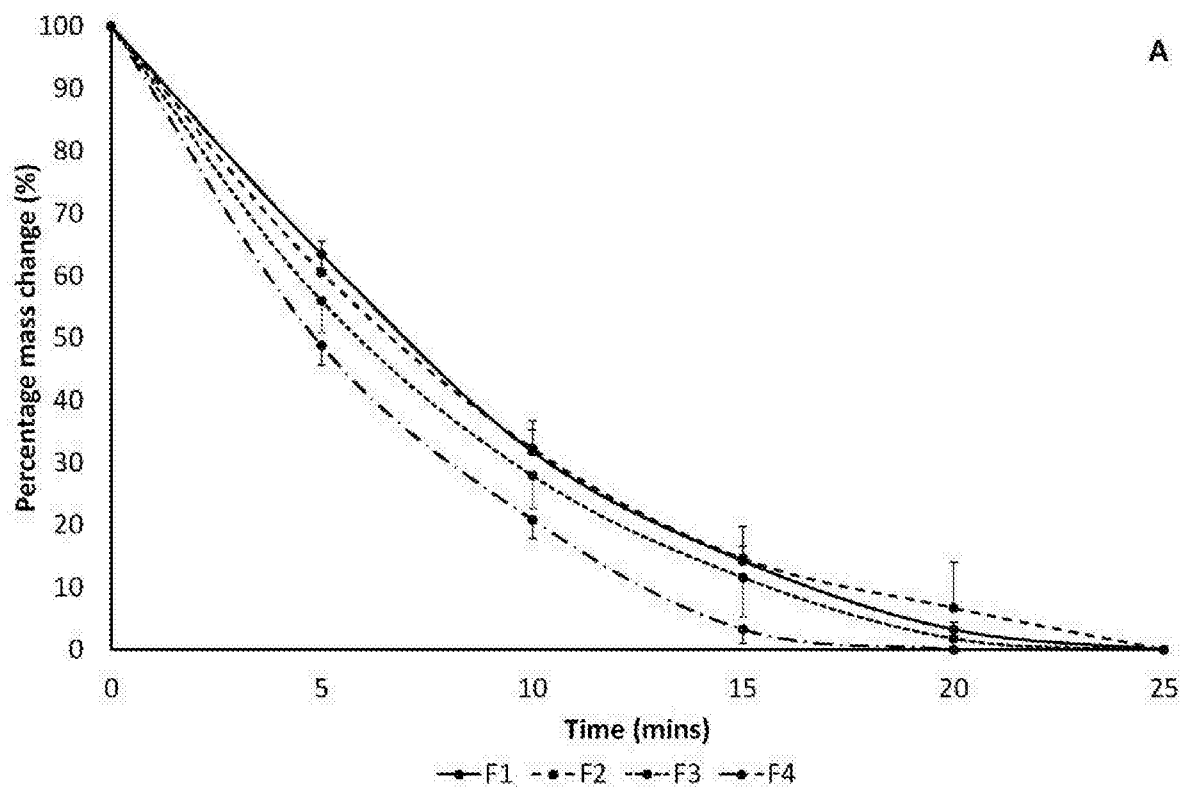


Figure 3A.

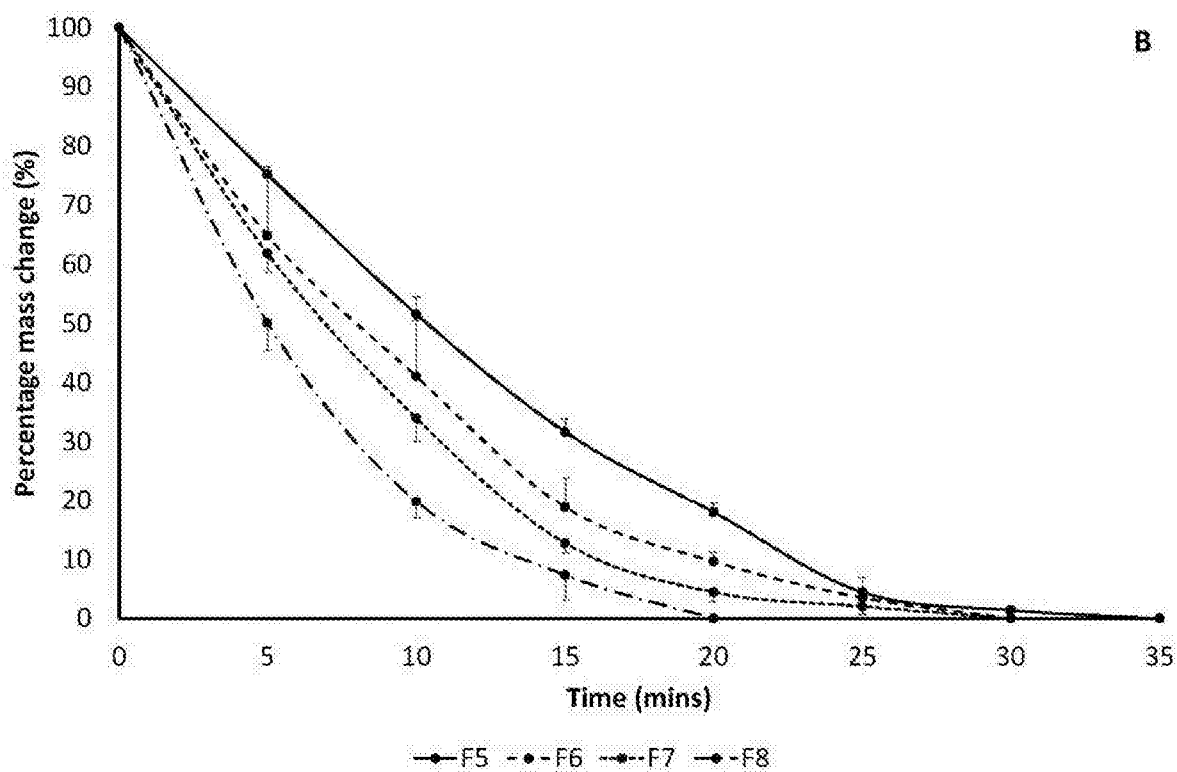


Figure 3B.

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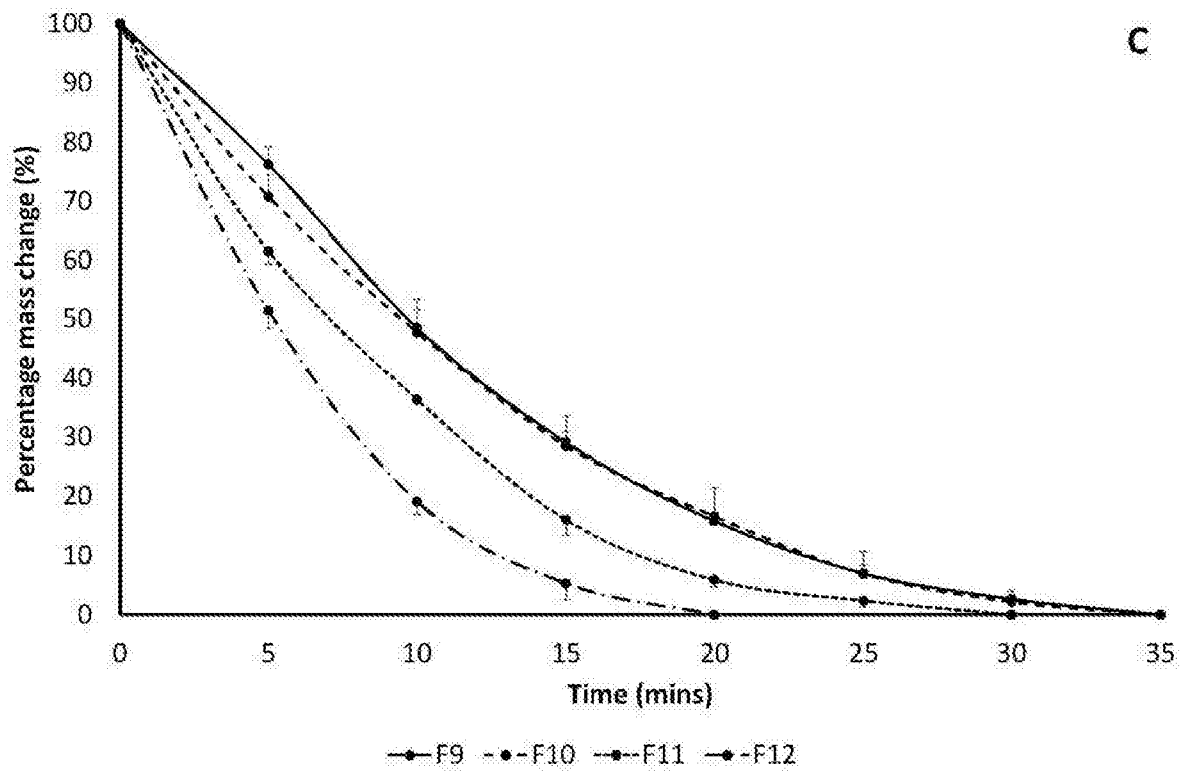


Figure 3C.

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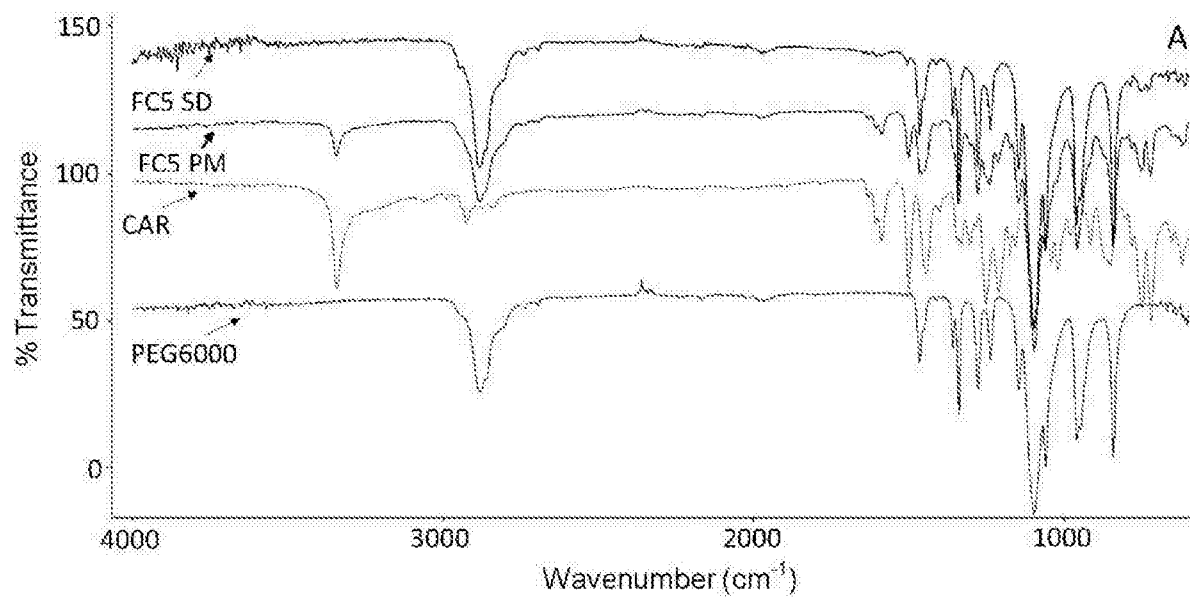


Figure 4A.

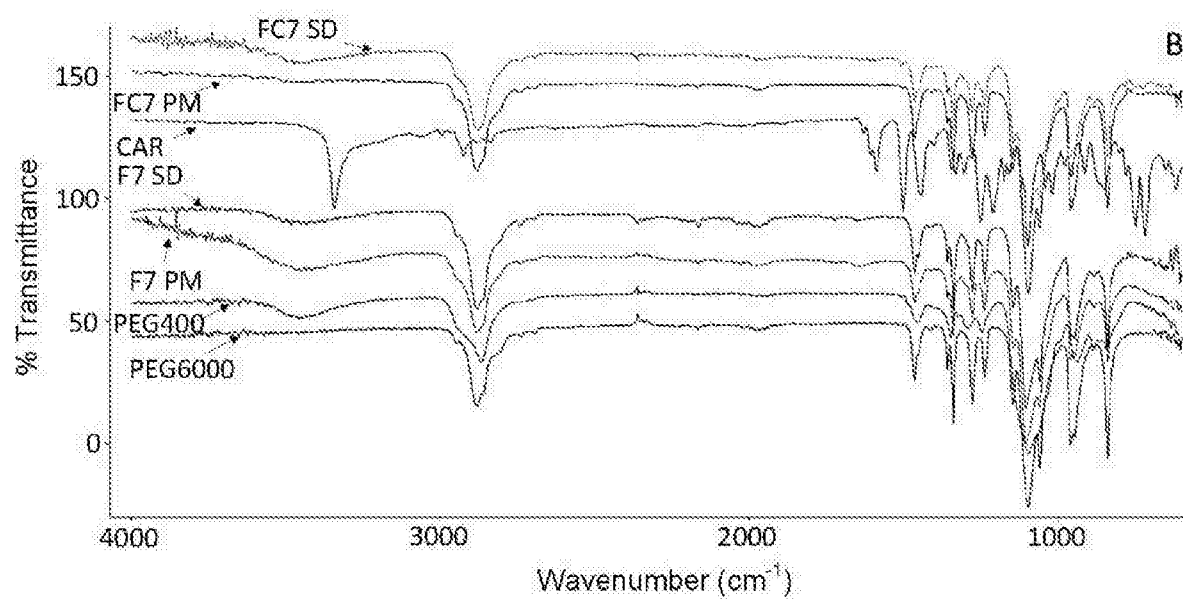


Figure 4B.

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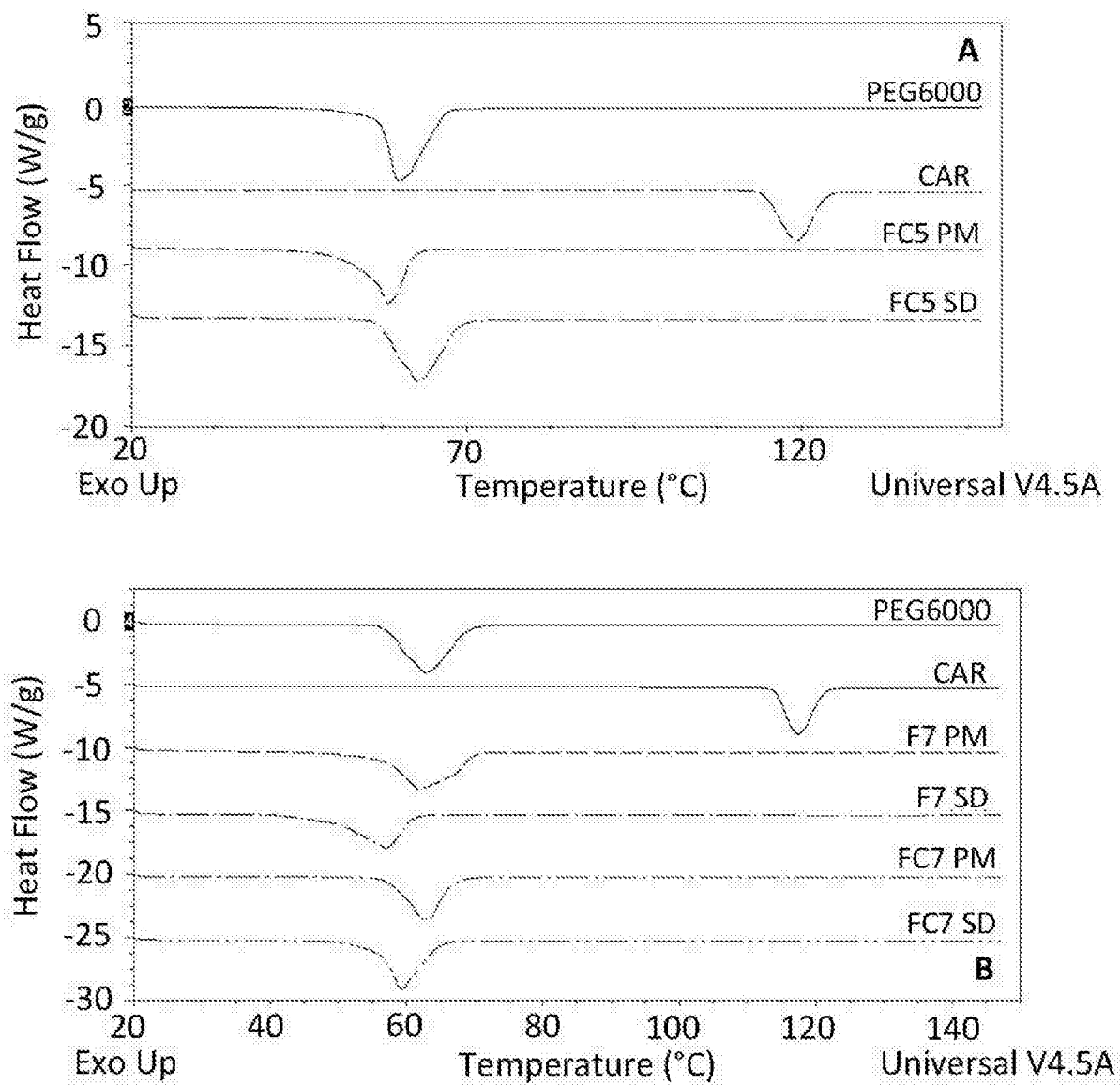


Figure 5.

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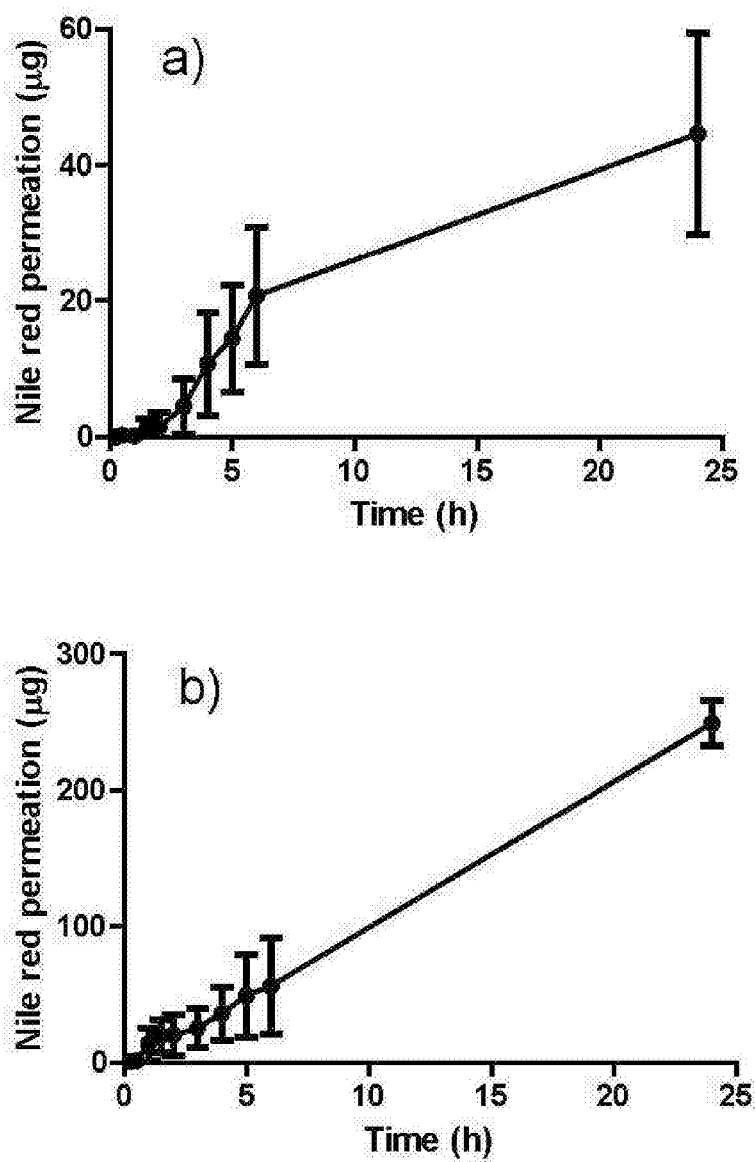


Figure 6.

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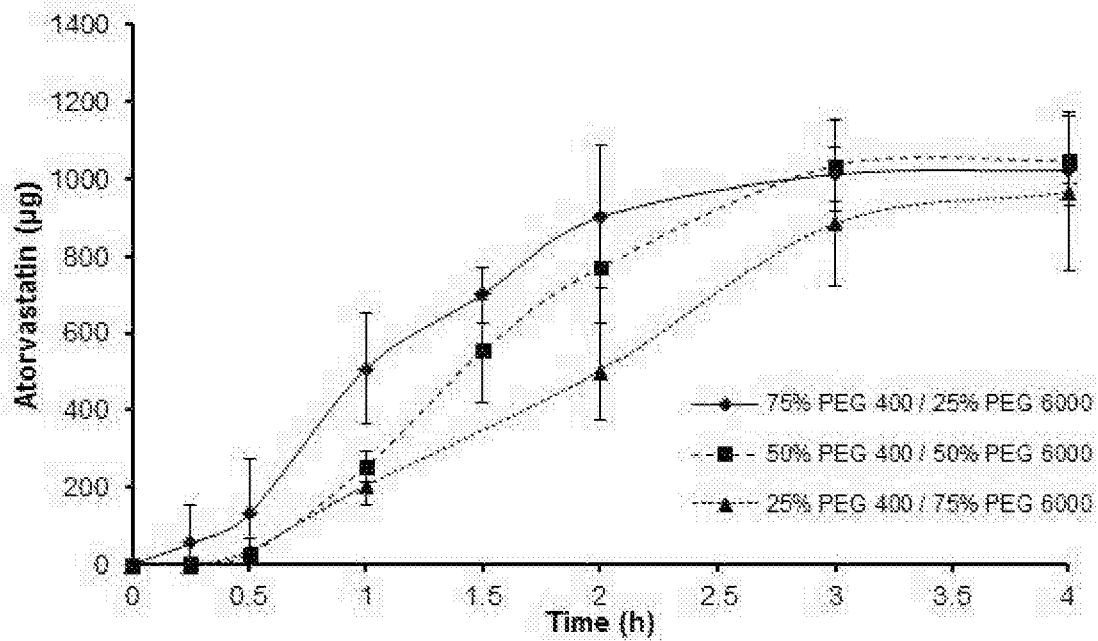


Figure 7.

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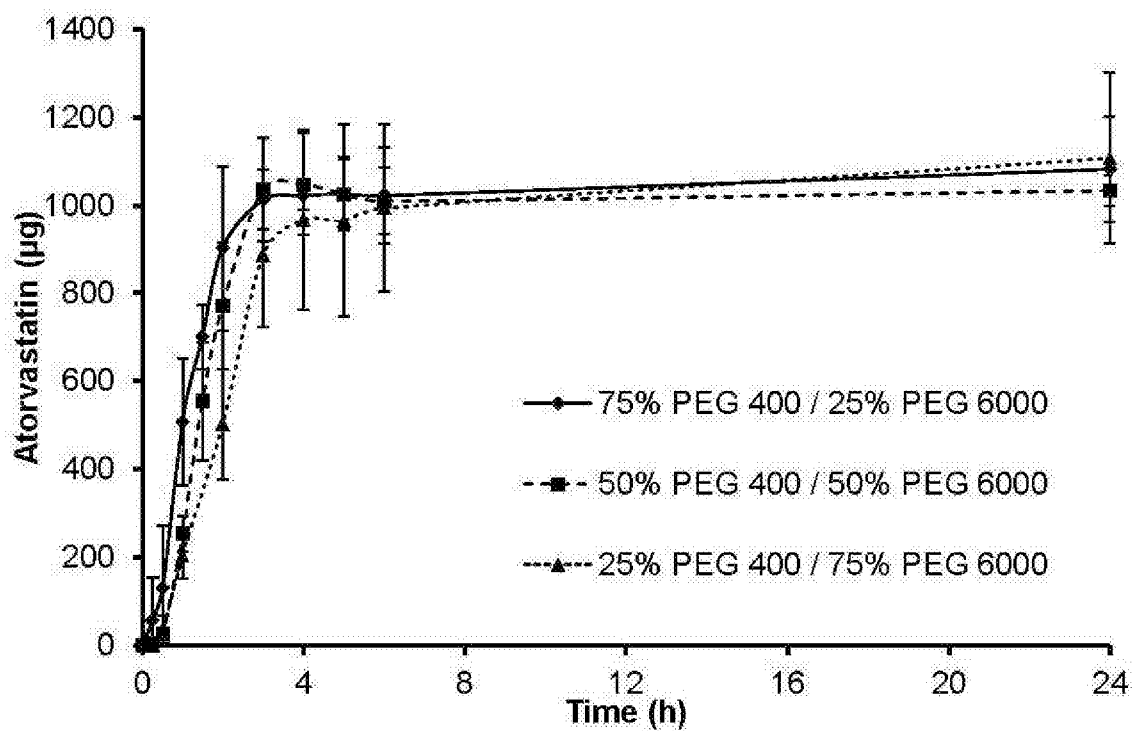


Figure 8.

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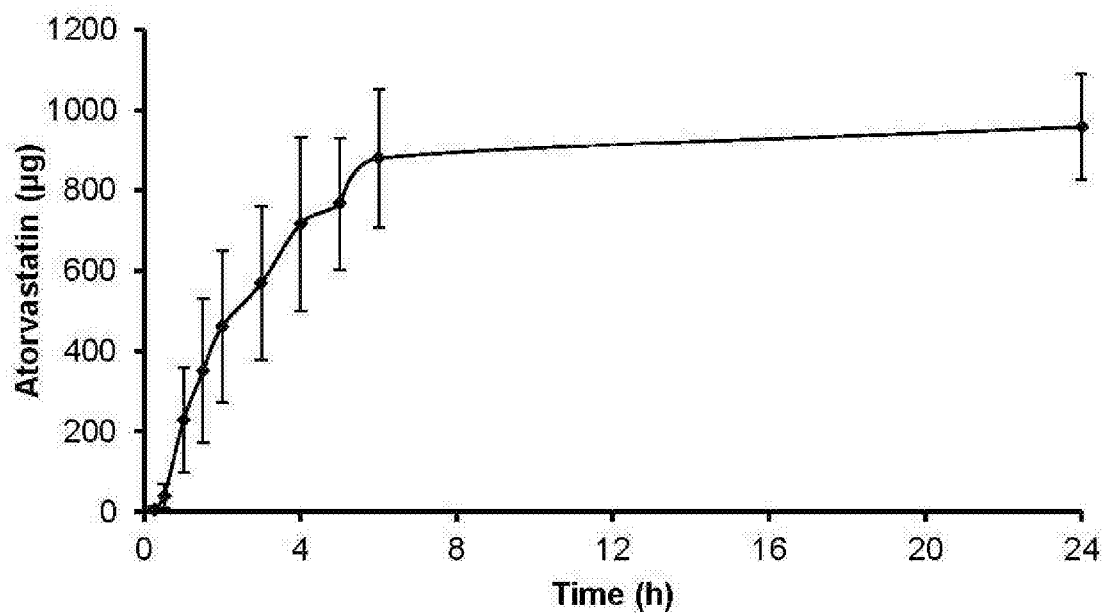


Figure 9.

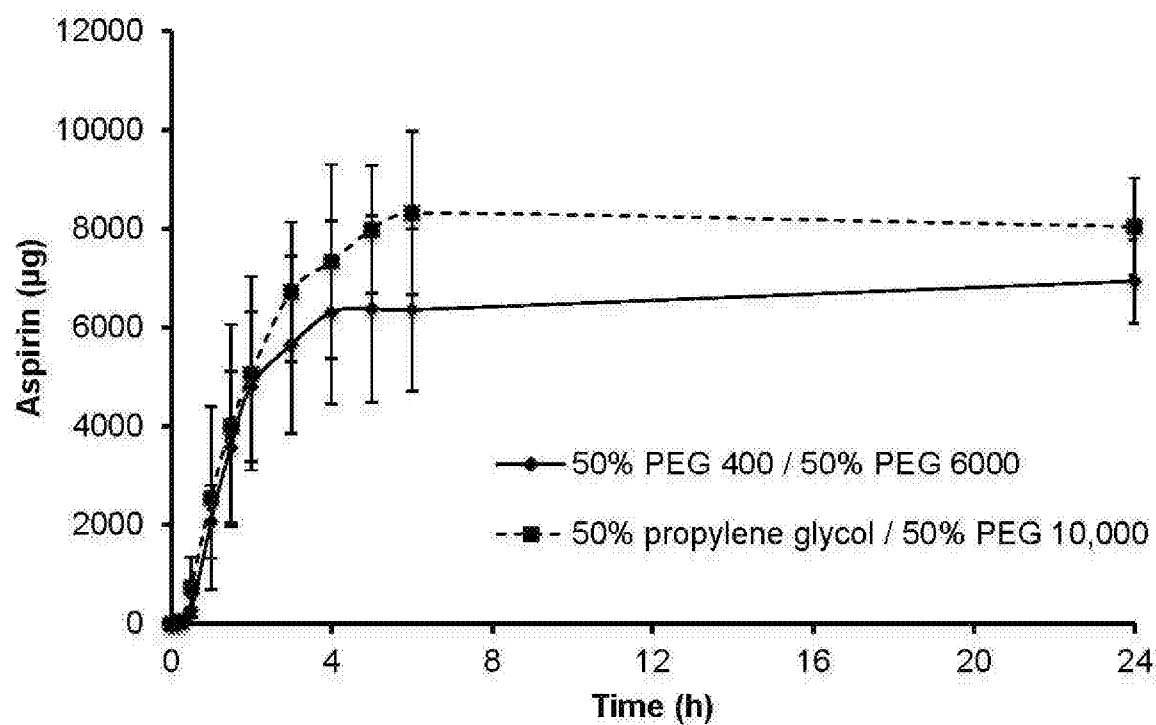


Figure 10.

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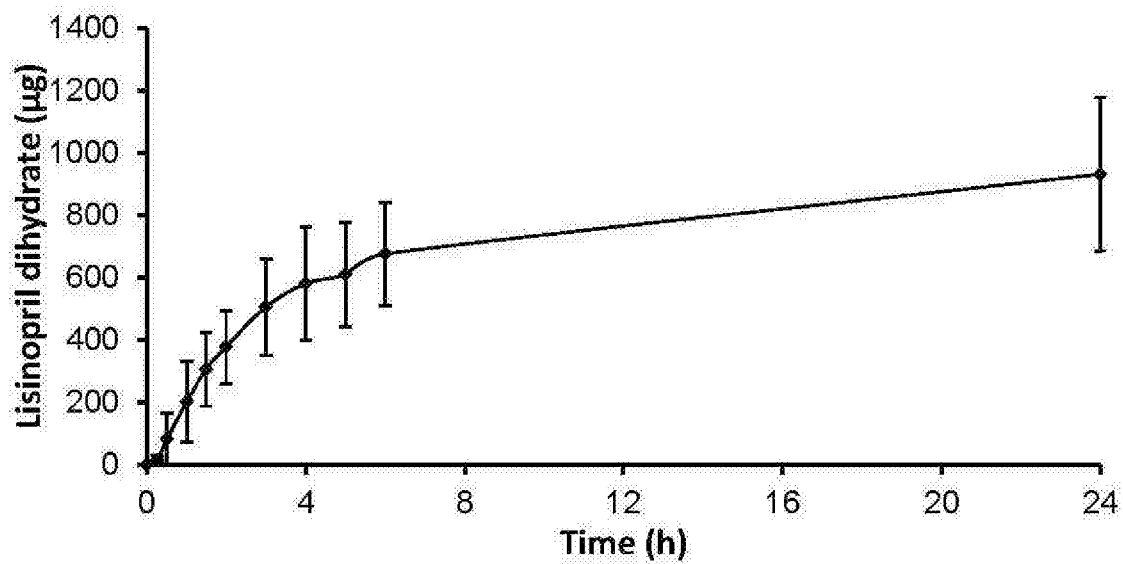


Figure 11.

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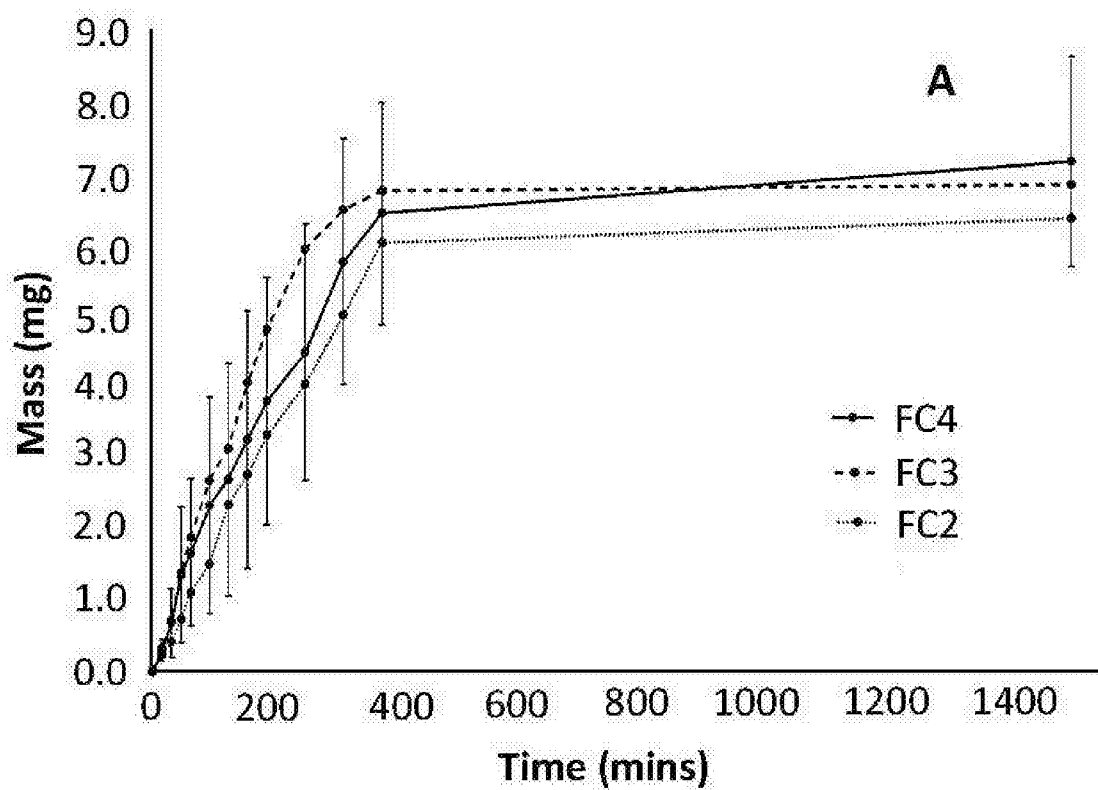


Figure 12A.

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Figure 12B.

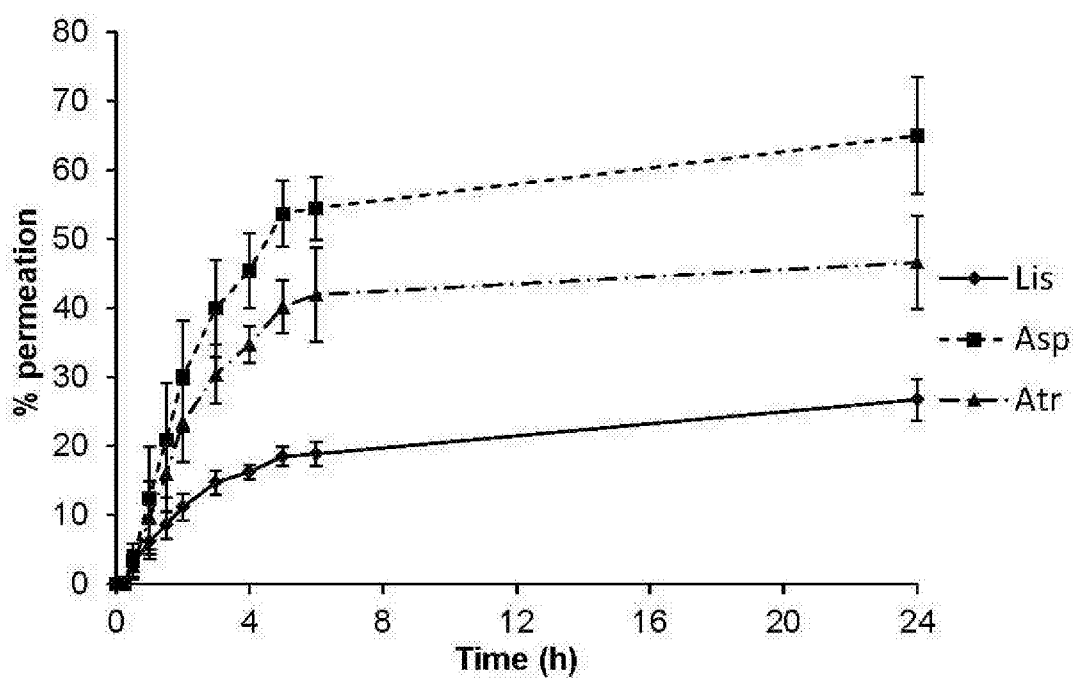
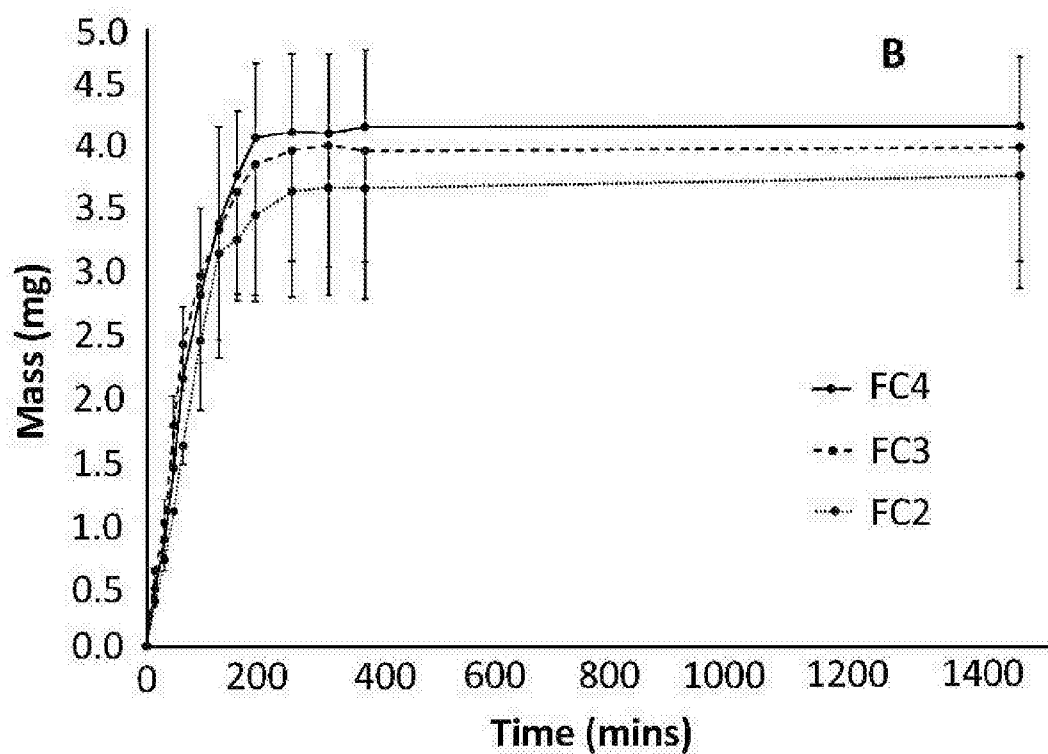


Figure 12C.

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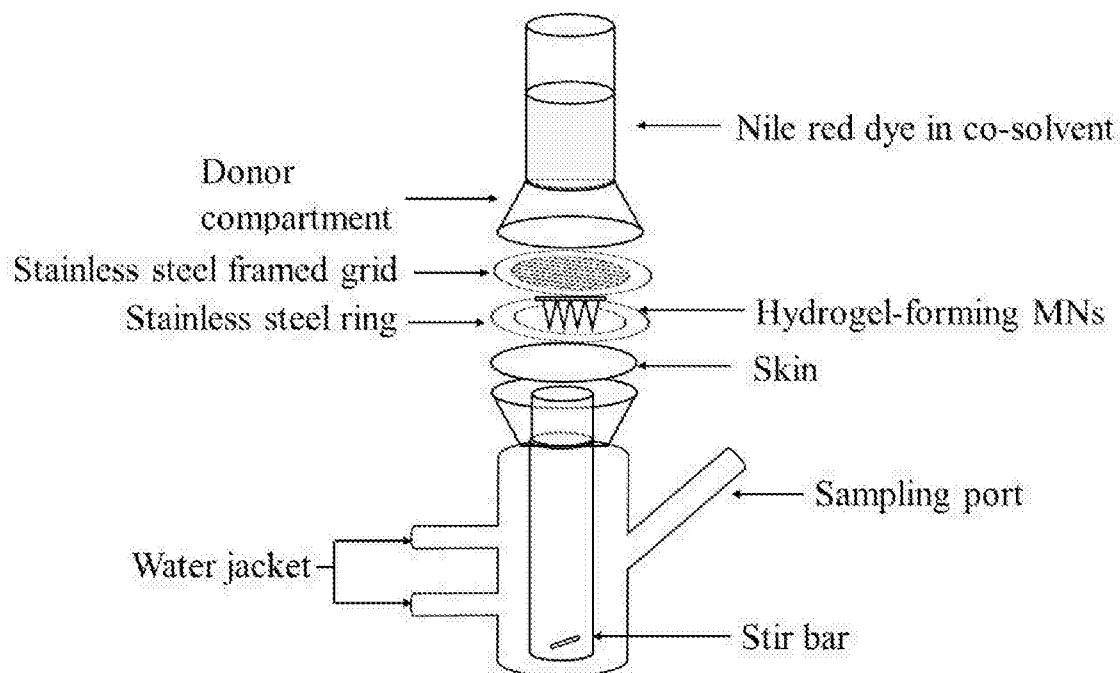


Figure 13.

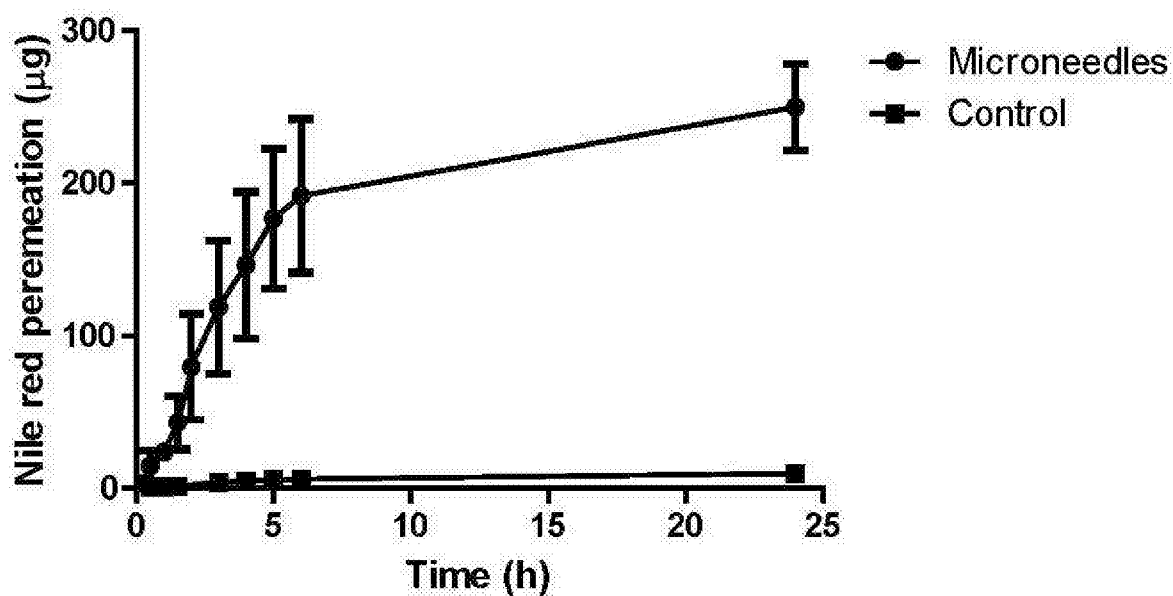


Figure 14.

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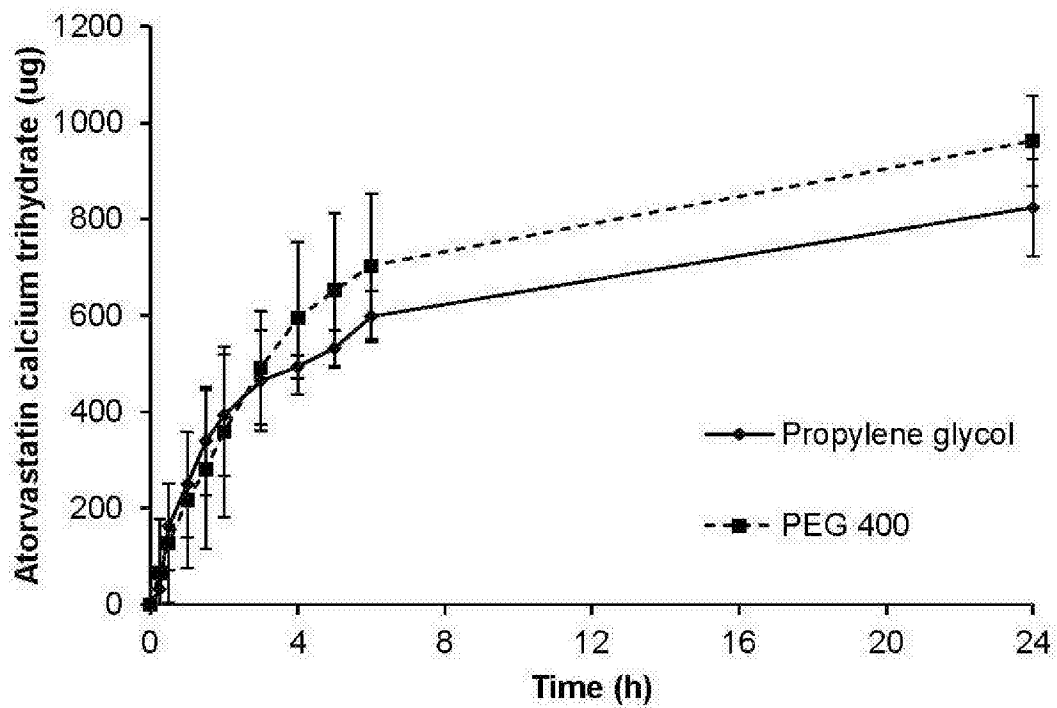


Figure 15.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/051247

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K9/00 A61K31/401	A61K47/10 A61K31/403
	A61K47/32 A61K31/60	A61K9/20 A61K31/40
ADD.		
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) 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 practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RYAN F. DONNELLY ET AL: "Hydrogel-Forming Microneedles Prepared from ?Super Swelling? Polymers Combined with Lyophilised Wafers for Transdermal Drug Delivery", PLOS ONE, vol. 9, no. 10, 31 October 2014 (2014-10-31), page e111547, XP55387280, DOI: 10.1371/journal.pone.0111547	1-7,9-21
Y	page 5, left column; conclusion on page 12; figure 5	8
Y	EP 2 679 242 A1 (HISAMITSU PHARMACEUTICAL CO [JP]) 1 January 2014 (2014-01-01) claims 1-8; example 5 ----- -/-	8
☒ Further documents are listed in the continuation of Box C. ☒ See patent family 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 application or patent 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 3 July 2017		Date of mailing of the international search report 12/07/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Konter, Jörg

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2017/051247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S SHEPPARD: "AMPHIPATHIC CHARACTER OF GELATIN SHOWN IN ITS ADSORPTION TO POLAR SURFACES", SCIENCE, 15 December 1945 (1945-12-15), page 545, XP55387334, DOI: DOI: 10.1126/science.100.2607.545 title -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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EP 2679242	A1	01-01-2014	EP 2679242 A1	01-01-2014
			JP 5876468 B2	02-03-2016
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