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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 December 2008 (04.12.2008)

PCT

(10) International Publication Number
WO 2008/146021 A1

(51) International Patent Classification:
A61M 5/31 (2006.01) *A61M 5/44* (2006.01)

(21) International Application Number:
PCT/GB2008/001871

(22) International Filing Date: 30 May 2008 (30.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0710433.4 31 May 2007 (31.05.2007) GB

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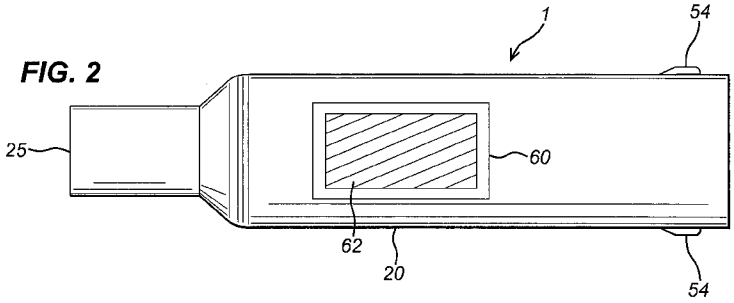
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** AUTO-INJECTOR

FIG. 2



(57) **Abstract:** There is provided an auto-injector (1) for a syringe (10) that is suitable for use in the injected delivery of drug to a patient. The auto-injector comprises a housing (20) arranged for receipt of a syringe containing a liquid drug formulation,- an actuating mechanism for actuating said syringe (10) to deliver said liquid formulation to a patient; and a visual indicator comprising a colour change material (62) that defines a first colour state below a transition temperature and a second colour state above said transition temperature. The visual indicator is arranged to allow the user to differentiate between a 'too cold to use' state (*i.e.* below the transition temperature) and a 'sufficiently warm to use' state.

WO 2008/146021 A1

Auto-injector

The present invention relates to an auto-injector for receipt of a syringe that is suitable for use in the injected delivery of a drug formulation to a patient.

It is well-known to use syringes for the delivery of injectable liquid drug formulation to a patient. Traditional syringes rely on puncturing of the patient's skin by a hollow needle through which the injectable drug (e.g. in solution or suspension form) is delivered to the muscle or tissue of the patient. It is also well-known to provide auto-injectors for use with syringes. Such auto-injectors typically comprise a body for housing the syringe and an actuating mechanism, which is triggered in use, to allow for delivery of the liquid drug formulation from the syringe.

Certain liquid drug formulations arranged for delivery by means of an auto-injector and syringe require cool storage (e.g. in a refrigerator) to prevent degradation of the drug. Such liquid drug formulations include for example, those based on therapeutic biologic type drug actives. The viscosity of such liquid drug formulations is however, temperature dependent. Often the refrigerated liquid drug formulation is too viscous to be delivered effectively by the syringe. Normal use therefore requires that the auto-injector and syringe containing liquid drug formulation be removed from the refrigerator and allowed to warm up (e.g. typically to room temperature) before the patient injects. Such warming up of the liquid drug formulation results in the viscosity thereof decreasing such that effective delivery thereof from the syringe is better enabled.

Problems can be encountered where insufficient time is allowed by the user for the warming up process such that the liquid drug formulation is still too viscous

for effective delivery by injection. Whilst such problems may to an extent be addressed by providing clear instructions for use, which define a minimum warming up period, Applicant has appreciated that it is desirable for a clear visual indication to be provided to the user to indicate that the warming up process has been completed. Effective delivery of warmed up, and therefore less viscous, liquid drug formulation is therefore enabled.

In solution, Applicant has now devised an auto-injector device which includes a temperature indicator comprising materials, which change colour over the desired temperature range. Thus, for example the temperature indicator might indicate one colour for an insufficiently warmed up device, which is not suitable for use, and another colour for a sufficiently warmed up device, which is now suitable for use. In another example, the temperature indicator may be provided to an indicium such that the indicium is blocked off (or in alternatives, revealed) for an insufficiently warmed up device, but revealed (or in alternatives, blocked off) for a sufficiently warmed up device.

According to one aspect of the present invention there is provided an auto-injector comprising

a housing arranged for receipt of a syringe containing a liquid drug formulation;

an actuating mechanism for actuating said syringe to deliver said liquid formulation to a patient; and

a visual indicator comprising a colour change material that defines a first colour state below a transition temperature and a second colour state above said transition temperature.

These and other embodiments of the present invention are set forth in the later description, which describes for illustrative purposes only various embodiments thereof.

There is provided an auto-injector device that is arranged for use with a syringe that contains a liquid drug formulation. The syringe is arranged to be suitable for use in the injected delivery of the liquid drug formulation to a patient.

The auto-injector comprises a housing that is arranged for receipt of the syringe and is therefore typically sized and shaped for this purpose.

The syringe suitably comprises a barrel for holding a volume of the liquid drug formulation; a needle at one end of the barrel; and a plunger that is axially movable within the barrel. The plunger is movable axially within the barrel so as to enable the liquid drug formulation to be expelled from the barrel and thence through the needle for injection into the patient.

In more detail, the barrel is selected such as to define a barrel chamber for containing a suitable volume of the liquid drug formulation. In aspects, that suitable volume is selected to correspond to a single dose of the drug formulation to be delivered to the patient. In other words, delivery of that single dose involves expelling all of the liquid drug formulation contents of the barrel chamber through the needle for injection into the patient.

The needle defines a needle bore, which is most typically of circular cross-section and of selected bore diameter. It may be appreciated that in aspects, the bore diameter may affect the force required to expel the liquid drug formulation through the needle and also the velocity at which the liquid drug formulation is expelled.

The selected needle bore may also, in aspects affect the degree of patient discomfort during injection. Smaller bore diameters, typically provide more patient comfort, whereas larger bore diameters enable more rapid / lower force delivery of the liquid through the needle. A compromise is therefore needed in

selecting needle bore to provide acceptable patient comfort and liquid delivery through the needle characteristics.

Examples of typical needles that are suitable for use therein include 12.5mm ("half inch") long thin wall needles of grade 23G, 25G or 27G. These have a needle bore of from about 0.2 to 0.4mm such as from 0.25 to 0.35mm.

The housing of the auto-injector is typically shaped to define a housing cavity within which the syringe is receivable. The housing cavity may be further shaped with any manner of grooves, indentations or other shaping or surface details to define a 'lock and key' relationship between the housing and the syringe. Colour guides, arrows and any other surface markings may also be employed.

Typically, the housing of the auto-injector is provided with a barrel receiving part for receiving the barrel of the syringe; a plunger receiving part for receiving the plunger of the syringe; and a needle receiving part for receiving the needle of the syringe.

Suitably, the plunger receiving part of the housing allows the plunger to be received thereby and for the plunger to be movable (e.g. axially) therein from a first position, in which it is somewhat withdrawn from the barrel to a second position, in which it is moved somewhat into the barrel.

Suitably, the needle receiving part of the auto-injector housing includes a needle delivery aperture through which the needle may protrude from the housing, for example during expelling of the liquid drug formulation through the needle for delivery to the patient.

In terms of function, the auto-injector is arranged to allow for actuation of the syringe. Thus, the auto-injector is provided with an actuating mechanism for actuating the syringe (e.g. typically by plunging the plunger axially into the barrel thereof) to deliver the liquid formulation to the patient.

The actuating mechanism typically includes an energy store for storing energy that can then be released to allow for actuation of the syringe. In aspects, the energy store comprises a mechanical energy store such as a spring (e.g. a compression or torsion spring). In other aspects, the energy store may be provided by a container of compressed liquid or gas propellant that on release provides a source of jet energy propulsion.

The energy store is suitably able to exert a force of up to 60N on the plunger of the syringe. Where the energy store is a compression spring the force exerted typically varies over the actuation profile such as from a range of 60 to 40N at the start of actuation to from 40 to 20N at the end of the actuation profile. Where the energy store is a compressed liquid or gas propellant a more constant force is typically exerted over the actuation profile.

In preferred embodiments, actuation of the actuating mechanism is responsive to a trigger (e.g. a user-actuable trigger). In embodiments, the trigger comprises a button, switch or lever arrangement.

In embodiments, a reset mechanism is provided for resetting the firing mechanism after actuation thereof. The reset mechanism may for example, comprise a spring, motor, mechanical arrangement or a reset coupling.

For safety and hygiene reasons, it is desirable that the needle does not protrude from the housing other than when expelling the liquid drug formulation during an injection procedure. Thus embodiments are envisaged in which, the housing is arranged such that the needle receiving part thereof allows for the needle of the syringe to be axially moveable therein from a first (i.e. rest) position in which the needle is wholly housed by the needle receiving part to a second (i.e. use) position in which at least the tip of the needle protrudes from that needle receiving part of the housing. In aspects, the housing includes biasing means (e.g. a spring) arranged such that the needle is normally biased towards the first

(i.e. rest) position, wherein such biasing means are overcome during the actuation of the syringe by the actuating mechanism to allow for movement of the needle to the second (i.e. use) position.

In embodiments, a needle retraction mechanism is provided for retracting the needle back into the needle receiving part of the housing after the injection procedure, that is to say retracting the needle from the second (i.e. use) position to the first (i.e. rest) position. The retraction mechanism may for example, comprise a spring, motor, mechanical arrangement or a reset coupling.

Representative auto-injectors that may be modified to incorporate a visual indicator in accord with the present invention include those described in United States Patent No.s US-A-4,553,962; US-A-4,378,015; US-A-5,304,128 and PCT Patent Application No.s WO99/22790 (Elan Corporation); WO00/09186 (Medijject Corporation); and WO2005/070,481 (The Medical House PLC) all of which are incorporated herein by reference.

In embodiments, the auto-injector is provided with child-resistant features to prevent undesirable actuation of the actuating mechanism by a young child.

The auto-injector further comprises a visual indicator. The visual indicator is suitably arranged to provide the user with a visual indication of the temperature state of the auto-injector, and particularly of the syringe and its contents (i.e. the liquid drug formulation), which at least allows the user to differentiate between a 'too cold to use' state and a 'sufficiently warm to use' state.

The visual indicator may be provided to the auto-injector by any suitable means.

In embodiments, a region of the housing and/or of the syringe is provided with the visual indicator. In embodiments, the visual indicator is provided as a coating (e.g. by painting or spraying on) to the region of the housing and/or of the syringe. In embodiments, the visual indicator is provided to a label, which is

provided to the region of the housing and/or of the syringe. In embodiments, the label is comprised of a plastic polymer or cellulosic (e.g. paper) material. In embodiments, the label is provided with an adhesive layer for adhesive application to the region of the housing and/or of the syringe.

In embodiments, an insulating layer is provided to the visual indicator. The insulating layer is typically provided as an outer layer to provide an insulating barrier between the visual indicator and temperature stimuli, which are external to (e.g. the housing and/or the syringe of) the auto-injector. Thus, the visual indicator will provide an indication that is representative of the temperature state of (e.g. the housing and/or the syringe of) the auto-injector rather than of any adjacent external stimuli. In embodiments, the insulating layer acts as a barrier to any heat transfer from the fingers and/or hand of the user, which might otherwise distort the temperature state of the visual indicator. In embodiments, the insulating layer comprises a clear (e.g. colourless) material such that the insulating layer does not prevent user inspection of the visual indicator. In embodiments, the insulating layer is provided as a window to the housing.

The visual indicator comprises a colour change material that defines a first colour state below a transition temperature and a second colour state above said transition temperature.

The colour change material is typically selected to have a transition temperature, which allows the user to differentiate between a 'too cold to use' state (i.e. below the transition temperature) and a 'sufficiently warm to use' state (i.e. above the transition temperature).

Typical applications of the auto-injector herein are with a syringe containing a liquid drug formulation, which is designed for refrigerated storage (e.g. at from 2-8°C) and for injected delivery at room temperature (e.g. at or about 18-30°C). In embodiments the transition temperature is thus, selected to be from 18 to 30°C, particularly from 20 to 25°C.

The first colour state is suitably visually distinct from the second colour state. In embodiments, the first colour state is one colour and the second colour state is another colour. In other embodiments, the first colour state is colourless and the second colour state is a colour or alternatively, the second colour state is colourless and the first colour state is a colour.

In embodiments, particularly where one colour state is colourless, the visual indicator is provided with an indicium, particularly a text indicium, which suitably lies beneath (i.e. underneath) the colour change material (e.g. provided to a base upon which the colour change material is applied).

In a first embodiment, the indicium comprises a 'not ready to use' indicium, which is visible when the colour change material is in a first colourless state, but which is obscured when the colour change material is in a second colour state. In a second embodiment, the indicium comprises a 'ready to use' indicium, which is obscured when the colour change material is in a first colour state, and which is visible when the colour change material is in a second colourless state.

Suitable colour change materials include thermochromic materials, which are selected to meet the requirements of the visual indicator. Thermochromic materials are known e.g. from Kirk-Othmer Encyclopaedia 3rd Edition, Vol. 6, p. 130.

Thermochromic materials can be applied as a coating or can form an integral part of the materials used to make the visual indicator (e.g. comprised within the housing and/or the syringe). Another possibility of applying thermochromic materials to the visual indicator is as a laminar covering in the form of a painting or ink. The thermochromic materials used can be in the form of fine pigments particles, microencapsulated materials and/or molecular materials.

Many thermochromic dyes undergo a colour change from a specific colour to

colourless in a reversible manner. There are also so-called low temperature thermochromic dyes, which change their colour from colourless at room temperature to a certain colour upon being cooled. Background colour pigments can be provided in combination with the thermochromic materials such that when the thermochromic material changes to colourless the background pigment becomes dominant for the colour. For example if a yellow background pigment is mixed with a red thermochromic material the visible colour will change from orange to yellow at the temperature the thermochromic materials changes colour.

Thermochromic materials are marketed e.g. by Sun Chemical and Clariant. Exemplary classes of thermochromic materials suitable herein are liquid crystals and leuco dyes. Preferably both classes of materials are encapsulated in suitable microcapsules.

Liquid crystals are very sensitive to temperature changes and change colour even in a temperature range of 0.1°C., typically from black to a colour. Application of liquid crystals typically requires highly specialized printing.

The colour change characteristics of liquid crystals are typically dependent on the selective reflection of certain wavelengths by the crystallic structure of the material, as it changes between a low-temperature crystallic phase, through an anisotropic chiral or twisted nematic phase, to a high-temperature isotropic liquid phase. The twisted nematic phase has the molecules oriented in layers with regularly changing orientation, which gives them periodic spacing. The light passing the crystal undergoes Bragg diffraction on these layers and the wavelength with the greatest constructive interference is reflected back, which is perceived as a spectral color. As the crystal undergoes changes in temperature, thermal expansion occurs, resulting in change of spacing between the layers, and therefore in the reflected wavelength. The color of the thermochromic liquid crystal can therefore continuously range from black through the spectral colors

to black again, depending on the temperature. Some such liquid crystal materials are cholesteryl nonanoate or cyanobiphenyls. Liquid crystals are sometimes microencapsulated, in the form of a suspension.

Leuco dyes typically change colour in a temperature increment of 3 to 6°C, in most cases from coloured to clear (uncoloured). The benefit of leuco dyes is that they can be easily applied by printing or by admixing with a polymer.

Suitable colour change materials herein are based on mixtures of leuco dyes with other chemicals, displaying a color change (usually between the colorless leuco form and the colored form) in dependence on temperature. The dyes usually employed in the form of microcapsules with the mixture sealed inside. The dyes most commonly used are spirolactones, fluorans, spiropyrans, and fulgides. The weak acids include bisphenol A, parabens, 1,2,3-triazole derivates, and 4-hydroxycoumarin and act as proton donors, changing the dye molecule between its leuco form and its protonated colored form.

Leuco dyes are usually used in combination with a pigment that produces a color change between the color of the base pigment and the color of the pigment combined with the color of the non-leuco form of the leuco dye.

The auto-injector herein is useful where the liquid drug formulation to be injected has a viscosity profile that is critically temperature dependent. It will be appreciated that the more viscous the formulation, the more force will be required to expel it through the needle for delivery to the patient.

In aspects, the syringe of the auto-injector herein contains a liquid drug formulation, which is designed for refrigerated storage (e.g. at from 2-8°C) and for injected delivery at room temperature (e.g. at or about 18-30°C). In embodiments the transition temperature is thus, selected to be within the range from 15 to 30°C, particularly from 15 to 25°C, preferably from 15 to 18°C.

The auto-injector herein has particular utility where that liquid drug formulation has a viscosity profile that changes critically on warming from a refrigerated storage temperature to room temperature. That utility is most pronounced where the liquid drug formulation is too viscous for effective injected delivery at the refrigerated storage temperature, but of sufficiently lower viscosity for effective injected delivery at room temperature.

One measure of 'ease of injected delivery' is the time for complete injected delivery of a dose of the liquid drug formulation, which for patient comfort reasons is preferably less than 10 seconds.

It will be appreciated from the earlier description, that viscosity is not the only factor affecting the 'ease of injected delivery' of a liquid drug formulation from a syringe in an auto injector. Bore diameter of the syringe needle and force (e.g. spring force) deliverable by the actuating mechanism are also critical factors. Nonetheless, Applicant has found that the auto-injector herein is of particular utility where the viscosity of the liquid drug formulation is less than 120 mPa.s (120 centipoise), preferably less than 100 mPa.s (100 centipoise) at a delivery temperature of 20°C.

According to a further aspect of the present invention there is provided a kit of parts comprising an auto-injector as described above; and a syringe containing a liquid drug formulation.

According to a further aspect of the present invention there is provided a kit of parts comprising an auto-injector as described above; and packaging therefor; and optionally a syringe containing a liquid drug formulation.

Suitable packaging typically comprises a container for the auto-injector and syringe. In aspects, the packaging comprises a compartment for the auto-

injector pre-loaded with the syringe. In aspects, the packaging comprises a separate compartment for a 'kit' of the auto-injector and the syringe.

The invention will now be described further with reference to the accompanying drawings in which:

Figure 1 is a sectional view from the side of a first auto-injector in accord with the present invention;

Figure 2 is a perspective view from the side of the first auto-injector of Figure 1;

Figures 3a and 3b show a visual indicator label suitable for use with the first auto-injector of Figures 1 and 2; and

Figure 4 shows a cross-sectional view of a visual applicator as applied to a housing part of an auto-injector in accord with the present invention.

Referring now to the drawings, Figure 1 shows an auto-injector device 1 herein that is arranged for use with a syringe 10 that contains a liquid drug formulation 5. The auto-injector device 1 comprises a housing 20 that is arranged for receipt of the syringe 10 and is sized and shaped for this purpose.

The syringe 10 comprises a barrel 12 for holding the liquid drug formulation 5; a hollow needle 14 at one end of the barrel 12; and a plunger 16 that is arranged for axial movement within the barrel 12 such as to enable the liquid drug formulation 5 to be expelled through the hollow needle 14. The needle 14 defines a needle bore 15, which is of circular cross-section (e.g. 23G, 25G or 27G bore diameter).

The housing 20 of the auto-injector device 1 defines a housing cavity within which the syringe 10 is received. In more detail, the housing 20 of the auto-injector is provided with a barrel housing part 22 that is provided with a first

barrel-retaining circular projection 30 against which a first circular barrel lip 13 of the syringe barrel 12 seats. The housing 20 is further provided with a light spring-retaining circular projection 32 against which a first end of a light compression spring 35 seats. The second end of the light compression spring 35 seats against a second circular barrel lip 11 of the syringe barrel 12. Overall, the syringe barrel 12 is therefore retained within the barrel housing part 22, within which (in the absence of any other restraints) it is axially movable subject to the biasing force of the light compression spring 35, which biases the syringe barrel 12 into the barrel housing part 22.

The function of this movable, but lightly spring-biased syringe barrel 12 critically affects the positioning of the syringe needle 14, which is in fixed relation to the syringe barrel 12. For safety and hygiene reasons, it is desirable that the needle 14 does not protrude from the housing 20 other than when expelling the liquid drug formulation 5 during an injection procedure. Thus, the housing 20 is arranged such that a needle receiving part 24 thereof wholly houses the needle 14 when the syringe barrel 12, and hence needle 14, are subject to the bias of the light compression spring 35. This position (as shown in Figure 1) corresponds to a normal rest position. As is described in more detail hereinafter, during actuation of the syringe 10 the biasing action of the light compression spring 35 is overcome and the syringe barrel 12 and needle 14 move axially such that the tip of the needle 14 protrudes out through the delivery aperture 25 of the needle-receiving part 24 of the housing 20 to enable the liquid drug formulation 5 to be delivered by injection to a patient.

Actuation of the syringe 10 occurs in response to plunging of the plunger 16 into the barrel 12 of the syringe 10, which causes the liquid drug formulation 5 to be expelled through the needle 14. The plunger-receiving part 26 of the housing 20 receives the syringe plunger 16. In response to actuation of an actuating mechanism the plunger 16 is axially movable within that plunger-receiving part 26 from a rest position, in which it is withdrawn from the barrel 16 (as shown in

Figure 1) to a delivery position, in which it is moved into the barrel 12 for expelling of the liquid drug formulation 5 contents thereof.

The actuating mechanism of the auto-injector device 1 comprises a carriage 40 that grips the head 17 of the syringe plunger 16. The carriage 40 is axially movable within the housing 20, and such axial movement is arranged to cause plunging of the plunger 16 into the syringe barrel 12. The carriage 40 seats against a first end of a strong compression spring 45, the other end of which seats against the far wall 29 of the housing 20, such that the strong spring 45 potentially acts to force the carriage 40, and hence plunger 16 towards the plunged in (i.e. delivery) position. The action of the strong spring 45 on the carriage is however, subject to the release of a trigger mechanism comprising lever release arms 50, which pivotally attach at pivots 51 to the housing 20 and whose finger ends 52 act on the carriage 40 to prevent its axial movement under the spring force of the strong spring 45.

The trigger mechanism is released by user pressing as shown by arrows A, A' on the release button ends 54 of the lever release arms to pivot the finger ends 52 thereof away from the carriage 40. The carriage 40, and hence syringe plunger 16 are then forcefully moved by release of energy stored in the strong spring 45. Two actions result. Firstly, the action of the light spring 35 is overcome such that the barrel 12 and needle 14 of the syringe move axially such that the tip of the needle 15 protrudes from the delivery aperture 25 of the needle-receiving part 24 of the housing 20. Secondly, the plunger 16 plunges into the syringe barrel 12 to force the liquid drug formulation 5 there from into the needle 14 and thence for delivery by injection to a patient from the needle tip 15 thereof.

Figure 2 shows that the housing 20 of the auto-injector device 1 is provided with a label 60 comprising a colour change material 62. The label 60 adhesively adheres to the surface of the housing 20. The colour change material 62 defines a first colour state (e.g. blue) below a transition temperature and a second

colour state (e.g. red) above said transition temperature. The transition temperature of the colour change material 62 is selected to allow the user to differentiate between a 'too cold to use' state (i.e. below the transition temperature) and a 'sufficiently warm to use' state (i.e. above the transition temperature).

In one application of the auto-injector device 1, the syringe 10 contains a liquid drug formulation, which is designed for refrigerated storage (e.g. at from 2-8°C) and for injected delivery at room temperature (e.g. at or about 18-30°C). Thus, the transition temperature of the colour change material (i.e. blue to red) is selected to be from 15 to 30°C, particularly from 15 to 25°C, preferably from 15 to 18°C.

In a typical use operation, the auto-injector device 1 is initially stored in a fridge at less than 5°C. The auto-injector device 1 is removed from the fridge and the label indicates the first (i.e. blue) 'too cold to use' colour state. Gradually, the device 1 and its liquid drug formulation 5 contents warm up until they reach near room temperature. Once the transition temperature is exceeded the label indicates the second (i.e. red) 'ready to use' colour state. The auto-injector device 1 may then be used by a patient in an injection procedure for injected delivery of the liquid drug formulation 5.

Figures 3a and 3b show an alternative label 160 comprising a colour change material 162, which can be used with the auto-injector device 1 of Figure 1 as an alternative to the label 60 of Figure 2. The colour change material 162 defines a colour state (e.g. red) below a transition temperature and a colourless state (e.g. clear) above said transition temperature. The transition temperature of the colour change material 162 is again selected to allow the user to differentiate between a 'too cold to use' state (i.e. below the transition temperature) and a 'sufficiently warm to use' state (i.e. above the transition temperature).

The label 160 is provided with a 'ready to use' text indicium 164 that lies on the surface of the label beneath and upon which the colour change material 162 is provided as an over-layer.

As shown at Figure 3a, the indicium 164 is obscured when the colour change material 162 is in the 'too cold to use' colour state but as shown at Figure 3b is visible when the colour change material is in the 'ready to use' colourless state.

Figure 4 shows in cross-sectional view part of the housing 220 of an auto-injector herein provided with a label 260 including a colour change material 262. The auto-injector may in aspects, have the form of the first auto-injector device 1 of Figure 1. The label 260 may in aspects, have the form of the label 60 of Fig. 2 or that of label 160 of Figs. 3a and 3b.

The label 260 of Fig. 4 is provided with a window 264 comprised of an insulating clear and colourless polymeric material. The window 264 acts as an insulating barrier between the colour change material 262 of the label 260 and any temperature stimuli, which are present externally to the housing 220 of the auto-injector. Thus, the colour change material 262 will adopt a colour state that provides a representative indication of the temperature state of the housing 220 of the auto-injector rather than that of any adjacent external stimuli (e.g. fingers and/or hand of the user).

The auto-injector of the invention is suitable for the injected delivery of drug, particularly for the treatment and/or prophylaxis of a number of diseases, disorders or conditions, including infections (viral, e.g. HIV infection, bacterial, fungal and parasitic); endotoxic shock associated with infection; inflammatory diseases/autoimmunity such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus (SLE), asthma, Alzheimer's Disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome and psoriasis; immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis and Guillain-Barr syndrome; graft-versus-host

disease; organ transplant rejection; pain; cancer (including solid tumours such as melanomas, hepatoblastomas, sarcomas, squamous cell carcinomas, transitional cell cancers, ovarian cancers and hematologic malignancies, acute myelogenous leukaemia, chronic myelogenous leukemia, gastric cancer and colon cancer); congenital disorders, e.g. cystic fibrosis and sickle cell anaemia; growth disorders; heart disease including ischaemic diseases such as myocardial infarction as well as atherosclerosis and intravascular coagulation; bone disorders such as osteopenia and osteoporosis; and metabolic/idiopathic disease, e.g. diabetes.

Appropriate drugs may thus be selected from biologically active agents, including chemical entities, polysaccharides, steroids and, especially, naturally occurring and recombinant proteins, including glycoproteins, polypeptides and oligopeptides and polymeric derivatives thereof. Particular proteins, polypeptides and oligopeptides include hormones, such as insulin, epinephrine, norepinephrine, adrenocorticotrophin, somatotropin, erythropoietin and oxytocin; cytokines, such as lymphokines, chemokines and interleukins and receptors therefor, e.g. interleukin (IL)-1α , IL-1β, IL-1R, IL-2, IL-3, IL-4, IL-5, IL-6, IL17, interferon (IFN)-α, IFN-β, IFN-γ, granulocyte monocyte colony stimulating factor, tumour necrosis factor-α; growth factors, such as nerve growth factor and platelet-derived growth factor; enzymes, such as tissue plasminogen activator; and, especially, immunoglobulins. Immunoglobulins include whole antibodies and functionally active fragments and/or derivatives thereof, for example polyclonal, monoclonal, recombinant, multi-valent, mono- or multi-specific, humanised or chimeric antibodies, single chain antibodies, Fab fragments, Fab' and $F(ab')_2$ fragments. Polymeric derivatives of such proteins, polypeptides and oligopeptides include derivatives formed between the protein, polypeptide or oligopeptide and a naturally occurring or synthetic polymer, e.g. a polysaccharide or a polyalylklene polymer such as a poly(ethyleneglycol) [PEG] or derivative thereof, e.g. methoxypoly(ethyleneglycol) [mPEG].

The auto-injector device herein has been found to be of particular utility where the drug is an immunoglobulin or a fragment thereof, especially a PEGylated or mPEGylated antibody fragment.

The liquid drug formulations herein are typically aqueous formulations, which comprise the drug in solution and additionally other optional formulation components, which may include buffers (e.g. lactate, acetate), NaCl, and pH modifiers (e.g. NaOH).

The auto-injector device herein has been found to be of particular utility wherein the concentration of the drug (e.g. a therapeutic biologic type drug) in the liquid drug formulation is quite high. In particular, where the drug is a pegylated antibody the auto-injector device has been found to be of particular utility wherein the concentration of the drug is greater than 100mg/ml, particularly greater than 150mg/ml such as 200mg/ml.

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described therein. They may take the form of product, method or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims

1. An auto-injector comprising

a housing arranged for receipt of a syringe containing a liquid drug formulation;

an actuating mechanism for actuating said syringe to deliver said liquid formulation to a patient; and

a visual indicator comprising a colour change material that defines a first colour state below a transition temperature and a second colour state above said transition temperature.

2. An auto-injector according to claim 1, wherein the syringe comprises a barrel for holding a volume of the liquid drug formulation; a needle at one end of said barrel; and a plunger that is axially movable within the barrel.

3. An auto-injector according to claim 2, wherein the barrel has a volume corresponding to a single dose of the liquid drug formulation.

4. An auto-injector according to either of claims 2 or 3, wherein the housing is provided with a barrel receiving part for receiving the barrel of the syringe; a plunger receiving part for receiving the plunger of the syringe; and a needle receiving part for receiving the needle of the syringe.

5. An auto-injector according to any of claim 1 to 4, wherein the actuating mechanism includes an energy store for storing energy that is releasable to actuate the syringe.

6. An auto-injector according to claim 5, wherein the energy store comprises a spring.

7. An auto-injector according to claim 5, wherein the energy store comprises a container of compressed liquid or gas.

8. An auto-injector according to any of claims 4 to 7, wherein the needle receiving part of the housing allows for the needle of the syringe to be axially moveable therein from a rest position, in which the needle is wholly housed by the needle receiving part, to a use position, in which at least the tip of the needle protrudes from that needle receiving part of the housing.

9. An auto-injector according to claim 8 wherein the housing includes biasing means arranged such that the needle is normally biased towards said rest position, wherein such biasing means are overcome during the actuation of the syringe by the actuating mechanism to allow for movement of the needle to the use position.

10. An auto-injector according to any of claims 1 to 9, wherein the visual indicator is provided to the housing.

11. An auto-injector according to claim 10, wherein the visual indicator is provided as a coating to the housing.

12. An auto-injector according to claim 10, wherein the visual indicator is provided to a label that is provided to the housing.

13. An auto-injector according to claim 12, wherein said label is comprised of a plastic polymer or cellulosic material.

14. An auto-injector according to either of claims 12 or 13, wherein the label is provided with an adhesive layer for adhesive application to the housing.

15. An auto-injector according to any of claims 1 to 14, wherein an insulating layer is provided to the visual indicator.

16. An auto-injector according to claim 15, wherein said insulating layer is provided as a window to the housing.

17. An auto-injector according to any of claims 1 to 16, wherein the transition temperature is selected to allow the user to differentiate between a first state below the transition temperature in which the auto-injector is too cold to use and a second state above the transition temperature in which the auto-injector is sufficiently warm to use.

18. An auto-injector according to any of claims 1 to 17, wherein the transition temperature is selected to be from 15 to 30°C, preferably from 15 to 18°C.

19. An auto-injector according to any of claims 1 to 18, wherein the first colour state is a first colour and the second colour state is a second colour.

20. An auto-injector according to any of claims 1 to 18, wherein the first colour state is colourless and the second colour state is a colour or the second colour state is colourless and the first colour state is a colour.

21. An auto-injector according to claim 20, wherein the visual indicator is provided with an indicium that lies beneath the colour change material such that said indicium is visible when the colour change material is in said colourless state, but which is obscured when the colour change material is in said colour state.

22. An auto-injector according to any of claims 1 to 21, wherein the colour change material is a thermochromic material.

23. An auto-injector according to claim 22, wherein said thermochromic material includes fine pigments particles, microencapsulated materials and/or molecular materials.

24. An auto-injector according to either of claims 22 or 23, wherein the thermochromic material comprises a liquid crystal or a leuco dye.

25. An auto-injector according to any of claims 1 to 24, wherein the housing receives a syringe containing a liquid drug formulation.

26. An auto-injector according to claim 25, wherein said liquid drug formulation is arranged for storage at from 2-8°C and for injected delivery at from 18-30°C.

27. An auto-injector according to claim 26, wherein the liquid drug formulation has a viscosity of less than 120 mPa.s at a delivery temperature of 20°C.

28. An auto-injector according to any of claims 25 to 27, wherein the liquid drug formulation comprises an aqueous formulation of a therapeutic biologic type drug.

29. An auto-injector according to claim 28, wherein said biologic type drug comprises an immunoglobulin or a fragment thereof.

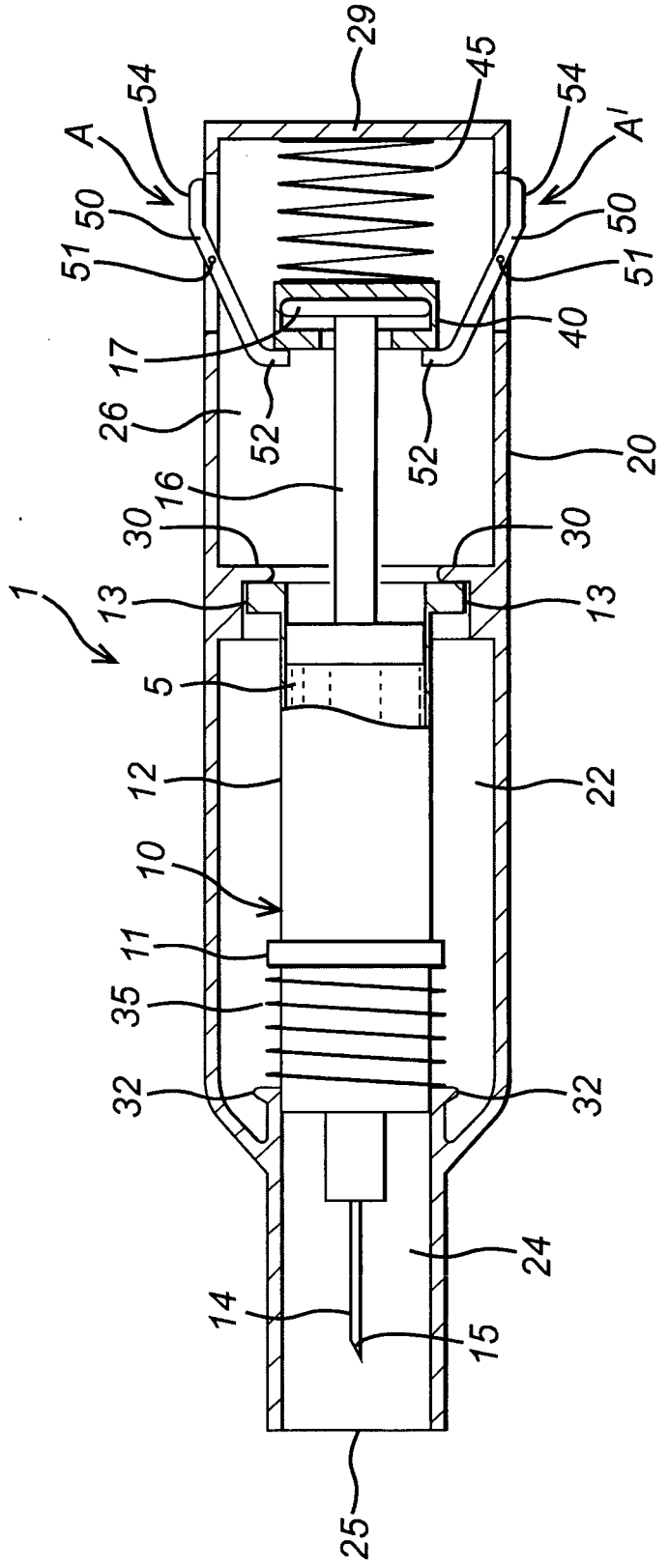
30. An auto-injector according to claim 29, wherein said biologic type drug comprises a PEGylated or mPEGylated antibody fragment.

31. An auto-injector according to any of claims 28 to 30, wherein said aqueous formulation comprise additional formulation component selected from the group consisting of buffers, NaCl, and pH modifiers.

32. An auto-injector according to any of claims 29 to 31, wherein the concentration of the drug in the liquid drug formulation is greater than 100mg/ml.

33. A kit of parts comprising an auto-injector according to any of claims 1 to 24; and a syringe containing a liquid drug formulation.

FIG. 1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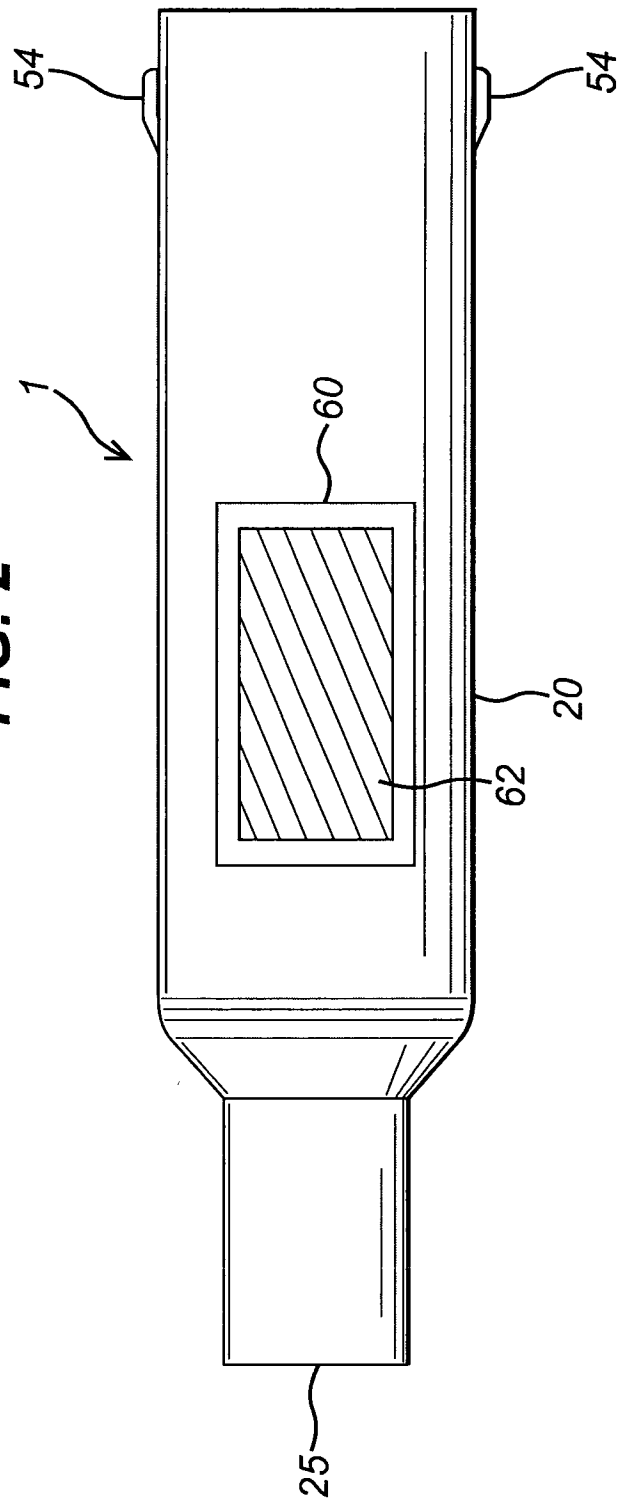


FIG. 2

FIG. 3a

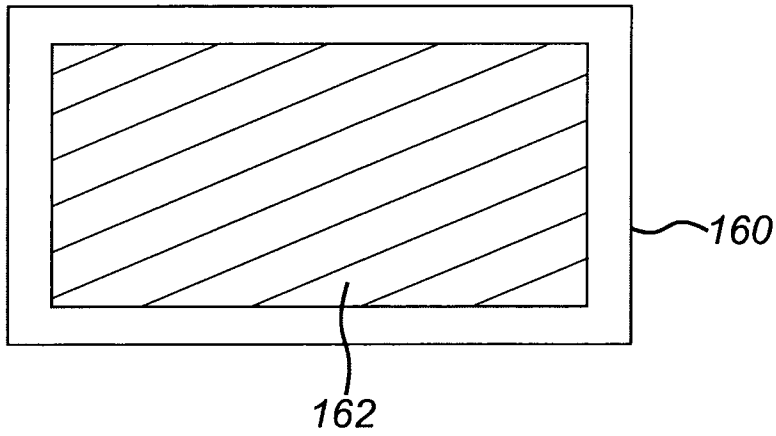


FIG. 3b

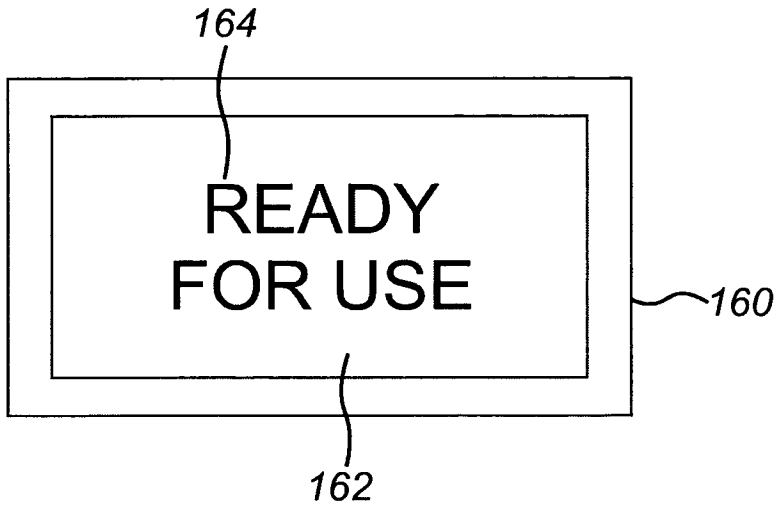
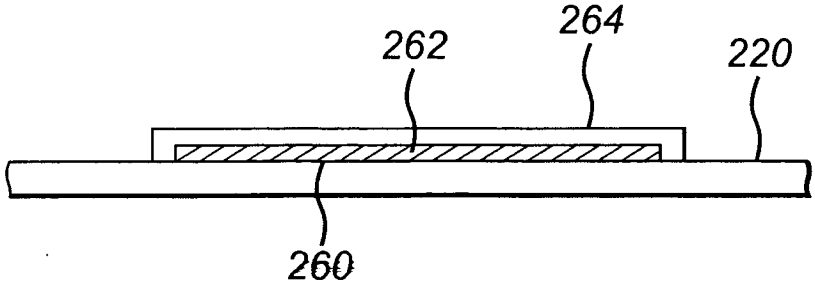


FIG. 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/001871

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/31 A61M5/44

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)
A61M

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/105927 A (TECPHARMA LICENSING AG [CH]; KIRCHHOFER FRITZ [CH]; STEFFEN BEAT [CH]) 24 December 2003 (2003-12-24) page 3, line 22 - line 25 page 4, line 4 - line 16	1-11,17, 19,25
A	-----	21
Y	WO 03/092771 A (PA KNOWLEDGE LTD; MARTIN JEFFREY [GB]; HUGHES MARTIN LAWRENCE [GB]) 13 November 2003 (2003-11-13) page 14, line 13 - page 15, line 7	1-11,17, 19,25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2008	04/09/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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