Description

# SPINDLE FOR A DRUG DELIVERY DEVICE

## BACKGROUND

### Field of the Present Patent Application

The present patent application is generally directed to a spindle for use with a dose setting mechanism of a drug delivery device. More particularly, the present patent application is generally directed to a spindle for use with drug delivery devices, such as pen type drug delivery devices. Such devices provide for self administration of medicinal product from a multi-dose cartridge and permit a user to set the delivery dose. The present application may find application in both disposable and reusable type drug delivery devices. However, aspects of the invention may be equally applicable in other scenarios as well.

### Background

Pen type drug delivery devices have application where regular injection by persons without formal medical training occurs. This is increasingly common among patients having diabetes where self-treatment enables such patients to conduct effective management of their disease.

One such prior art pen type drug delivery device is described in WO 2004/078293 and is illustrated in Figures 1 through 12 of the present application. WO 2004/078293 is herein entirely incorporated by reference and to which the reader is directed for any further information.

As illustrated in Figures 1 to 5, there is shown a drug delivery device in a plurality of operating positions: for dose setting and for dose administration or injection. The drug delivery device comprises a housing having a first cartridge retaining part 2, and

second main (exterior) housing part 4. A cartridge 8 from which a number of doses of a medicinal product may be dispensed is provided in the cartridge retaining part 2. A piston 10 is retained in a first end of the cartridge. A removable cap 12 is releasably retained over a second end of the cartridge retaining part 2.

An insert 16 is provided at a first end of the main housing 4 and is secured against rotational or longitudinal motion. The insert 16 is provided with a threaded circular opening 18. A first helical groove 19 extends from a first end of a spindle 20. The spindle 20 is generally circular in cross section. The first end of the spindle 20 (a distal end) extends through the threaded opening 18 in the insert 16. A second helical groove 24 extends from a second end of the spindle 20 (a proximal end). In the illustrated arrangement, the second helical groove 24 comprises a series of part helical grooves rather than a complete helical groove.

The first helical groove 19 and the second helical groove 24 are oppositely disposed, i.e., the grooves are of opposite hand. The second end of the spindle 20 (i.e., the proximal end) is provided with a receiving recess. A driver 30 extends about the spindle 20 and is provided at a first end with a first radially extending flange 32. A second radially extending flange 34 is provided spaced a distance along the driver 30 from the first flange 32. An intermediate helical groove 36 is provided on an outer part of the driver 30 extending between the first flange 32 and the second flange 34. Further, a part nut 40 is provided engaging the intermediate helical groove 36 and splined to the housing 4 such that part nut 40 does not rotate relative to the housing but is allowed to move axially with respect to the housing 4. A helical groove extends along the entire internal surface of the driver 30. The second helical groove 24 (a male helical groove) of the spindle 20 is adapted to work within said helical groove in the driver.

A shoulder 37 is formed between a second end of the driver 30 (a proximal end of the driver 30) and an extension 38 provided at the second end of the driver 30. The extension 38 has reduced inner and outer diameters in comparison to the remainder of the driver 30. A second end of the extension 38 is provided with a radially outwardly

directed flange 39. Figure 13 illustrates a close up view of the driver 30 and spindle 20 illustrated in Figures 1-5.

A clutch 60 is located adjacent the second end of the driver 30. The clutch 60 is generally cylindrical and is provided at a first end (a distal end) with a series of circumferentially directed saw teeth 66 (See, e.g., Figure 7). Each saw tooth comprises a longitudinally directed surface and an inclined surface. Towards the second end 64 (a proximal end) of the clutch 60 there is located a radially inwardly directed flange 62. The flange 62 of the clutch 60 is disposed between the shoulder 37 of the driver 30 and the radially outwardly directed flange 39 of the extension 38.

The second end of the clutch 60 is provided with a plurality of dog teeth 65 (See, e.g., Figure 8). The clutch 60 is keyed to the drive sleeve 30 by way of splines (not shown) to prevent relative rotation between the clutch 60 and the drive sleeve 30. In one preferred arrangement, a clicker 50 is provided with said clicker and the clutch 60 each extending approximately half the length of the drive sleeve 30. The clicker 50 and the clutch 60 are engaged as shown in Figures 6 and 7, for example.

A dose dial sleeve 70 is provided outside of the clicker 50 and clutch 60 and radially inward of the main housing 4. The dose dial sleeve 70 comprises a distal end and a proximal end. A helical groove 74 is provided about an outer surface of the dose dial sleeve 70. The main housing 4 is provided with a window 44 through which a part of an outer surface of the dose dial sleeve 70 may be viewed.

The main housing 4 is further provided with a helical rib 46, adapted to be seated in the helical groove 74 on the outer surface of the dose dial sleeve 70. In one preferred arrangement, the helical rib 46 extends for a single sweep of the inner surface of the main housing 4. A first stop is provided between the splines 42 and the helical rib. A second stop, disposed at an angle of 180" to the first stop, is formed by a frame surrounding the window 44 in the main housing 4.

Returning to Figures 1-5, a dose dial grip 76 is disposed about an outer surface of the second end of the dose dial sleeve 70. An outer diameter of the dose dial grip 76 preferably corresponds to the outer diameter of the main housing 4. The dose dial grip 76 is secured to the dose dial sleeve 70 to prevent relative movement between these two components. The dose dial grip 76 is provided with a central opening 78. An annular recess 80 located in the second end of the dose dial grip 76 extends around the opening 78. A button 82 of generally 'T' section is provided at a second end of the device. A stem 84 of the button may extend through the opening 78 in the dose dial grip 76, through the inner diameter of the extension 38 of the drive sleeve 30 and into the receiving recess 26 at the proximal end of the spindle 20. The stem 84 is retained for limited axial movement in the drive sleeve 30 and against rotation with respect thereto. A head 85 of the button 82 is generally circular. A skirt 86 extends from a periphery of the head 85. The skirt 86 is adapted to be seated in the annular 10 recess 80 of the dose dial grip 76.

Operation of the drug delivery device is described with reference to Figures 9, 10 and 11. In Figures 9, 10 and 11 arrows, A, B, C, D, E, F and G represent the respective movements of the button 82, the dose dial grip 76, the dose dial sleeve 70, the driver 30, the clutch 60, the clicker 50 and the part nut 40 in one arrangement.

To dial a dose in the arrangement illustrated in Figure 9, a user rotates the dose dial grip 76 (arrow B). With the clicker 50 and clutch 60 engaged, the driver 30, the clicker 50, the clutch 60 and the dose dial sleeve 70 rotate with the dose dial grip 76. Torque is transmitted through the saw teeth 56, 66 between the clicker 50 and the clutch 60. A flexible arm 52 deforms and drags a toothed member 54 over the splines 42 to produce a click. Preferably, the splines 42 are disposed such that each click corresponds to a conventional unit dose, or the like.

The helical groove 74 on the dose dial sleeve 70 and the helical groove in the driver 30 have the same lead. This allows the dose dial sleeve 70 (arrow C) to extend away from the main housing 4 (See, also Figure 15). In this manner, the driver 30 (arrow D) climbs the spindle 20 at the same rate. At the limit of travel, a radial stop 104 (See,

e.g., Figure 12) on the dose dial sleeve 70 engages either a first stop or a second stop provided on the main housing 4 to prevent further movement. Rotation of the spindle 20 is prevented due to the opposing directions of the overhauled and driven threads on the spindle 20. The part nut 40, keyed to the main housing 4, is advanced along the intermediate thread 36 by the rotation of the drive sleeve 30 (arrow D).

As mentioned above, a first helical groove form 19 extends from a first or distal end of a spindle 20 towards the proximal end. This first helical groove form 19 extends roughly half the length of the spindle 20. The spindle 20 is of generally circular in cross section however other arrangements may also be used. The distal end of the spindle 20 is threadedly extended through the threaded opening 18 in the insert 16. A pressure foot 22 is located at the first end or distal end of the spindle 20 and disposed to abut a second end of the cartridge piston 10.

A second helical groove form 24 extends from a proximal end of the spindle 20. As illustrated, the second helical groove form 24 comprises a series of part male helical grooves rather than a complete helical groove form. The driver 30 comprises an inner helical groove that extends along an internal surface of the driver 30. As illustrated, this inner helical groove extends along the entire internal surface of the driver from the distal to the proximal end of the driver 30. The second male helical groove form 24 of the spindle 20 is adapted to work within this helical groove.

Although the spindle 20 and the driver 30 arrangement illustrated in Figures 1 – 13 has certain advantages as described and discussed in WO 2004/078293, this spindle and driver arrangement have certain design limitations. For example, the fabrication of the spindle and driver presents certain manufacturing challenges. As described above, this prior art design comprises a spindle 20 comprising two opposite handed groove forms 19, 24. The first groove form 19 is a female groove form and this female groove form mates with the threaded insert 16 of the main outer diameter of the cylindrical form. The second groove form 24 comprises a plurality of male protrusions that engage with the continuous groove in the driver 30.

This continuous groove is molded along the entire length of the internal surface of the driver 30.

In this prior art drug delivery device, when the driver 30 is rotated relative to the spindle 20 during dose setting, because the driver is coupled to the number sleeve which is threaded to the housing, the driver 30 moves axially. The axial distance moved by the driver 30 will be dependent upon the pitch of the number sleeve groove 74 which is generally similar to the pitch of the continuous internal groove on the driver 30. As such, this prior art spindle 20 and driver 30 arrangement requires that the driver 30 be provided with an internal helical groove over roughly the entire inner surface of the driver 30. In this arrangement, the driver 30 does not disengage from the spindle helical groove 24 during either a dose setting step or during a dose administration step.

This arrangement, therefore, presents certain design and manufacturing challenges. For example, during the molding of driver 30 and in particular, during the process of molding the internal helical groove of driver 30, this step requires that a threaded core pin be spun out of the driver during a de-molding step from the injection mold tooling. This processing step has a disadvantages. For example, rotating the threaded core pin requires complex gear mechanisms within the molding tool, with flexible water cooling pipes or sealed rotating joints required to enable this rotating core pin to be cooled. Rotating the core extends the cycle time of the tool and generally adds tool complexity and increased maintenance costs.

There is, therefore, a general need to take these issues into consideration in the design and development of a spindle for certain drug delivery devices, such as reusable (i.e., resettable) or disposable (i.e., non-resettable) drug delivery devices.

SUMMARY

Embodiments of the present invention seek to provide an improved dose setting mechanism suitable for reusable (i.e., resettable) or disposable (i.e., non-resettable) drug delivery devices.

This advantage is provided by a spindle as defined in one embodiment. The spindle according to an embodiment of the present invention has two overlapping helical grooves. One of said grooves may be coupled to or engaged with a driver such that when a user sets a dose by rotating a rotating sleeve (like a dose dial sleeve), said driver also rotates. The other of said grooves may be coupled to or engaged with a part of the drug delivery device body (like an internal or external housing). Preferably, the spindle is manufactured with a simple open and shut (molding) tool without a threaded core pin.

According to an exemplary embodiment, a spindle for driving a bung of a cartridge comprises a generally circular shaft having an outer surface. The generally circular shaft extends from a distal end to a proximal end of the circular shaft. A first helical groove is provided along a first portion of the outer surface. The first helical groove having a first pitch. A second helical groove provided along a second portion of the outer surface of the generally circular shaft. The second helical groove overlapping the first helical groove. The second helical groove having a second pitch.

The first helical groove of the spindle may be a helical female groove. Further, the second helical groove may be a helical female groove. In addition, said first helical groove and/or said second helical groove may extend along an outer surface of the shaft from about said distal end of said spindle to about said proximal end of said spindle.

For interaction with said spindle, a dose setting mechanism is provided with a driver for driving said spindle and/or a drug delivery body (like a housing). The driver may comprise a helical groove form that engages said first helical groove of said spindle and the drug delivery body may comprise a helical groove form that engages said

second helical groove of said spindle. Preferably, said helical groove on said driver and/or said helical groove on said drug delivery body comprises a partial groove form, like a helical groove of less than one turn. The helical groove on said driver and/or the helical groove on said drug delivery body may be designed as a male helical groove.

In another arrangement, a dose setting mechanism for use with a drug delivery device is provided. This mechanism comprising a housing and a rotating sleeve in rotatable engagement with respect to the housing. A driver is releasably coupled to the rotating sleeve. A spindle having two overlapping helical grooves is operatively coupled to the driver such that when a user sets a dose by rotating the rotating sleeve, the driver also rotates.

A dose setting mechanism with a spindle according to the present invention may be a resettable dose setting mechanism, wherein the driver comprises a first component and a second component, with said first and said second components being operatively coupled together so that they rotate together when a user sets a dose. Further, when a user resets said dose setting mechanism and said first component rotates back to its original position, a dose limiting device may return to an initial position.

It is further preferred to provide a cartridge holder releasably coupled to said dose setting mechanism. This may be achieved by way of a bayonet coupling. The cartridge holder usually comprises a removable cartridge.

These as well as other advantages of various aspects of the present invention will become apparent to those of ordinary skill in the art by reading the following detailed description, with appropriate reference to the accompanying drawings.

## BRIEF DESCRIPTION OF THE DRAWINGS

Exemplary embodiments are described herein with reference to the drawings, in which:

Figure 1 illustrates a sectional view of a first embodiment of the known drug delivery device in a first, cartridge full, position;

Figure 2 illustrates a sectional view of the drug delivery device of Figure 1 in a second, maximum first dose dialed, position;

Figure 3 illustrates a sectional view of the drug delivery device of Figure 1 in a third, maximum first dose dispensed, position;

Figure 4 illustrates a sectional view of the drug delivery device of Figure 1 in a fourth, final dose dialed, position;

Figure 5 illustrates a sectional view of the drug delivery device of Figure 1 in a fifth, final dose dispensed, position;

Figure 6 illustrates a cut-away view of a first detail of the drug delivery device of Figure 1;

Figure 7 illustrates a partially cut-away view of a second detail of the drug delivery device of Figure 1;

Figure 8 illustrates a partially cut-away view of a third detail of the drug delivery device of Figure 1;

Figure 9 illustrates a first relative movement of parts of the drug delivery device shown in Figure 1 during dialing up of a dose;

Figure 10 illustrates the relative movement of parts of the drug delivery device shown in Figure 9 during dialing down of a dose;

Figure 11 illustrates the relative movement of parts of the drug delivery device shown in Figure 9 during dispensing of a dose;

Figure 12 illustrates a partially cut-away view of the drug delivery device of Figure 1 in the second, maximum first dose dialed, position;

Figure 13 illustrates a sectional view of the spindle and the driver illustrated in Figures 1-2;

Figure 14 illustrates an arrangement of a drug delivery device;

Figure 15 illustrates the drug delivery device of Figure 14 with a removed cap;

Figure 16 illustrates a sectional view of the first arrangement of the drug delivery device of Figure 15 in a first position;

Figure 17 illustrates a sectional view of the first arrangement of the drug delivery device of Figure 15 in a second position;

Figure 18 illustrates a sectional view of the first arrangement of the drug delivery device of Figure 15 in a third position;

Figure 19 illustrates a first arrangement of the driver illustrated in Figures 16 - 18 comprising a first driver portion and a second driver portion;

Figure 20 illustrates a distal end of the spindle of the dose setting mechanism illustrated in Figures 16 - 18;

Figure 21 illustrates a sectional view of a second arrangement of a dose setting mechanism of the drug delivery device illustrated in Figure 14;

Figure 22 illustrates a partial sectional view of the second embodiment of the dose setting mechanism illustrated in Figure 21;

Figure 23 illustrates a close up view of Gap a illustrated in Figure 21;

Figure 24 illustrates a second arrangement of a driver comprising a first driver portion and a second driver portion;

Figure 25 illustrates the dose setting mechanism illustrated in either Figures 2-5 or Figures 6-8;

Figure 26 illustrates the dose setting mechanism illustrated in Figure 25 in which a user has set a dose;

Figure 27 illustrates a driver that may be used with a dose setting mechanism of the drug delivery device illustrated in Figure 14 – 15;

Figure 28 illustrates a spindle coupled to the driver illustrated in Figure 27; and

Figure 29 illustrates a close up view of a spindle according to the present invention that may be used with a dose setting mechanism of a drug delivery device.

DETAILED DESCRIPTION

The terms „drug" or "medication" or "medicinal product" or "medicament", as used herein, mean a pharmaceutical formulation containing at least one pharmaceutically active compound,

wherein in one embodiment the pharmaceutically active compound has a molecular weight up to 1500 Da and/or is a peptide, a proteine, a polysaccharide, a vaccine, a DNA, a RNA, a antibody, an enzyme, an antibody, a hormone or an oligonucleotide, or a mixture of the above-mentioned pharmaceutically active compound,

wherein in a further embodiment the pharmaceutically active compound is useful for the treatment and/or prophylaxis of diabetes mellitus or complications associated with

diabetes mellitus such as diabetic retinopathy, thromboembolism disorders such as deep vein or pulmonary thromboembolism, acute coronary syndrome (ACS), angina, myocardial infarction, cancer, macular degeneration, inflammation, hay fever, atherosclerosis and/or rheumatoid arthritis,

wherein in a further embodiment the pharmaceutically active compound comprises at least one peptide for the treatment and/or prophylaxis of diabetes mellitus or complications associated with diabetes mellitus such as diabetic retinopathy,

wherein in a further embodiment the pharmaceutically active compound comprises at least one human insulin or a human insulin analogue or derivative, glucagon-like peptide (GLP-1) or an analogue or derivative thereof, or exedin-3 or exedin-4 or an analogue or derivative of exedin-3 or exedin-4.

Insulin analogues are for example Gly(A21), Arg(B31), Arg(B32) human insulin; Lys(B3), Glu(B29) human insulin; Lys(B28), Pro(B29) human insulin; Asp(B28) human insulin; human insulin, wherein proline in position B28 is replaced by Asp, Lys, Leu, Val or Ala and wherein in position B29 Lys may be replaced by Pro; Ala(B26) human insulin; Des(B28-B30) human insulin; Des(B27) human insulin and Des(B30) human insulin.

Insulin derivates are for example B29-N-myristoyl-des(B30) human insulin; B29-N-palmitoyl-des(B30) human insulin; B29-N-myristoyl human insulin; B29-N-palmitoyl human insulin; B28-N-myristoyl LysB28ProB29 human insulin; B28-N-palmitoyl-LysB28ProB29 human insulin; B30-N-myristoyl-ThrB29LysB30 human insulin; B30-N-palmitoyl- ThrB29LysB30 human insulin; B29-N-(N-palmitoyl-Y-glutamyl)-des(B30) human insulin; B29-N-(N-lithocholyl-Y-glutamyl)-des(B30) human insulin; B29-N-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N-(ω-carboxyheptadecanoyl) human insulin.

Exendin-4 for example means Exendin-4(1-39), a peptide of the sequence H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

Exendin-4 derivatives are for example selected from the following list of compounds:

H-(Lys)4-des Pro36, des Pro37 Exendin-4(1-39)-NH2,
H-(Lys)5-des Pro36, des Pro37 Exendin-4(1-39)-NH2,
des Pro36 [Asp28] Exendin-4(1-39),
des Pro36 [IsoAsp28] Exendin-4(1-39),
des Pro36 [Met(O)14, Asp28] Exendin-4(1-39),
des Pro36 [Met(O)14, IsoAsp28] Exendin-4(1-39),
des Pro36 [Trp(O2)25, Asp28] Exendin-4(1-39),
des Pro36 [Trp(O2)25, IsoAsp28] Exendin-4(1-39),
des Pro36 [Met(O)14 Trp(O2)25, Asp28] Exendin-4(1-39),
des Pro36 [Met(O)14 Trp(O2)25, IsoAsp28] Exendin-4(1-39); or

des Pro36 [Asp28] Exendin-4(1-39),
des Pro36 [IsoAsp28] Exendin-4(1-39),
des Pro36 [Met(O)14, Asp28] Exendin-4(1-39),
des Pro36 [Met(O)14, IsoAsp28] Exendin-4(1-39),
des Pro36 [Trp(O2)25, Asp28] Exendin-4(1-39),
des Pro36 [Trp(O2)25, IsoAsp28] Exendin-4(1-39),
des Pro36 [Met(O)14 Trp(O2)25, Asp28] Exendin-4(1-39),
des Pro36 [Met(O)14 Trp(O2)25, IsoAsp28] Exendin-4(1-39),
wherein the group -Lys6-NH2 may be bound to the C-terminus of the Exendin-4 derivative;

*or an Exendin-4 derivative of the sequence*
H-(Lys)6-des Pro36 [Asp28] Exendin-4(1-39)-Lys6-NH2,
des Asp28 Pro36, Pro37, Pro38Exendin-4(1-39)-NH2,
H-(Lys)6-des Pro36, Pro38 [Asp28] Exendin-4(1-39)-NH2,

H-Asn-(Glu)5des Pro36, Pro37, Pro38 [Asp28] Exendin-4(1-39)-NH2,
des Pro36, Pro37, Pro38 [Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-(Lys)6-des Pro36, Pro37, Pro38 [Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-Asn-(Glu)5-des Pro36, Pro37, Pro38 [Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-(Lys)6-des Pro36 [Trp(O2)25, Asp28] Exendin-4(1-39)-Lys6-NH2,
H-des Asp28 Pro36, Pro37, Pro38 [Trp(O2)25] Exendin-4(1-39)-NH2,
H-(Lys)6-des Pro36, Pro37, Pro38 [Trp(O2)25, Asp28] Exendin-4(1-39)-NH2,
H-Asn-(Glu)5-des Pro36, Pro37, Pro38 [Trp(O2)25, Asp28] Exendin-4(1-39)-NH2,
des Pro36, Pro37, Pro38 [Trp(O2)25, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-(Lys)6-des Pro36, Pro37, Pro38 [Trp(O2)25, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-Asn-(Glu)5-des Pro36, Pro37, Pro38 [Trp(O2)25, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-(Lys)6-des Pro36 [Met(O)14, Asp28] Exendin-4(1-39)-Lys6-NH2,
des Met(O)14 Asp28 Pro36, Pro37, Pro38 Exendin-4(1-39)-NH2,
H-(Lys)6-desPro36, Pro37, Pro38 [Met(O)14, Asp28] Exendin-4(1-39)-NH2,
H-Asn-(Glu)5-des Pro36, Pro37, Pro38 [Met(O)14, Asp28] Exendin-4(1-39)-NH2,
des Pro36, Pro37, Pro38 [Met(O)14, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-(Lys)6-des Pro36, Pro37, Pro38 [Met(O)14, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-Asn-(Glu)5 des Pro36, Pro37, Pro38 [Met(O)14, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-Lys6-des Pro36 [Met(O)14, Trp(O2)25, Asp28] Exendin-4(1-39)-Lys6-NH2,
H-des Asp28 Pro36, Pro37, Pro38 [Met(O)14, Trp(O2)25] Exendin-4(1-39)-NH2,
H-(Lys)6-des Pro36, Pro37, Pro38 [Met(O)14, Asp28] Exendin-4(1-39)-NH2,
H-Asn-(Glu)5-des Pro36, Pro37, Pro38 [Met(O)14, Trp(O2)25, Asp28] Exendin-4(1-39)-NH2,
des Pro36, Pro37, Pro38 [Met(O)14, Trp(O2)25, Asp28] Exendin-4(1-39)-(Lys)6-NH2,
H-(Lys)6-des Pro36, Pro37, Pro38 [Met(O)14, Trp(O2)25, Asp28] Exendin-4(S1-39)-(Lys)6-NH2,
H-Asn-(Glu)5-des Pro36, Pro37, Pro38 [Met(O)14, Trp(O2)25, Asp28] Exendin-4(1-39)-(Lys)6-NH2;

or a pharmaceutically acceptable salt or solvate of any one of the afore-mentioned Exedin-4 derivative.

Hormones are for example hypophysis hormones or hypothalamus hormones or regulatory active peptides and their antagonists as listed in Rote Liste, ed. 2008, Chapter 50, such as Gonadotropine (Follitropin, Lutropin, Choriongonadotropin, Menotropin), Somatropine (Somatropin), Desmopressin, Terlipressin, Gonadorelin, Triptorelin, Leuprorelin, Buserelin, Nafarelin, Goserelin.

A polysaccharide is for example a glucosaminoglycane, a hyaluronic acid, a heparin, a low molecular weight heparin or an ultra low molecular weight heparin or a derivative thereof, or a sulphated, e.g. a poly-sulphated form of the above-mentioned polysaccharides, and/or a pharmaceutically acceptable salt thereof. An example of a pharmaceutically acceptable salt of a poly-sulphated low molecular weight heparin is enoxaparin sodium.

Pharmaceutically acceptable salts are for example acid addition salts and basic salts. Acid addition salts are e.g. HCl or HBr salts. Basic salts are e.g. salts having a cation selected from alkali or alkaline, e.g. Na+, or K+, or Ca2+, or an ammonium ion N+(R1)(R2)(R3)(R4), wherein R1 to R4 independently of each other mean: hydrogen, an optionally substituted C1-C6-alkyl group, an optionally substituted C2-C6-alkenyl group, an optionally substituted C6-C10-aryl group, or an optionally substituted C6-C10-heteroaryl group. Further examples of pharmaceutically acceptable salts are described in "Remington's Pharmaceutical Sciences" 17. ed. Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, Pa., U.S.A., 1985 and in Encyclopedia of Pharmaceutical Technology.

Pharmaceutically acceptable solvates are for example hydrates.

Referring to Figure 14, there is shown a drug delivery device 201 in accordance with a first arrangement of the present invention of Applicants' dual helical spindle and driver

configuration. In this arrangement, the drug delivery device 201 may comprise either a resettable or a non-resettable drug delivery device.

The drug delivery device 201 comprises a housing having a first cartridge retaining part 202 and dose setting mechanism 204. A first end of the cartridge retaining means 202 and a second end of the dose setting mechanism 204 are secured together by retaining features. In this illustrated arrangement, the cartridge retaining means 202 is secured within the second end of the dose setting mechanism 204. A removable cap 203 is releasably retained over a second end or distal end of a cartridge retaining part. As will be described in greater detail, the dose setting mechanism 204 comprises a dose dial grip 212 and a window or lens 214. To set a dose of medication contained within the drug delivery device 201, a user rotates the dose dial grip 212 and the window allows a user to view the dialed dose by way of a dose scale arrangement 216.

Figure 15 illustrates the medical delivery device 201 of Figure 14 with the cover 203 removed from the distal end of the medical delivery device. As illustrated, a cartridge 220 from which a number of doses of a medicament may be dispensed is provided in the cartridge housing 206. Preferably, the cartridge 220 contains a type of medicament that must be administered often, such as once or more times a day. One such medicament is insulin. A bung or stopper (not illustrated in Figure 14) is retained in a first end or a proximal end of the cartridge 220.

As mentioned previously, the dose setting mechanism 204 of the drug delivery device illustrated in Figure 14 may be utilized as a reusable (and hence resettable) drug delivery device. Alternatively, the dose setting mechanism 204 of the drug delivery device illustrated in Figure 14 may be utilized as a non-reusable (non-resettable) drug delivery device.

Where the drug delivery device 201 comprises a reusable drug delivery device, the cartridge is removable from the cartridge housing 206. The cartridge 220 may be removed from the device without destroying the device but merely by the user disconnecting the dose setting mechanism 4 from the cartridge holder 220.

In use, once the removable cap 203 is removed, a user can attach a suitable needle assembly to the distal end of the cartridge holder. Such needle unit may be screwed onto a distal end of the housing or alternatively may be snapped onto this distal end. A replaceable cap 203 is used to cover the cartridge holder 206 extending from the dose setting mechanism 204. Preferably, the outer dimensions of the replaceable cap 203 are similar or identical to the outer dimensions of the dose setting mechanism 204 so as to provide an impression of a unitary whole when the replaceable cap 203 is in position covering the cartridge holder 202.

Figure 16 illustrates a sectional view of the dose setting mechanism 204 removably connected to the cartridge holder 206. The dose setting mechanism 204 comprises an outer housing 240 containing a spindle 242, a number sleeve 210, a clutch 226, and a driver 230. As will be described in greater detail below, the spindle comprises a first groove 219 and a second groove 221 that preferably overlaps with the first groove 219. The first helical groove 219 extends from a first end of the spindle 242. In one arrangement, the spindle 242 is of generally circular shape however other arrangements may also be used. The first end of the spindle 242 (a distal end 243) extends through a pressure plate 264. A spindle bearing 250 is located at the distal end 243 of the spindle 242. The spindle bearing 250 is disposed to abut a second end of the cartridge piston 218. The driver 230 extends about the spindle 242.

The clutch 226 is disposed about the driver 230, between the driver 230 and the number sleeve 210. The clutch 226 is located adjacent the second end of the driver 230. The number sleeve 210 has a tubular body 224 and is provided outside of the clutch 226 and radially inward of the housing 240. The main housing 204 is provided with a window 214 through which a part of an outer surface 211 of the number sleeve 224/210 may be viewed.

Returning to Figures 14-15, a dose dial grip 212 is disposed about an outer surface of the second end of the number sleeve 210. An outer diameter of the dose dial grip 212 preferably corresponds to the outer diameter of the housing 240. The dose dial grip

212 is secured to the number sleeve 210 to prevent relative movement between these two components. In one preferred arrangement, the dose dial grip 212 and button 205 comprise a one piece component that is rotationally coupled to a clutch and drive sleeve and axially coupled to the number sleeve 210. However, alternative coupling arrangements may also be used.

As illustrated in Figures 16-18, in this arrangement, driver 230 comprises a first driver portion 244 and a second driver portion 246 and these portions extend about the spindle 242. Both the first and the second driver portions 244, 246 are generally cylindrical. As can be seen from Figure 19, the first driver portion 244 is provided at a first end with a first radially extending flange 256. A second radially extending flange 258 is provided spaced a distance along the first driver portion 244 from the first flange 256. An intermediate helical groove 262 is provided on an outer part of the first driver portion 244 extending between the first flange 256 and the second flange 258. A portion or a part helical groove 268 extends along an internal surface of the first driver portion 244. One of the overlapping grooves 219, 221 of the spindle 242 is adapted to work within this part helical groove 268.

A dose limiter 238 (illustrated in Figure 16) is located between the driver 230 and the housing 240, disposed between the first flange 256 and the second flange 258. In the illustrated arrangement, the dose limiter 238 comprises a nut. The dose limiter 238 has an internal helical groove matching the helical groove 262 of the driver 230. In one preferred arrangement, the outer surface of the dose limiter 238 and an internal surface of the housing 240 are keyed together by way of splines. This prevents relative rotation between the dose limiter 238 and the housing 240 while allowing relative longitudinal movement between these two components.

Referring back to Figures 15-18, essentially, in normal use, the operation of the dose setting mechanism 204 occurs as follows. To dial a dose in the arrangement illustrated in Figures 14-18, a user rotates the dose dial grip 212. The driver 230, the clutch 226 and the number sleeve 210 rotate along with the dose dial grip 212.

The number sleeve 210/224 extends in a proximal direction away from the housing 240. In this manner, the driver 230 essentially climbs one of the grooves 219, 221 provided along the surface of the spindle 242. At the limit of travel, a radial stop on the number sleeve 210 engages either a first stop or a second stop provided on the housing 240 to prevent further movement. Rotation of the spindle 242 is prevented due to the opposing directions of the overhauled and driven threads on the spindle 242. The dose limiter 238, which in this arrangement is keyed to the housing 240, is advanced along the thread 262 by the rotation of the driver 230. Other dose limiter 238 configurations may also be used.

Figure 15 illustrates a preferred arrangement of Applicants' medical delivery device after a desired dose has been dialed. In this illustration, a desired dose of 79 International Units ("IU") has been dialed. When this desired dose has been dialed, the user may then dispense the desired dose of 79 IU by depressing the dial grip 212. As the user depresses the dial grip 212, this displaces the clutch 226 axially with respect to the number sleeve 210, causing the clutch 226 to disengage from the number sleeve 210. However the clutch 226 remains keyed in rotation to the driver 230. The number sleeve 210 is now free to rotate.

In this illustrated arrangement, the driver 230 is prevented from rotating with respect to the main housing 204. However, the driver 230 is free to move axially with respect to the main housing 204. The longitudinal axial movement of the driver 230 causes the spindle 242 to rotate and thereby to advance the piston 218 in the cartridge 220 in the distal direction.

In normal use, the first and second portions 244, 246 of the driver 230 are coupled together when the dose dial sleeve 210 is rotated. That is, in normal use, the first and second portions 244, 246 of the driver 230 are coupled together with the dose dial sleeve 210 when a user sets a dose by turning the dose dial grip 212. After each dispensed dose, the spindle 242 is pushed in a distal direction, acting on the bung 218 of the cartridge 220 to continue to expel a dialed dose of medication out of an attached needle assembly releasably connected to the distal end 208 of the cartridge holder 206.

After a user uses the drug delivery device 201 to dispense all of the medication contained in the cartridge 220, the user may wish to replace the empty cartridge in the cartridge holder 206 with a new cartridge. The user must then also reset the dose setting mechanism 204: for example, the user must then retract or push the spindle 242 back into the dose setting mechanism 204.

If the user decides to replace an empty cartridge and reset the device 201, the first and second driver portions 244, 246 must be de-coupled from one another. After decoupling the first driver portion 244 from the second driver portion 246, the first driver portion 244 will be free to rotate while the second driver portion 246 will not be free to rotate.

During a device resetting step, rotating the first driver portion 244 achieves at least two results. First, rotation of the first driver portion 244 will reset the axial position of the spindle 242 with respect to the dose setting mechanism 204 since rotation of the first driver portion 244 causes the spindle 242 to rotate. Rotation of the spindle 242 (because the spindle is threadedly engaged with a nut 266) causes it to move in a proximal direction back into the dose setting mechanism. In addition, Figure 20 illustrates an arrangement for connecting the spindle 242 to a spindle guide 248. In Figure 20, the spindle 242 comprises a first spline 251 and a second spline 252 defining first and second groove 219 and 212, respectively. The spindle guide 248 comprises an essentially circular member having an aperture. The aperture includes two inner protruding members 255, 257 that engage the first and second splines 251, 252 respectively, so that the spindle guide 248 locks onto the spindle and rotates along with the spindle during spindle rotation.

Rotation of the first driver portion 244 will also axial move or reset a dose limiter 238 to an initial or start position. That is, as the first driver portion 244 is rotated back to an initial start position, because the dose limiter 238 is threadedly engaged to the outer groove and splined to an inner surface of a housing portion, such as the outer housing 240. In this configuration, the dose limiter 238 is prevented from rotating but will move

along the outer groove 262 of the first driver portion 244 as this portion is rotated during a resetting step.

Referring to a first driver arrangement illustrated in Figure 16, the two portions of the driver 230 are decoupled when the first driver portion 244 is pulled axially away from the second driver portion 246. This may be achieved by the use of a biasing means (such as at least one spring) that interacts together when the cartridge holder 206 is removed from the front or distal end of the device to first lock the relative rotation between the spindle 242 and a spindle guide 248 through which the spindle passes, and then to push this spindle guide 248 and also nut 266 axially a fixed distance. Because the spindle 242 is rotationally locked to this spindle guide 248 and is threadedly engaged with the spindle nut 266, the spindle 242 will move axially.

The spindle 242 may be coupled via a groove engaged to the first driver portion 244. The first driver portion 244 is prevented from rotation by a clutched connection to the second driver portion 246. In one preferred arrangement, the second driver portion 246 is prevented from rotation by a clicker detent 75 (cf. Figure 1). The clicker detent 75 may reside between the clutch and the flange 280 on the second driver portion 246. Therefore, axial movement of the spindle 242 decouples the two driver portions 244, 246 so that the clutched connection becomes de-coupled.

This sequence of operation as the cartridge holder 206 is removed or disconnected from the dose setting mechanism 204 is illustrated in Figures 16-18. In Figure 16, the various component parts of the drug delivery device include: the dose setting housing 240, the cartridge 220, the spindle 242, the first driver portion 244, the second driver portion 246, the spindle bearing 250, the spindle guide 248, a spring plate 254, a main spring 260, the pressure plate 264, the cartridge holder 206, the spindle nut 266 and a second spring 270. In this preferred arrangement, the spindle guide 248 is rotationally fixed relative to the spindle 242. In addition, the spring plate 254, pressure plate 264 and spindle nut 266 are rotationally fixed relative to the outer housing.

In Figure 16, the cartridge holder 206 is fitted via apertures in the pressure plate 264 and applies a load to the spring plate 254. This compresses the first biasing means or main spring 260. These apertures in the pressure plate 264 (not shown) allow the pressure plate 264 to move away from the spring plate 254 (in a distal direction towards the cartridge holder 206) under the action of the second biasing means or second spring 270. This will open up a Gap "a" as shown in Figure 16. Gap "a" is a gap created between the pressure plate 264 and the spring plate 254. This will also open Gap "b", a gap between the spindle nut 266 and the spring plate 254. This Gap b is illustrated in Figure 16. The Gap b in conjunction with the light force from the second spring or biasing means 270 moves the spindle nut 266 towards the distal end of the drug delivery device 201. This applies light pressure to the spindle guide 248.

The spindle guide 248 is compressed under the action of the second spring 270 between the spindle nut 266 and pressure plate 264. This light force coupled with the friction coefficient on either side of a flange of the spindle guide 248 through which this force acts, provides a resistance to rotation of the spindle guide 248 and therefore a resistance to rotation of spindle 242 as well. One advantage of this configuration is that at the end of a dose, it is advantageous to prevent the spindle 242 from back-winding into the dose setting mechanism 204 under light residual loads that may remain from the cartridge bung 218. By preventing the spindle 242 from back-winding in a proximal direction, a distal end 243 of the spindle 242 (and hence the spindle bearing 250) remains on the bung 218. Maintaining the distal end 243 of the spindle 242 on the bung 218 helps to prevent a user from administrating a potential under-dose.

When the user delivers a dose, as the dispense force increases, the rearward load on the spindle nut 266 increases to a point at which the spindle nut 266 travels back in a proximal direction and compresses the second spring 270. This releases the axial force acting on the spindle guide 248. This removes the resistance to rotation of the spindle guide 248 and hence spindle 242. This configuration therefore prevents back-winding of the spindle 242 under low loads caused by the cartridge bung 218 but does

not add to the dispense force once this dispense force has increased above a certain threshold level.

Figure 17 illustrates the dose setting mechanism 204 of Figure 16 with the cartridge holder 206 rotated to release a connection type between the housing 240 of dose setting mechanism 204 and the cartridge holder 206. In one arrangement, this connection type 222 is a bayonet type connection. However, those of ordinary skill in the art will recognize that other connection types 222 may be used as well such as threads, snap locks, snap fits, luer locks and other similar connection types. In the arrangement illustrated in Figures 16 - 18, by rotating the cartridge holder 206 with respect to housing 240, features that were initially acting on the spring plate 254 to compress the main biasing means 260 through apertures in the pressure plate 264, rotate so that they now release this force created by the main biasing means 260. This allows the spring plate 254 to move in a distal direction until the spring plate 254 contacts the spindle nut 266 on an inside face of the spindle nut 266.

In this second condition, the previous discussed Gap "a" (from Figure 16) has now been reduced to a Gap "c" (as seen in Figure 17). In this manner, the relative high axial force from the main biasing means 260 acts through the spring plate 254 to the spindle nut 266 and from the spindle nut 266 through the spindle guide 248 to the pressure plate 264. This relative high axial force from the main biasing means 260 is sufficient to prevent the spindle guide 248, and hence spindle 242, from rotating.

After sufficient rotation of the cartridge holder 206, the cartridge holder 206 disengages from the connection type 222 with the housing 240. The cartridge holder 206 is then driven in an axial direction away from the housing 240 by the main biasing means 260 (i.e., in a distal direction). However, during this movement, the main spring 260 continues to load the cartridge holder 206 through the spindle guide 248 and therefore the spindle 242 is prevented from rotation. As the spindle 242 is also threaded to the first driver portion 244, the first driver portion 244 is also pulled axially in a distal direction and in this manner becomes disengaged from the second driver portion 246. The second driver portion 246 is axially fixed and is prevented from rotation. In one

arrangement, the second driver portion 246 is prevented from rotation by clicker elements and prevented from axial movement by its axial coupling to the number sleeve.

Figure 18 illustrates the dose setting mechanism illustrated in Figure 16 in a third position, that is, with the cartridge holder 206 removed. As the cartridge holder 206 is removed from the housing 240, the bayonet features shown in Figure 18, (illustrated as round pegs extending radially inwards on inside of inner housing) limit travel of the pressure plate 264 but allows Gap "c" (as shown in Figure 17) to increase to a wider Gap "d" (as shown in Figure 18). As a result, Gap "e" develops. Gap "e" removes the high spring force created by the main biasing means 260 from the spindle guide 248. The dose setting mechanism 204 in Figure 17 is now ready to be reset.

To reset this dose setting mechanism 204, a user retracts the spindle 242 in a proximal direction back into the housing 240 by pushing on the distal end 243 of the spindle 242. Therefore, during this re-setting step of the dose setting mechanism 204, as the spindle 242 is pushed back into the dose setting mechanism 204, the movement of the spindle 242 causes the spindle nut 266 to move back against a light spring force created by the second biasing means 270. This movement releases the axial load and hence resistance to rotation from the spindle guide 248. Therefore, as the dose setting mechanism 204 is reset by the spindle 242 rotating back into the dose setting mechanism 204, the spindle guide 248 also rotates.

As the spindle 242 is pushed back further into the dose setting mechanism 204, the spindle 242 rotates through the spindle nut 266 by way of one of the helical grooves provided along the surface of the spindle 242. As the first driver portion 244 is de-coupled from the second driver portion 246, the first driver portion 244 rotates (with the flexible elements 302, 303 running on a conical surface groove 290 formed by the first annular ring 291 on the second half of the drive sleeve 246, Figures 16 and 17). This accommodates the axial and rotational movement of the spindle 242.

As the first driver portion 244 rotates during reset, first driver portion 244 also re-sets the dose nut. More specifically, as the first driver portion 244 rotates, the dose nut which is not rotatable since it is splined to an inner surface of the housing 240, traverses along the helical groove 262 provided along an outer surface of the first driver portion 244 and traverses back to an initial or starting position. In one preferred arrangement, this starting position of the dose nut resides along the first radial 256 flange of the first driver portion 244.

After the dose setting mechanism 204 has been reset, the dose setting mechanism 204 must be re-connected to the cartridge holder 206. When re-connecting these two components, the process generally works in reverse. However, this time the axial compression of the main spring 260 causes the first driver portion 244 to re-engage with the second driver portion 246. In this manner, the flexible elements re-engage with the second annular ring 294 on the second driver portion 246.

Figure 19 illustrates a first arrangement of the second driver portion 246 and the first driver portion 244 illustrated in Figures 16. As shown in Figure 19, second driver portion 246 is generally tubular in shape and comprises a first annular groove 290 at a distal end of the second driver portion 246. The first annular groove 290 comprises a conical face 291. The second driver portion further comprises a second annular groove 294 and at least one spline 296 positioned along a surface of the second driver portion.

The first driver portion 244 is also generally tubular in shape and comprises a first and a second flexible element 302, 303 and a plurality of spline recesses 300. The plurality of recesses 300 releasably connect the longitudinal spline 296 of the first driver portion 244 to second driver portion 246 when both first and second driver portions 244, 246 are pushed axially together so that they releasably engage one another. When pushed together, the flexible elements 302, 303 of the first driver portion 244 are pushed over the first annular groove 290 of the second driver portion 246 and then stop when the flange 280 of the second driver portion abuts the first axial flange 256 of the first driver portion 244.

The first driver portion 244 also includes a plurality of ratchet features 304. These ratchet features 304 are provided at a distal end 306 of the first driver portion 244. These ratchet features 304 engage similar ratchet features on the spring plate 254 which are splined to the housing 240. (See e.g., Figures 16 - 18) At the end of the re-setting step, these ratchet features engage one another so as to prevent the first driver portion 244 from rotating, thereby ensuring that as the spindle 242 is reset further, the first drive portion moves axially to re-engage the second drive portion 246 rather than rotate on the conical face 290. These features also orientate the spring plate 254 relative to the second driver portion 244 so that the two driver portions 244, 246 engage easily during assembly or after reset. Therefore, these ratchet features also prevent the coupling features 300, 296 from clashing with one another.

As mentioned above, the first driver portion 244 also includes a helical member 268. This helical member, preferably a partial helical member comprises less than one turn of a helix, engages a helical groove 219, 221 provided along the spindle 242. By way of this engagement, during a dose setting step, the driver portion 244 can be rotated while the spindle does not rotate during this step.

A second arrangement of resettable dose setting mechanism is illustrated in Figures 21-23. Figure 21 illustrates a section view of a second arrangement of a dose setting mechanism 400. Those of skill in the art will recognize that dose setting mechanism 400 may include a connection mechanism for releasably connecting to a cartridge holder, like the cartridge holder 206 illustrated in Figure 15. Figure 22 illustrates a portion of the dose setting mechanism illustrating the driver operation. Figure 23 illustrates a close up view of the coupling between the first driver portion and the second driver portion illustrated in Figure 22. The second arrangement of the dose setting mechanism 400 operates in a similar fashion to the first arrangement of the dose setting mechanism 204 illustrated in Figures 14-15.

With reference to Figures 21 - 23, the dose setting mechanism 400 comprises a dose dial grip 402, a spring 401, a housing 404, a clutch 405, a number sleeve 406, and an

inner housing 408. Similar to the driver 230 illustrated in Figures 15 - 18, driver 409 of dose setting mechanism comprises a first driver portion 407 and a second driver portion 412. In one arrangement, the first driver portion 407 comprises a first component part 410 and a second component part 411. Alternatively, the first driver portion 407 is an integral component part.

As illustrated in Figures 21 and 22, the driver 409 is de-coupled from the dose setting mechanism 400 when the first driver portion 407 is pushed axially towards the second driver portion 412 (i.e., pushed in a proximal direction). In one arrangement, this may be achieved by pushing axially on a distal end of the spindle 414. This does not require any mechanism associated with removal of a cartridge holder. The mechanism is also designed such that the first and second driver portions 407, 412 and the spindle 414 remain locked together rotationally during dose setting as well as during dose administration.

An axial force on the spindle 414 causes the spindle 414 to rotate due to its threaded connection to the inner housing 408. This rotation and axial movement of the spindle 414 in turn causes the first driver portion 407 to move axially towards the second driver portion 412. This will eventually de-couple the coupling elements 450 between the first driver portion 407 and second driver portion 412. This can be seen from Figures 23 and 24.

This axial movement of the first driver portion 407 towards the second driver portion 412 results in certain advantages. For example, one advantage is that the metal spring 401 will compress and will therefore close the Gap a illustrated in Figures 21 - 23. This in turn prevents the clutch 405 from disengaging from a clicker 420 or from the number sleeve 406. The second driver 412 is prevented from rotation since it is splined to the clutch 405. The clicker 420 is splined to the housing 404 or to the inner housing 408. Therefore, when the Gap a is reduced or closed up, the second driver portion 412 cannot rotate relative to either the housing 404 or the number sleeve 406. As a consequence, the number sleeve 406 cannot rotate relative to the housing 404. If the number sleeve 406 is prevented from rotating then, as the spindle 414 is retracted

back into the dose setting mechanism 400 and thereby re-set, there will be no risk of the number sleeve 406 being pushed out of the proximal side of the dose setting mechanism 400 as a result of a force being applied on the spindle 414.

Similarly, when the drug delivery device is being dispensed, the user applies an axial load to a dose button 416. The dose button 416 is axially coupled to the clutch 405 and this prevents relative axial movement. Therefore, the clutch 405 moves axially towards the cartridge end or the distal end of the dose setting mechanism 400. This movement disengages the clutch 405 from the number sleeve 406, allowing for relative rotation while closing up the Gap a.

As described above, this prevents the clutch 405 from rotating relative to the clicker 420 and hence relative to the housing 404. However, in this scenario, it also prevents the coupling between the first driver portion 407 and the second driver portion 412 from becoming disengaged. Therefore, any axial load on the spindle 414 only disengages the first and second driver portions 407, 412 when the dose button 416 is not axially loaded. This therefore does not happen during dispense.

With the dose setting mechanism 400, as a user dials a dose with the dose dial grip 402, the metal spring 401 is selected to be strong enough to maintain engagement of both clutched couplings: the clutched coupling between the clutch 405 and the number sleeve 406 and clutched coupling between the first driver portion 407 and second driver portion 412.

Figure 24 shows in detail a first arrangement of the first driver portion 407 and the second driver portion 412 illustrated in Figure 21. As illustrated in Figure 24, the second driver portion 412 is generally tubular in shape and comprises at least one drive dog 450 located at a distal end of the second driver portion 412. The first driver portion 407 also has a generally tubular shape and comprises a plurality of recesses 452 sized to engage with the drive dog 450 on the second driver portion 412. The construction of the drive dog and recesses allow disengagement with the drive dog 450 when the first and second driver portions are axially pushed together. This

construction also creates a rotational coupling when these components are sprung apart. A dose limiter 418 is provided on first driver portion 407 and operates similarly to the dose limiter 128 illustrated in Figure 3.

In this arrangement, the first driver portion 407 comprises a first portion (first component part) 411 that is permanently clipped to a second portion (second component part) 410. In this arrangement, the first component part 411 comprises the drive dogs 452 and the second component part 410 includes the outer groove for the last dose 418 nut as well as an internal groove 454. This internal groove 454 is used to connect to the spindle 414 and drives the spindle 414 during dose administration.

In the illustrated arrangement, the internal groove 454 comprises a part helical groove rather than a complete helical groove. One advantage of this arrangement is that it is generally easier to manufacture.

As may be seen from the arrangement illustrated in Figures 21-22 there is, in addition, certain feature enhancements over the dose setting mechanism 204 lustrated in Figures 16-18. These can be added independently of the ability to re-set the device to replace an empty cartridge with a new cartridge. These enhancements, therefore, are relevant to both a re-settable and non-re-settable dose setting mechanism.

One of the advantages of both arrangements illustrated but perhaps in particular in the arrangement illustrated in Figures 21-22 is that the dose setting mechanism 400 has a reduced number of components over other known dose setting mechanisms. In addition, apart from the metal coil spring 401, all of these components making up the dose setting mechanism 400 may be injection molded using inexpensive and unsophisticated tooling. As just one example, these components making up the dose setting mechanism 400 may be injection molded without the expense and sophistication of a rotating core.

Another advantage of a dose setting mechanism 400 comprising an inner housing 408 is that the dose setting mechanism 400 can be designed, with a slight modification, as

a drug delivery device platform that is now capable of supporting both re-settable and non-resettable drug delivery devices. As just one example, to modify the re-settable dose setting mechanism 400 variant illustrated in Figures 21-22 into a non-resettable drug delivery device, the first driver portion 411 and 410 and the second driver portion 412 can be molded as one unitary part. This reduces the total number of drug delivery device components by two. Otherwise, the drug delivery device illustrated in Figures 21-22 could remain unchanged. In such a disposable device, the cartridge holder would be fixed to the housing or alternatively made as a single one piece body and cartridge holder.

The illustration in Figures 21-22 shows an inner housing 408 having a length "L" 430 generally similar in overall length to the dose setting mechanism 400. As will be described, providing the inner housing 408 with a length of "L" 430 has a number of advantages over other known dose setting mechanisms that do not utilize an inner body or an inner body having a length generally equal to that of the length of a dose setting mechanism.

The inner housing 408 comprises a groove 432 provided along an external surface 434 of the inner housing. A groove guide 436 provided on an inner surface 438 of the number sleeve 406 is rotatably engaged with this groove 432.

One advantage of this dose setting mechanism 400 utilizing the inner housing 408 is that the inner housing 408 can be made from an engineering plastic that minimizes friction relative to the number sleeve 406 groove guide 436 and the groove 432. For example, one such an engineering plastic could comprise Acetal. However, those of ordinary skill in the art will recognize that other comparable engineering plastics having a low coefficient of friction could also be used. Using such an engineering plastic enables the material for the outer housing 404 to be chosen for aesthetic or tactile reasons with no friction related requirements since the outer housing 404 does not engage any moving components during normal operation.

The inner housing 408 also enables the number sleeve 406 to be provided with a helical groove on an inner surface 438 of the number sleeve 406, rather than providing such a helical groove on an external surface 440 of the number sleeve 406. Providing such an internal groove results in a number of advantages. For example, this results in the advantage of providing more surface area along the outer surface 440 of number sleeve 406 so as to provide the scale arrangement 442. More number sleeve surface area may be used for drug or device identification purposes. Another advantage of providing the helical groove 436 on the inner surface 438 of the drive sleeve 406 is that this inner groove 436 is now protected from dirt ingress. In other words, it is more difficult for dirt to become logged in this inner groove interface than if the groove were provided along the outer surface 440 of the number sleeve 406. This feature is particularly important for a re-settable drug delivery device which will have to function over a much longer period of time compared to a non-resettable device.

The effective driving diameter (represented by 'D') of the grooved interface between the number sleeve 406 and the inner housing 408 is reduced compared to certain known drug delivery devices for the same outer body diameter. This improves efficiency and enables the drug delivery device to function with a lower pitch (represented by 'P') for this groove and groove guide connection. In other words, as the helix angle of the thread determines whether when pushed axially, the number sleeve will rotate or lock to the inner body wherein this helix angle is proportional to the ratio of P/D.

The number sleeve 406 can be made the length of the mechanism "L" 430 rather than having to split this length into the space required for the number sleeve 406 and a space required for a clicker and a dose limiter. One advantage of this configuration is that it ensures a good axial engagement between the number sleeve 406 and the outer housing 404. This improves the functionality (and perceived quality) of the dose setting mechanism when a user uses the drug delivery device to dial out a maximum settable dose. Figure 26 illustrates the dose setting mechanism 400 dialed out to a maximum settable dose of 80 International Units ("IU").

Another advantage is that it enables the scale arrangement 442 to be hidden within the outer housing 404 even when the number sleeve 406 is fully dialed out as may be seen from Figure 26. However, the design does not limit the position of the window 444 but allows this window 444 to be positioned at near the dose dial grip 402 of the device. However, in arrangements illustrated in Figure 25 and 26, the scale arrangement 442 will only be visible by way of the window 444.

In addition, the driver 409 (whether made in two portions or just one unitary component) can be made with a plain internal through hole plus a thread form that can be molded with axially moving core pins. This avoids the disadvantage of a driver having an internal thread with more than one turn and therefore requires a core pin to be rotated out several turns during a de-molding process.

One potential disadvantage of utilizing a dose setting mechanism comprising the inner housing 408 is that the use of the inner housing 408 adds a component part to the overall dose setting mechanism 400. Consequently, this inner housing 408 will tend to increase the overall wall thickness that must be designed to fit between the clutch 405 and number sleeve 406. One way to work around this design issue, is to reduce the diameter of the clutch 405. This in turn can be achieved because the thread form between the driver 409 and the spindle 414 comprises a male internal feature 454 on the driver 409 and a female external groove form on the spindle 414 that is overlapping with (on a similar diameter with) the spindle groove form that interfaces with the groove along the inner surface of the inner housing 408 or body portion 516.

The overlapping of groove forms on the spindle 414 reduces the effective diameter of the thread interface with the driver 409. This also reduces the potential outer diameter of the driver 409 enabling the addition of the inner housing 408 without increasing the overall outer diameter of the dose setting mechanism 400. Another added benefit of the reduced effective diameter of the thread interface with the driver 409 is that it improves efficiency of the drug delivery device during dispense as explained above.

The window 444 through which the scale arrangement 442 may be viewed can either be just an aperture in the outer housing 404 or can include a clear lens or window designed to magnify the scale arrangement (i.e., printed or laser marked dose numbers) along a portion of the outer surface 440 on the number sleeve 406.

The connection of a cartridge holder into the outer housing 404 can be achieved using either a screw or bayonet type connection. Alternatively, any similarly robust design used in drug delivery devices requiring a largely cylindrical part to be removed and then reattached could also be used.

As described above, the first arrangement of the drug delivery device illustrated in Figures 16-20 and the second arrangement of the drug delivery device illustrated in Figures 21-24 comprise a spindle having two helical grooves. Specifically, this spindle has two opposite handed overlapping groove forms that preferably extend over at least a majority of a length of the spindle. Each groove form is effectively continuous over a number of turns. In one preferred arrangement, each groove of the spindle engages either a non-continuous helical groove form on a body portion or a driver. Preferably, either or both a non-continuous thread form on a body and a driver consists of less than one complete turn of thread.

The spindle and driver configuration of these preferred arrangements can be used in a drug delivery device, such as an injection pen type device. With certain injection pen type devices, robust tool design is one very important issue to reducing the overall manufacturing costs, and also providing for good dose accuracy. As such, the spindle and driver design of Applicants application may also be used in various types of drug delivery devices, such as reusable or disposable pen type injection devices.

The lead of both groove forms on the spindle assist to control the accuracy of the dose dispensed. This is in contrast to certain prior art devices where the dose accuracy is dependent on both the groove form on the spindle and the groove form on the driver.

One exemplary arrangement of Applicants' spindle and driver arrangement is illustrated in Figures 27 and 28. Figure 27 illustrates a driver 530 and a body portion 516 that may be used in a drug delivery device, such as the drug delivery device illustrated in Figures 14-26. In Figure 27, the driver 530 is illustrated as a single component. However, similar to the driver 230 illustrated in Figures 15-18, driver 530 *may alternatively comprise a first driver portion and a second driver portion.*

As illustrated in Figures 27-28, the driver 530 comprises a generally tubular member extending between a distal end 531 and a proximal end 532. The driver 530 has a first groove form 568 at the distal end. Preferably, the first groove form 568 comprises a partial male groove form that engages one of the helical grooves along the surface 560 of the spindle 542.

Also illustrated in Figure 27 is a housing insert 516. Housing insert 516 comprises a groove portion 520 that engages a helical groove provided on spindle 542.

In one exemplary arrangement of the design of a spindle and driver as illustrated in Figures 27-28, the driver 530 comprises a male groove form 568 located at a distal end 531 of the driver. This male groove form 568 resides on an internal surface 571 of the driver 530 and preferably comprises a groove form of less than one turn. This groove form engages a first groove 519 provided along a surface of the spindle 542. In a preferred arrangement, this first spindle groove 519 is effectively continuous not just for a portion of the spindle surface 560 but for a majority of the length of the spindle as illustrated. In this instance, if the driver 530 is rotated during dose setting relative to the spindle 542 (as discussed above), then the axial displacement of the spindle 542 relative to the housing during dose dispense will be dependent on the pitch of the helical grooves 519 and 521 on the spindle 542 and will not be dependent on the pitch of the male groove form 568 on the driver. This is in contrast to what occurs in *the prior art drug delivery device illustrated in Figures 1 – 13 and discussed above.*

Figure 28 illustrates the spindle 542 engaged to the driver 530 and insert 516. In one arrangement, the two pitches of the spindle are certain discrete proportions of each

other such as the same pitch 1:1 or ratios such as 2:1, 1.66:1. However, if the grooves are not overlapping as with prior art there are no limitations to the ratios of the two pitches and the spindle can equally be molded in an open and shut tool construction. In contrast to the spindle of the prior art drug delivery device illustrated in Figures 1-13 where molding of the driver 30 requires a core pin that must to be rotated out of the mold, the driver 530 illustrated in Figure 27, (because it has less than one turn of groove), can be advantageously molded using two cores, neither of which rotate during mold release. For example, during the molding process of this driver 530, these two cores can be merely moved axially during a part ejection step. Consequently, the use of two such molds can significantly reduce the cost, the maintenance, and the cycle time of the molding tool used to mold this preferred driver configuration.

The preferred design of this spindle 542 having two overlapping grooves may be embodied in several ways. As mentioned above, one key advantage of such a spindle construction is that the spindle 542 and driver 530 arrangement may be molded by way of a less complex method. Moreover, the advance of the spindle 542 in the distal direction when the driver 530 is advanced during dose administration is dependent on the magnitude of the pitch of the first and the second groove forms 519, 521 of the spindle 542. Therefore, the dose dispensed is linked only to the dimensions of the spindle and no other component. This spindle could therefore be made from a material that has a very low or consistent shrinkage to improve dose accuracy.

Additionally however as the helical groove form 568 of the driver 530 is a male form and radially protrudes inwardly as illustrated in Figure 27, rather than a female form that cuts radially outwards into a tubular body of the driver, as the prior art driver illustrated in Figures 1-12. With such a male form as illustrated in Figure 27, the outer diameter D1 570 of the driver 530 can be reduced over other prior art type devices. One advantage of reducing the outer diameter D1 570 of the driver 530 is that this reduced diameter enables the overall diameter of the drug delivery device to be more compact. One advantage of a more compact drug delivery device is that it brings the visual appearance of the drug delivery device closer to that of typical writing pens. As just one example, the outer diameter D2 of the drug delivery device 201 illustrated in

Figure 14 can be made smaller than the outer diameter D3 of the drug delivery device illustrated in Figure 1.

Furthermore, if the driver 530 engages the spindle groove 519 only at the distal end 531 of the driver (in contrast to where the driver 30 engages the spindle helix over a larger portion of the spindle as illustrated in the spindle and driver arrangement of Figures 1-13), the spindle 542 can extend in a proximal direction beyond the end of the driver 530. One benefit of such a driver and spindle arrangement is that it enables the overall length of the drug delivery device to be reduced. As just one example of this benefit is that the overall length L2 11 of the prior art drug delivery device illustrated in Figures 1-13 can be reduced to a shorter overall length of L3 120 of the drug delivery device 201 illustrated in Figure 14.

In the driver and spindle arrangement illustrated in Figures 27-28, this arrangement may be utilized in a disposable or non-resettable drug delivery device. In an alternative arrangement, the driver may be split into multiple portions (e.g., two or more) that are separated axially. In such an arrangement, a first driver portion (closest to the cartridge) would engage with the spindle helix and in engagement with a dose limiting mechanism, similar to the dose mechanism 238 illustrated in Figure 16. The short non-continuous thread form 568 on the first driver portion and continuous groove form 519 on the spindle enables a design for a drug delivery device where just this first driver portion rotates as the spindle is pushed back into the second driver portion. There is no need for the two driver portions to be concentrically disposed. Such a configuration would add to the overall outer diameter of the drug delivery device.

Another advantage of using the spindle 542 having two overlapping groove forms 519, 521 is that such an arrangement creates radial space within the drug delivery device. In one arrangement, this radial space may be used to introduce an inner body component within the drug delivery device, such as the inner body 208 illustrated in Figure 21 and as described in detail above.

However as can be seen from the spindle 542 illustrated in Figure 28 it is advantageous to have a pitch of thread interface with the driver 530 to be a specific multiple of a pitch of a groove form 520 with the spindle 542. One reason for this is that it can ensure that both groove forms 519, 521 cross over one another at certain defined angular planes that are rotated around the axis of the spindle 542.

As just one example, in the case of the spindle illustrated in Figure 28, the pitch of the driver 530 to spindle groove form 519 is equal to that of the spindle groove 521 to housing portion 516 groove form. One advantage of this configuration is that it ensures that with two equally spaced starts for each groove form, the groove forms cross over one another every 90°. With the typical groove pitches used, this enables the spindle 542 to be molded with a two slide open and shut tool construction. Of course other ratios may also be used. However, as one of skill in the art will recognize, there are a certain limited number of range of ratios that will enable the spindle to be molded easily with injection mould tooling. Alternatively if the ratio is 2:1, the grooves cross over every 60° and with carefully designed thread forms this ratio can still be molded with an open and shut mold tool construction.

In one of Applicants preferred drug delivery device spindle and driver arrangements, the ratio of these two spindle groove form pitches define a certain mechanical advantage of the drug delivery device. In one arrangement, this mechanical advantage may be defined by the formula (A+B)/A. In this formula, A may define the groove pitch between the spindle 519 and housing portion 516 and B may define the groove pitch between the spindle helical groove 521 and the driver groove portion 568. As such, the mechanical advantage in turn defines a maximum dial out distance for a given maximum dose value. As just one example, a mechanical advantage of three to one ("3:1") and a maximum dose of 80 International Units ("IU") would result in a dial out distance of 33,12 millimeters (mm) for a nominal cartridge internal diameter of 9,6 mm.

This dial out distance can affect an overall length of a drug delivery device. In particular, significantly affects the length of the drug delivery device if the numbers on

the number sleeve are to remain hidden inside the housing when the maximum dose is dialed as illustrated in Figures 25-26.

Figure 29 shows in a close up view a spindle 642 according to the present invention that may be used with a dose setting mechanism as described above. The spindle 642 has a first helical groove 619 and a second helical groove 621 provided along the outer surface of the shaft. The first helical groove 619 is a drive sleeve form groove and the second helical groove 621 is a body (housing) form groove. As indicated by reference numeral 622 cuts are provided in the outer shape of the spindle to give open and/or shut a (molding) tool for manufacturing said spindle 642.

Exemplary embodiments of the present invention have been described. Those skilled in the art will understand, however, that changes and modifications may be made to these embodiments without departing from the true scope and spirit of the present invention, which is defined by the claims.

Claims

1. A spindle for driving a bung of a cartridge, said spindle comprising:
a generally circular shaft having an outer surface, said generally circular shaft extending from a distal end to a proximal end of said circular shaft;
a first helical groove provided along a first portion of said outer surface of said generally circular shaft, said first helical groove having a first pitch; and
a second helical groove provided along a second portion of said outer surface of said generally circular shaft, said second helical groove overlapping said first helical groove, said second helical groove having a second pitch.

2. The spindle of claim 1 wherein said first helical groove comprises said first pitch of a first hand; and
said second helical groove comprising said second pitch of an opposite hand to said first hand of said first helical groove.

3. The spindle of claims 1 or 2 wherein said first pitch of said first helical groove is equivalent to said second pitch of said second helical groove.

4. The spindle of any of claims 1 to 3 wherein said second helical groove provided along said second portion of said outer surface of said generally circular shaft overlaps substantially all of said first helical groove.

5. The spindle of any of claims 1 to 4 wherein said first helical groove and/or said second helical groove comprises a helical female groove.

6. The spindle of any of claims 1 to 5 wherein said first helical groove and/or said second helical groove extends along said outer surface of said generally circular shaft from about said distal end of said spindle to about said proximal end of said spindle.

7. The spindle of any of claims 1 to 6 wherein said first pitch of said first helical groove provided along said first portion of said outer surface has a first diameter and said second pitch of said second helical groove provided along said second portion of said outer surface has a second diameter,
wherein said first diameter is generally equally to said second diameter.

8. A dose setting mechanism for use with a drug delivery device comprising a spindle according to any of claims 1 to 7 and further comprising a driver for driving said spindle, with said driver comprising a helical groove form that engages said first helical groove of said spindle.

9. A dose setting mechanism for use with a drug delivery device comprising a spindle according to any of claims 1 to 7 and further comprising a drug delivery body with a helical groove form that engages said second helical groove of said spindle.

10. The dose setting mechanism of claims 8 or 9 wherein said helical groove on said driver and/or on said drug delivery body comprises a partial groove form, preferably a helical groove of less than one turn.

11. The dose setting mechanism of any of claims 8 to 10 wherein said helical groove on said driver and/or on said drug delivery body comprises a male helical groove.

12. The dose setting mechanism of any of claims 9 to 11 wherein said helical groove form on said drug delivery device body comprises an inner body and/or an outer body.

13. A dose setting mechanism for use with a drug delivery device, preferably according to any of claims 8 to 12, said mechanism comprising:
a housing;
a rotating sleeve in rotatable engagement with respect to said housing;
a driver releasably coupled to said rotating sleeve; and
a spindle having two overlapping helical grooves, said spindle operatively coupled to said driver, such that when a user sets a dose by rotating said rotating sleeve, said driver also rotates.

14. The dose setting mechanism of claim 13 where said dose setting mechanism comprises a resettable dose setting mechanism, wherein said driver comprises a first component and a second component, said first and said second component being operatively coupled together so that they rotate together when said user sets said dose.

15. The dose setting mechanism of claim 13 wherein said dose setting mechanism comprises a non-resettable dose setting mechanism.