AXIALLY ADJUSTABLE CONNECTION OF PISTON ROD TO PISTON FOR DRIVE MECHANISM OF A DRUG DELIVERY DEVICE

Description

Field of the Invention

This invention relates to a drive mechanism for a drug delivery device that allows a user to select single or multiple doses of an injectable medicinal product and to dispense the set dosage of the product and to apply said product to a patient, preferably by injection. In particular, the present invention relates to such devices, which are handled by the patients themselves.

Background and Prior Art

Drug delivery devices allowing for multiple dosing of a required dosage of a liquid medicinal product, such as liquid drugs, and further providing administration of the liquid to a patient, are as such well-known in the art. Generally, such devices have substantially the same purpose as that of an ordinary syringe.

Drug delivery devices of this kind have to meet a number of user specific requirements. For instance in case of those with diabetes, many users will be physically infirm and may also have impaired vision. Therefore, these devices need to be robust in construction, yet easy to use, both in terms of the manipulation of the parts and understanding by a user of its operation. Further, the dose setting must be easy and unambiguous and where the device is to be disposable rather than reducible, the device should be inexpensive to manufacture and easy to dispose. In order to meet these requirements, the number of parts and steps required to assemble the device and an overall number of material types the device is made from have to be kept to a minimum.

Typically, the medicinal product to be administered is provided in a cartridge that has a moveable piston or bung mechanically interacting with a piston rod of a

drive mechanism of the drug delivery device. By applying thrust to the piston in distal direction, a certain amount of the medicinal fluid is expelled from the cartridge.

Due to inevitable manufacturing tolerances there may for instance persist axial clearance between a cartridge's piston and the piston rod. Typically, prior to a primary use of the device, an end-user has to conduct a so-called priming of the drive mechanism in order to ensure, that already with an initial dose setting and a subsequent dose dispensing step, an accurate amount of the medicinal product is disposed in a predefined way.

Since a self-administering user might be physically infirm, it is desirable to simplify or even to eliminate the need for such a user-conductible priming procedure.

Document EP 1 911 479 A1 discloses a dose dispensing device, wherein a piston and a piston rod are electromagnetically or magnetically coupled, wherein the piston and piston rod comprise a magnetic effect generating members.

Since the generation of an electromagnetic field requires a supply of electric energy, such a solution is generally not applicable to drug delivery devices of pen-injector type.

Further, document US 6,196,999 B1 discloses a coupling mechanism, wherein a syringe plunger coupling element having the form of a rearwardly extending cylindrical extension is centrally located on a rearward face of a syringe plunger. This coupling element contains an interior T-shaped cavity, wherein the walls of said cavity are knurled to aid the grip of the coupling mechanism. The coupling mechanism is located on the forward end of a plunger drive ram proximate to the syringe plunger and is in the form of two pawls. These pawls are biased away from the plunger drive ram's axis of symmetry by means of springs. Operation of a motor advances the drive ram forwardly along its longitudinal axis to move the

pawls of the coupling mechanism toward and inter engagement with the cylindrical extension of the syringe plunger.

As the advancing pawls initially enter the cavity of plunger extension, their forward ends are forced toward one another by the walls of the cavity, overcoming the outward bias of the springs. In order to eliminate an initial clearance between plunger and drive ram, the pawls have to fully enter the cavity to grip the knurled wall of the cavity. Henceforward, the syringe plunger and drive ram will move in a cooperated motion.

These known solutions feature the common drawback, that for elimination of axial clearance between piston rod and piston, the piston rod has to be axially shifted. Axial clearance- and backslash elimination implies to bring the piston rod in direct abutment position with a cartridge's piston. Such axial displacement of the piston rod for the purpose of clearance elimination is regarded as disadvantageous, because it typically involves a respective actuation of dose setting or dose dispensing means by the user.

Object of the Invention

Embodiments of the present invention seek to provide a drive mechanism for a drug delivery device featuring improved and facilitated clearance and manufacturing tolerance elimination. An embodiment of the invention provides to redundantize a priming procedure to be conducted by the end user. The invention further focuses on improvements related to patient safety and intends to simplify the general device handling. It is a further object of the invention, to provide a drive mechanism for a drug delivery device with clearance eliminating means being inexpensive to produce and being easy to assemble. Finally, a further embodiment of the invention provides a method of eliminating clearance in a drive mechanism of a drug delivery device.

Summary of the Invention

In a first aspect, a drug delivery device for dispensing of a dose of a medicinal product, typically a medicinal fluid, such as a fluid drug is provided. The drug delivery device comprises a housing, a cartridge comprising the medicinal product, and a drive mechanism.

The drive mechanism comprises a holder for the product-containing cartridge comprising the medicinal product, wherein the cartridge has a piston being slidably arranged therein in an axial direction. The drive mechanism further comprises a piston rod to be operably engaged with the cartridge's piston for dispensing of a well-defined dose of the medicinal product. With a distal outlet, the container may be engaged with a needle, a cannula, an infusion tube or similar delivery devices in a fluid-transferring way. The cartridge itself may be designed as replaceable or disposable ampoule, carpule or syringe. Its piston is displaceable in distal direction for purging or expelling a pre-defined dose of medicinal product from the container in an accurate way.

The drive mechanism further comprises at least one adjusting member being axially displaceable or being slidably arranged in axial direction relative to the piston and/or relative to the piston rod and/or a proximal end. The adjusting member serves to eliminate axial clearance between the piston and the piston rod, that might be due to manufacturing or assembly tolerances of the drive mechanism, the drug delivery device and their various components. The adjusting member is attached to a proximal end of the piston or is pre-assembled to a distal portion of the piston rod and further comprises a receptacle to receive a distal portion of the piston rod.

The drive mechanism is further provided with an interlock means adapted to interact with the adjusting member for mutually locking in position the piston rod's distal portion in place at an arbitrary position inside the adjusting member's receptacle to establish a mechanical coupling rigid in compression of piston rod and piston, irrespective of the relative distance between piston and piston rod. In this way, interaction of adjusting member and interlock means effectively provides a clearance- or backslash-elimination, wherein the piston rod itself may remain stationary, e.g. with respect to the cartridge or with respect to a housing component of the drug delivery device.

By arranging the adjusting member axially between piston and piston rod, the adjusting member itself may provide a clearance-compensating function, e.g. by means of an axial movement relative to the piston and/or relative to the piston rod. Such axial movement of the adjusting member is predominately governed by the amount of clearance to be eliminated. As soon as the adjusting member reaches a clearance-eliminating position or configuration, it is typically immobilized by the interlock means, thus providing a rigid mechanical coupling of piston and piston rod either directly or indirectly, e.g. by means of the adjusting member.

If the piston and the corresponding piston rod are mutually locked in position by adjusting member and interlock means, any axial movement, preferably any distally directed axial movement of the piston rod is directly and unalteredly transferred to the cartridge's piston. The axial movement of the adjusting member relative to the piston and/or relative to the piston rod may be conducted during or after assembly of the drive mechanism or the corresponding drug delivery device, respectively.

In typical configurations, a relative movement of adjusting member, piston and/or piston rod only occurs during assembly of the drive mechanism or the drug delivery device. Subsequent mechanical interaction of the interlock means with the adjusting member for immobilizing the same either with the piston or with the piston rod may be conducted after the drive mechanism or after the drug delivery device have been assembled.

The interlock means and/or the adjusting member provide an at least unidirectional coupling of piston rod and piston. At least a cooperated movement of piston and piston rod in distal direction is provided. It is not generally required to have a bi-directional coupling of piston and piston rod. In particular, in configurations with a re-usable drive mechanism, adjusting member and interlock means may allow the piston rod to be moved in proximal direction while the cartridge's piston remains stationary.

In a second aspect of the invention, the interlock means is adapted to provide a retention force being substantially larger than an axially directed force required to displace or to move the adjusting member and/or the piston rod, preferably in distal direction. In particular, the retention force to be provided by the interlock means is substantially larger than the sum of static and dynamic friction forces required to axially move the piston inside the cartridge plus a force required to expel the medicinal product from the cartridge and to dispense said product in biological tissue. In effect, the interlock means and its interaction with the adjusting member has to be dimensioned in such a way, that the mutual locking in position of piston and piston rod remains unaffected during and after repeated sequences of dose setting and dose dispensing steps.

In a further preferred aspect, the adjusting member is attached to a proximal end of the piston and further comprises a receptacle to receive a distal portion of the piston rod. Alternatively, the adjusting member is attached or pre-assembled to the distal portion of the piston rod. The receptacle comprises an axial extension allowing for a relative clearance-compensating motion of piston and piston rod, in particular during assembly of the drive mechanism or the drug delivery device, respectively. Depending on the geometric variations of the various mechanical compounds of the drive mechanism, a post-assembly position of the piston rod's distal end inside the adjusting member's receptacle may vary within certain tolerable limits. The distal portion of the piston rod may be slidably and/or threadedly received in the receptacle of the adjusting member.

Irrespective of these clearance or backslash variations, the interlock means is adapted to immobilize and/or to lock in position the piston rod's distal end with the adjusting member's receptacle. In this way, a mechanical coupling rigid in compression of piston rod and piston can be established, wherein the actual axial distance between piston and piston rod may vary due to manufacturing and/or assembly tolerances.

In a further aspect, the interlock means is accordingly adapted to lock the piston rod's distal portion in place at an arbitrary position inside the adjusting member's receptacle to establish a mechanical coupling rigid in compression of piston rod and piston irrespective of a relative distance between piston and piston rod. Therefore, the interlock means may be designed as positive, frictional or adhesive lock, adapted to lock in position the adjusting member's receptacle and the piston rod irrespective of their mutual distance, as soon as piston and piston rod are axially offset within certain limits, governed by the size of the receptacle.

In a further embodiment, the adjusting member's receptacle and the distal portion of the piston rod are mutually bonded or welded, e.g. by means of an appropriate adhesive or by means of deposition of energy in a region, where receptacle and piston rod overlap in radial direction. Energy deposition for the purpose of mutually welding the adjusting member and the piston rod's distal portion can for instance be provided by electromagnetic radiation, e.g. by laser irradiation of the respective portions.

According to a further embodiment, a deformable adhesive disposed in the adjusting member's receptacle is adapted to provide a clearance-eliminating axial displacement of piston rod and adjusting member, especially during assembly and manufacture of the drive mechanism and/or the drug delivery device. The interlocking of the adjusting member and the piston rod is then achieved in a second step by curing of said adhesive. The curing of said adhesive and hence the immobilization and mutual interlocking of adjusting member and piston rod can be supported or triggered by energy deposition, e.g. by means of irradiation with electromagnetic radiation or by application of thermal energy.

Typically, in this embodiment, the receptacle is only partially filled with the plastically deformable adhesive, such that the piston rod's distal portion is at least partially insertable into said receptacle. Furthermore, it is of advantage, when the piston rod's cross-sectional area is substantially smaller than the corresponding cross-sectional area of the receptacle. Preferably, upon insertion of the piston rod's distal end into said receptacle, at least one circumferential gap between an

inner surface of the receptacle and a circumferential outer surface of the piston rod's distal portion may persist in order to receive and to absorb at least portions of the deformable adhesive purged and squeezed during insertion of the piston rod's distal portion into said receptacle.

In a further embodiment, the adjusting member is preassembled with the distal portion of the piston rod by means of the deformable non-cured adhesive. This kind of assembly might be of advantage since the adjusting member itself does not have to be mounted and attached to the piston's proximal end surface. A desired abutment configuration of adjusting member and piston is preferably reached during assembly of the drive mechanism and its various components.

Since the adhesive during assembly is not yet cured and remains deformable, it allows for a clearance-compensating or clearance-eliminating axial motion of adjusting member, piston and/or piston rod. In a typical assembly configuration, it is intended, that the piston rod with its pre- and provisionally assembled adjusting member is axially displaced during assembly of the drive mechanism at least until the adjusting member with its distal portion entirely abuts against the cartridge's piston. Thereafter, when said abutment configuration has been reached, the adhesive is to be cured, thus immobilizing and rigidly connecting adjusting member and piston rod.

In a further preferred embodiment, in a pre-assembly configuration, the adjusting member comprises a first adhesive component in its receptacle and the piston rod at its distal portion comprises a second adhesive component of a two-component adhesive. As soon as the two component are brought into contact, e.g. during a final assembly of the drive mechanism or the drug delivery device, a curing procedure may be triggered accordingly, which may lead to a bonded connection of adjusting member and piston rod even without supply of external energy for curing purposes. Also here, curing of said two-component adhesive might be supported and accompanied by additional deposition of energy.

Those embodiments implying a bonded connection between adjusting member's receptacle and distal portion of the piston rod are preferably applicable with disposable drive mechanisms and disposable drug delivery devices. For refillable drug delivery devices, wherein a used or empty cartridge might be replaced by a new one, the interlock means are preferably adapted to provide a releasable mutual interlocking of piston, piston rod and/or adjusting member.

In another aspect of the invention, the interlock means is adapted to radially clamp the adjusting member's receptacle and the piston rod's distal portion. In this configuration, either the receptacle is reducible with respect to its inner diameter or the piston rod's distal portion is adapted to radially expand. This radial clamping mechanism is adapted to be activated irrespective of the position of piston rod and receptacle. In typical embodiments, the receptacle comprises a hollow cylindrical shape and the distal portion of the piston rod may be of corresponding cylindric shape, respectively. The degree of clamping between piston rod and adjusting member's receptacle has to exceed the axial force required to displace the adjusting member and/or the piston in distal direction.

In a further preferred embodiment, the piston rod at its distal portion or at its distal extension comprises at least one radially moveable or radially pivotable jaw adapted to interact with the adjusting member's receptacle, in particular with the inner sidewalls of the receptacle. Furthermore, the jaw has a slanted inner surface, which is adapted to engage with a correspondingly slanted surface of an axially moveable lock rod. Additionally, the piston rod comprises a hollow shaft adapted to slidingly receive the axially moveable lock rod. Due to the corresponding bevelled surfaces of lock rod and the at least one distally arranged jaw, an axial movement of said lock rod in distal direction is at least partially transferred to a radially outwardly directed movement of the jaw, leading to the intended radial clamping of the adjusting member and the jaw and hence to a radial clamping of adjusting member and piston rod.

This embodiment is generally further adapted to provide a reversible clamping effect. By axially removing said lock rod in proximal direction, the radial clamping can be reduced or even suspended.

In a further embodiment, the interlock means comprises at least one eccentrically supported clamping member to mutually clamp the adjusting member and the piston rod. Typically, the eccentrically supported clamping member is rotatably or pivotally mounted with or in the piston rod. The clamping member itself may be rotatably or pivotally mounted to the axis of symmetry of the piston rod. In this case, the clamping member itself comprises an eccentric outer geometry. For instance, it may comprise an oval or ellipsoidal shape. Additionally or alternatively, the clamping member may comprise a radially symmetric shape but may be supported off-axis.

The eccentrically supported clamping member directly or indirectly interacts with sidewalls of the adjusting member's receptacle. In an indirect interacting embodiment, the clamping member of e.g. oval shape might be surrounded or enclosed by radially deformable jaws provided at the piston rod's distal portion. By pivoting or rotating said clamping member, a radially directed force acting on the jaws leads to a radial expansion of the piston rods distal extension, leading to the intended clamping effect.

In another aspect of the invention, the adjusting member is pre-assembled to the piston rod's distal portion. During or even after assembly of the drive mechanism or the respective drug delivery device, the adjusting member is axially displaced with respect to the piston rod until it reaches an abutment position with the piston's proximal face. When this abutment position has been reached, in which axial clearance between piston and adjusting member has been eliminated, the adjusting member is at least locked in position with respect to the piston rod. As a consequence, any subsequent distally directed displacement of the piston rod is then directly and unalteredly transferred to the pistons free of clearance.

In a further preferred embodiment, the interlock means comprises a blocking ring arranged on the outer circumference of the piston rod's distal portion. The blocking ring is adapted to radially prop against an inside wall, hence radially inwardly facing wall of the adjusting member's receptacle. The blocking ring is further adapted to impede an axial movement of piston rod and adjusting member towards each other. Hence, the blocking ring only allows a distal movement of the blocking ring relative to the piston rod or a proximal movement of the piston rod relative to the blocking ring.

The coupling of receptacle and distal portion of the piston rod by means of the blocking ring only allows for an enlargement of axial distance between the blocking ring and a proximal end section of the piston rod. Any counter-directed axial movement of blocking ring and piston rod is effectively prevented by the blocking ring. The same applies to the relative movement of the adjusting member and the blocking ring. In this way, the assembly of piston rod and adjusting member by means of the blocking ring can be interpreted as a kind of telescope-like extending arrangement, wherein the blocking ring impedes axial contraction of said assembly.

In a further embodiment, the piston rod comprises a hollow shaft being adapted for axial insertion and guiding of a lock rod. Said lock rod is adapted to activate a locked mode and/or for eliminating axial clearance between the receptacle and the cartridge's piston. By means of the lock rod, adapted to prop against a proximal end face of the adjusting member's receptacle, the adjusting member is driven and pushed in distal direction until it moves up against a proximal face of the piston.

According to another preferred embodiment, the adjusting member and the piston rod are threadedly engaged and are further rotatably biased by a spring member. In this way, the spring member serves to rotate the adjusting member relative to the piston rod, wherein due to the threaded engagement the adjusting member moves in distal direction for the purpose of clearance compensation or elimination.

In a final assembly configuration, in which axial clearance between piston and adjusting member is substantially eliminated, a distally directed forward movement of the piston rod is directly and unalteredly transferred to the piston, due to the interlocking function of the interlock means.

In a further embodiment, an interlock member is moveably arranged in radial direction at the piston rod and radially engages with a corresponding recess at an inner surface of the adjusting member. By means of the interlock member, a clearance-eliminating relative rotation between piston rod and adjusting member can be selectively released and/or interlocked. If for instance the threaded engagement of piston rod and adjusting member is of self-locking type, the interlock member may only serve to release the clearance-eliminating relative rotation of piston rod and adjusting member. As soon as the adjusting member abuts against the piston's proximal end face, the rotation will autonomously stop and due to the self-locking threaded connection of piston rod and adjusting member, a distally directed displacement of the piston rod can be unalteredly transferred to the piston.

In a further preferred embodiment, the adjusting member and the distal portion of the piston rod each comprise threaded receptacles facing towards each other. These receptacles are further threadedly engaged by means of a threaded adjustment sleeve. This adjustment sleeve is rotatably biased by the spring member relative to the piston rod or relative to the adjusting member. In this embodiment, it is important, that the threaded engagement of adjusting member, adjusting sleeve and/or piston rod is of self-locking type.

If the spring member rotatably couples the adjustment sleeve and a piston rod's distal portion, by releasing said rotational motion, in a first adjustment step, the adjustment sleeve together with the adjusting member will be is set in rotational movement relative to the piston rod, accompanied by a respective axial displacement of the adjusting member in distal direction. When an abutment configuration of adjusting member and piston has been reached, in a second

adjustment step, the adjustment sleeve may still be subject to the spring-induced rotational movement. As a consequence, the adjusting sleeve may rotate and axially shift with respect to both receptacles of piston rod and adjusting member until a predefined spring deflection is depleted.

Due to the self-locking property of the threaded engagement of adjustment sleeve and receptacles of adjusting member and piston rod, an additional axial interlock becomes superfluous. The inventive interlock means is then provided by the self-locking threaded interaction of adjusting member, adjustment sleeve and piston rod.

In another aspect, the invention provides a drug delivery device for dispensing of a dose of a medicinal product comprising a housing, a cartridge filed with the medicinal product to be dispensed, e.g. insulin, and further comprising the drive mechanism according to the present invention.

In a further aspect, the housing of the drug delivery device comprise a through opening or at least a transparent window for delivery of an adhesive or for the delivery of energy adapted for curing of adhesive disposed between the adjusting member's receptacle and the piston rod's distal portion. In case the housing comprises a transparent window, especially for the deposition of electromagnetic radiation, said window is preferably substantially transparent for the electromagnetic radiation to be used. Said radiation is intended for e.g. curing of an adhesive or for directly welding and/or interlocking of piston rod and adjusting member.

In another aspect, there is provided a method of eliminating clearance between a piston and a piston rod in a drive mechanism in accordance with any of the above-mentioned aspects.

Additionally or alternatively, the through opening of the housing may be adapted to provide access to an interlock mechanism by means of an applicable tool to be inserted into said through opening for engagement and actuation of the interlock mechanism.

In still another aspect, the invention provides a method of eliminating clearance between a piston and a piston rod in a drive mechanism of a drug delivery device. The drive mechanism typically comprises a holder to hold a medicinal product-containing cartridge that has a piston being slidably arranged therein in an axial direction. The piston rod is to be operably engaged with the cartridge's piston for dispensing of a dose of the medicinal product. Said method of eliminating clearance during or after assembly of the drive mechanism comprises the steps of axially moving of the piston rod relative to an adjusting member and/or axially moving the adjusting member relative to the piston for eliminating axial clearance between the piston and the piston rod. After this first step, piston and piston rod are mutually locked in position irrespective of their distance by an interlock means, which is adapted to interact with the adjusting member.

To summarize, the invention provides axial clearance elimination for a drug delivery device's drive mechanism, wherein production and manufacturing-related geometric tolerances of mechanical components can be eliminated and compensated on site, i.e. before the drive mechanism or the drug delivery device is distributed to end-consumers. Thanks to the clearance elimination, product and manufacture of various components of drive mechanism and drug delivery device can be kept in a low cost range in a mass production process. Inevitable manufacturing or assembly-related tolerances can be eliminated in a fast, reliable and cost-saving way. Furthermore, general handling of the device and user security can be advantageously enhanced.

The term „medicinal product ", as used herein, means 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 such as 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.

It will be apparent to those skilled in the pertinent art, that various modifications and variations can be made to the present invention without departing from the spirit and scope of the invention. Further, it is to be noted, that any reference signed used in the appended claims are not to be construed as limiting the scope of the present invention.

Brief Description of the Drawings

Without limitation, the present invention will be explained in greater detail below in connection with preferred embodiments and with reference to the drawings in which:

Fig. 1 schematically illustrates a first embodiment of the invention in cross-sectional view,

Fig. 2 shows the embodiment according to Fig. 1 in a clearance-eliminated configuration, and

Fig. 3 schematically depicts the embodiment according to Figs. 1 and 2 with interlocked piston and piston rods,

Fig. 4 in cross-sectional illustration shows another embodiment of the invention in a pre-assembly configuration,

Fig. 5 illustrates the embodiment according to Fig. 4 during interlocking of piston and piston rod by means of externally supplied energy or adhesive,

Fig. 6 schematically depicts another embodiment, wherein an adjusting member's receptacle is partially filled with an adhesive,

Fig. 6a shows the configuration of Fig. 6 in cross-section along A-A,

Fig. 7 schematically illustrates the embodiment according to Fig. 6 with adjusting member and piston rod in a clearance-eliminated configuration,

Fig. 7a shows a cross-section of Fig. 7 along A-A,

Fig. 8 depicts in cross-sectional illustration another embodiment comprising a clamping member,

Fig. 9 illustrates the clamping member according to Fig. 8 in an enlarged view in release configuration,

Fig. 10 schematically illustrates the embodiment according to Fig. 8 with the clamping member in locked position,

Fig. 11 shows the clamping member according to Fig. 10 in an enlarged view,

Fig. 12 in cross-section schematically illustrates another embodiment with the adjusting member being axially displaceable mounted on a distal portion of the piston rod,

Fig. 13 depicts the adjusting member according to Fig. 12 in an enlarged view in a pre-clearance-eliminating configuration,

Fig. 14 shows the embodiment according to Fig. 12 with the adjusting member in final assembly position,

Fig. 15 illustrates an enlarged view of the adjusting member at the end of a clearance-eliminating assembly step,

Fig 16 shows the embodiment according to Fig. 12 and 14 with removed lock rod and

Fig. 17 reflects the corresponding enlarged view of the adjusting member,

Fig. 18 in a perspective illustration shows the blocking ring, and

Fig. 19 illustrates another perspective illustration of the blocking ring,

Fig. 20 in cross-sectional illustration depicts another clearance-eliminating embodiment, wherein the adjusting member is threadedly engaged with the piston rod,

Fig. 21 depicts the embodiment according to Fig. 20 after releasing a rotational movement of adjusting member and piston rod, and

Fig.22 shows a final assembly configuration of the embodiment according to Fig. 20 and 21 in a clearance-eliminated configuration,

Fig. 23 schematically illustrates another embodiment, wherein adjusting member and piston rod comprises oppositely directed receptacles interconnected by means of a threaded adjustment sleeve,

Fig. 24 shows the embodiment according to Fig. 23 with a spring-biased clearance eliminating rotation of adjusting member and adjustment sleeve, and

Fig. 25 depicts the embodiment according to Fig. 23 and 24 in a post-clearance elimination configuration..

Detailed Description

In the embodiment according to Figs. 1 to 3 the drive mechanism of a drug delivery device 10 is illustrated in a first embodiment. The mechanism comprises a cartridge 16 filled with a medicinal product to be dose-wise dispensed. The cartridge 16 is mounted in a cartridge holder 14 having a stepped down neck portion towards its distal end, which, in the embodiment according to Figs. 1 to 3 is located on the left hand side.

In proximal direction, directed to the right hand side in Figs 1 to 3, the cartridge 16 has an axially slideably arranged piston 18, which - under an impact of a distal movement of a driven piston rod 26 - is stepwise moved in distal direction for the purpose of expelling or purging an exact and precise amount of the medicinal product contained in the cartridge. The piston rod 26 is radially secured by means of a mount 32. It is axially displaceable by means of a not further illustrated dose dispensing or drive mechanism. The cartridge holder 14 is further connected with a proximal housing component 12. Cartridge holder 14 and housing component 12 are arranged in an interleaved manner, wherein a stepped down neck portion 15 of the cartridge holder is received in a corresponding receptacle of a distally located receiving portion 13 of the housing component 12.

In Fig. 1 there is further illustrated a gap 34 between a distal end section 22 of the piston rod 26 and a proximal end face of the piston 18. The axial size of this clearance 34 may vary due to manufacturing and geometric tolerances of the components of the drive mechanism or due to varying positions of the piston 18 inside the cartridge 16. In order to eliminate or to bypass a backslash effect of this gap 34, there is provided an adjusting member 20 of hollow-cylindrical shape forming a receptacle for the distal portion 22 of the piston rod 26.

The adjusting member 20 may be pre-assembled to the piston's proximal end face. Alternatively, the adjusting member 20 may also be pre-assembled provisionally to the distal portion of the piston rod 26. During assembly of the drive mechanism or the respective drug delivery device, the piston rod 26, eventually together with its mount 32 might be axially inserted in distal direction with respect

to the housing component 12, as it is obvious from a comparison of the configuration of Fig. 2 with the configuration of Fig. 1.

As can be further seen from Fig. 2, the axial size of the gap 34 has been reduced, but a small slit-like gap between bottom face of the adjusting member 20 and proximal end face of the piston rod 26 still persists. Even though the gap 34 has not entirely vanished, axial clearance between piston 18 and piston rod 26 is effectively eliminated by means of inserting a lock rod 28 and by activating a locked mode of a coupling element 22 arranged at the piston rod's 26 distal end.

By inserting the lock rod 28 in distal direction into and through the hollow and shaft-like piston rod 26, due to mutually corresponding bevelled surfaces 28, 30 of coupling element 22 and lock rod 24, the coupling element 22 is moved radially outwardly with the effect of generating a clamping effect with the adjusting member's 20 receptacle.

In this way, by insertion of said lock rod 24, a radially acting clamping effect of the piston rod's 26 distal portion 22 and the adjusting member 20 can be achieved. As a consequence, a subsequent distally directed axial movement of the piston rod 26 is directly and unalteredly transferred to the piston 18 and according to the axial displacement of piston 18 or piston rod 26, a well-defined amount of medicinal product is expelled from the container 16.

Since the invention provides clearance elimination and an at least unidirectional axial coupling of piston rod 26 and piston 18 irrespective of their relative distance, a conventional priming procedure for deploying and preparing a drive mechanism and/or a respective drug delivery device for a first dose setting and dispensing becomes obsolete. Effective clearance and backslash elimination can already be obtained during assembly of the drive mechanism, e.g. when the piston rod is placed mounted inside the housing component 12. Activation of dose setting or dose dispensing means to be actuated by the end-user becomes superfluous.

In the embodiment according to Figs. 4 and 5, the interlock mechanism of adjusting member 46 and piston rod 48 varies from the embodiment as illustrated and described with respect to Fig. 1 to 3. Instead of a radially acting clamping of a piston rod's coupling element 22, here, the proximal housing component 42 comprises a through opening or a transparent window 44, for the delivery of either some kind of adhesive or for the purpose of energy deposition. Comparable to the embodiment according to Figs. 1 to 3, also here, the adjusting member 46 comprises a receptacle adapted to slidably receive a distal portion 49 of the piston rod 48.

As soon as a final assembly position has been reached, as illustrated in Fig. 5, the adjusting member 46 and the piston rod 48 are mutually interlocked by means of energy deposition, provided by e.g. a radiation source 50, such as a laser. In this way, by deposition of thermal energy in an overlapping region of adjusting member 46 and piston rod 48, a direct welding of adjusting member 46 and piston rod 48 can be achieved.

Additionally or alternatively, it is conceivable, that an adhesive or some other fixing means is externally supplied by means of the through opening 44 for locking in position adjusting member 46 and piston rod 48. The drug delivery device 40 according to the embodiment of Fig. 4 and 5 is preferably adapted for single-used drug delivery devices, since adjusting member 46 and piston rod 48 are inseparably connected by means of welding or bonding.

In Figs. 6 through 7a, a further embodiment is illustrated, wherein the piston rod 52 comprises a downward pointing and radially stepped down distal portion 55, which is adapted for insertion into an adjusting member 54 serving as a corresponding receptacle. In a pre-assembly configuration as for instance illustrated in Figs. 6 and 6a, the receptacle 54 is partially filled with a deformable, preferably non-cured adhesive 58.

By subsequent insertion of the piston rod's 52 distal portion 55 into said receptacle 54, the adhesive 58 squeezes between various circumferential gaps formed between the radially outward circumferential wall of the piston rod's 52 distal portion 55 and the corresponding inward facing sidewall of the receptacle 54. The filling of said gaps becomes evident by a comparison of Fig. 6a and 7a illustrating the cross-sectional area along A-A as given in Fig. 6 and 7. In order to form adhesive-receiving axial gaps, the piston rod 52 at its distal stepped down portion 55 comprises radially outwardly protruding and axially extending ribs 53. These ribs 53 further serve to provide a radial guiding during insertion of the distal portion 55 into said receptacle 54. Furthermore, as illustrated in Fig. 6 and 7, the piston rod 52 comprises a socket 56 being adapted to abut against the receptacle's 54 side wall in axial direction.

After having introduced the piston rod's 52 distal portion 55 at least partially into the receptacle 54 and into said adhesive 58, the adhesive 58 is cured for locking into position of receptacle 54 and piston rod 52. This way, any further distal displacement of the piston rod 52 can be directly and unalteredly transferred to the piston 18 in a clearance-free way.

The receptacle 54 may be pre-filled with adhesive 58 before assembly of the drive mechanisms components. Alternatively, when making use of a two-component adhesive, it is conceivable, to provide the stepped down distal portion 55 of the piston rod 52 with a first component of said adhesive and to dispose a second component of such adhesive into the receptacle 54. As soon as piston rod 52 and receptacle 54 mate, the two-component adhesive starts to cure with the effect of interconnecting piston rod 52 and adjusting member 54.

Alternatively, it is conceivable, that the adjusting member 54 is provisionally pre-assembled to the piston rod's 52 distal portion 55. Then, during assembly, the adjusting member 54 is brought into abutting contact with the piston 18, wherein the elastically or plastically deformable adhesive 58 allows for the required clearance-compensating motion. By deposition of thermal energy, e.g. by means

of external heat treatment or by means of irradiation by an applicable electromagnetic radiation, curing of said adhesive 58 can be conducted and accelerated.

In Fig. 8 to 11, another embodiment comprising a clamping member, in particular an eccentrically designed or eccentrically supported clamping member is illustrated. Also here, a receptacle-forming thrust piece 64 is disposed at the piston's 18 proximal end face. The receptacle 64 is opened towards the piston rod 62 being slidably disposed in axial direction. The receptacle 64 is further adapted to receive the piston rod's 64 distal portion comprising two jaws 68, 69, as illustrated in Fig. 9. The jaws 68, 69 being elastically deformable in radial direction form a receptacle 67 there between adapted to house a clamping member 66 of oval or elliptic shape.

The receptacle 67 comprises smaller dimensions in radial direction than in axial direction. Hence, by a rotation of the clamping member 66 of about 90°, the oppositely located jaws 68, 69 experience a radially outwardly directed force leading to a radial expansion of the jaws 68, 69. Due to this clamping member-induced radial widening, the jaws 68, 69 clamp with an inward facing wall of the receptacle 64, as illustrated in Figs. 10 and 11.

Even though the illustrated embodiment of Figs. 8 to 11 illustrates a rather centrally supported clamping member 66, with a non-circular external shape, similar embodiments comprising a non-centrally but eccentrically supported clamping member of arbitrary shape are also within the scope of the present invention.

Furthermore, the radial clamping of piston rod 62 and receptacle or thrust piece 64 is reversible, thus allowing to suspend the mechanical coupling of receptacle 64 and piston rod 62, e.g. for replacing of an empty cartridge 16. Also, the housing component 12 may comprise a not particularly illustrated through opening

allowing for insertion of a tool adapted for turning and twisting of the clamping member 66.

In Figs. 12 to 19 a further embodiment of the present invention is illustrated. Here, the receptacle-forming thrust piece 78 comprises a blocking ring 80 circumferentially surrounding a stepped down neck portion 84 of the piston rod's 76 distal end section. The blocking ring 80 allows for a unidirectional relative axial movement of thrust piece 78 and piston rod 76. Hence, the thrust piece 78 is allowed to be moved in distal direction towards the piston 18 of the cartridge 16 relative to the piston rod 76. A counter-directed relative axial movement is inhibited by the blocking ring 80.

As illustrated in Figs. 13 and 17, the stepped down neck portion 84 of the piston rod 76 further comprises a socket 85, that serves as axial catch for the blocking ring 80.

Typically, the receptacle-containing thrust piece 78 is pre-assembled to the piston rod 76 as illustrated in Fig. 12 and 13. During or after assembly of housing components 72, 74 of the drive mechanism 70 or respective drug delivery device, a gap 34 is formed between the distal face of the thrust piece 78 and the proximal face of the piston 18. For eliminating this axial clearance 34, a lock rod 82 is axially inserted and urged through the hollow piston rod 76.

The lock rod 82 with its distal end is moved up against a bottom of the thrust piece's receptacle, as illustrated in Fig. 15. By further driving the lock rod 82 in distal direction, the thrust piece 78 is driven in distal direction until it abuts against the proximal end face of the piston 18, as illustrated in Figs. 14 and 15. Since the blocking ring 80 impedes a respective counter-directed relative movement of thrust piece 78 and piston rod 76, after elimination of axial clearance 34, the lock rod 82 can be removed from the piston rod 76 leaving the drive mechanism in a configuration as illustrated in Figs. 16 and 17.

Due to the radial clamping provided by the blocking ring 80, any subsequent axial movement of the piston rod 76 in distal direction is directly and unalteredly transferred to the thrust piece 78 via the blocking ring 80. Consequently, a dose dispensing axial movement of the piston rod 76 is transferred to a corresponding dose-dispensing movement of the piston 18.

Figs. 18 and 19 further illustrate the shape and geometry of the blocking ring 80 in various perspective illustrations. The blocking ring typically has a somewhat rectangular or quadratic contour. It is preferably made of metal, such as brass or steel. It therefore provides a large resistivity against geometric deformations and is suitable for transferring of axially directed forces.

In Figs. 20 through 22, a further embodiment is illustrated, wherein the adjusting member 90 and the piston rod 92 are threadedly engaged. Here, the adjusting member 90 comprises a receptacle with an inner thread 94 and the distal portion of the piston rod 92 comprises a corresponding outer thread 96. Furthermore, also the piston rod 92 at its distal end section comprises a receptacle for receiving a spring element 98, preferably designed as torsion spring. With its distal end, the torsion spring 98 is coupled to the adjusting member 90 and with its proximal end, the torsion spring 98 is coupled to the piston rod 92. Further, there is provided an interlock member 100, which is adapted to selectively release and to interlock a rotative movement of adjusting member 90 and piston rod 92.

As illustrated in Fig. 20, during or after assembly of the drive mechanism or the respective drug delivery device, an axial gap 34 is persists between the piston 18 and a distal end face of the adjusting member 90. By actuation, preferably by pressing down the interlock member 100, the adjusting member 90 starts to rotate under the effect of the torsion spring 98, as illustrated in Fig. 21. Due to the threaded engagement of the adjusting member 90 and the piston rod 92, the adjusting member 90 also moves in distal direction until the gap 34 and respective axial clearance is eliminated such that the adjusting member 90 with a distal end

face moves up against a proximal end face of the piston 18, as illustrated in Fig. 22.

When axial clearance has been eliminated and adjusting member 90 abuts against the cartridge's 16 piston 18, the interlock member 100 returns in its interlock position, either by manual actuation or autonomously, e.g. by means of a separate spring element.

Alternatively or additionally, it is also conceivable, to make use of a self-locking threaded engagement of adjusting member 90 and piston rod 92. In such a configuration, the return of the interlock member 100 into an interlocking position becomes redundant since an axial and distally directed movement of the piston rod 92 would be transferred to a corresponding axial displacement of adjusting member 90 and piston 18 devoid of any rotative movement of the adjusting member 90 relative to the piston rod 92.

In Figs. 23 to 25, another embodiment of a threaded engagement of adjusting member 112 and piston rod 116 is illustrated. Here, adjusting member 112 and piston rod 116 are not in direct but rather indirect threaded engagement by means of an interjacent adjustment sleeve 114. The adjusting member 112 comprises a receptacle 128 to receive the adjustment sleeve 114. Correspondingly, the piston rod 116 comprises a receptacle 130 to receive an opposite proximal portion of said adjustment sleeve 114. For a threaded engagement of piston rod 116 and adjustment sleeve 114, the receptacle 130 of the piston rod 116 comprises an inner thread 120 matching with the outer thread 118 of the adjustment sleeve 114. Similarly, also the adjusting member's 112 receptacle 128 comprises a respective inner thread 122.

Additionally, the adjustment sleeve 114 and the piston rod 116 are spring biased by means of a spring element 126, which is preferably of torsion spring-type. Starting from a configuration according to Fig. 23, wherein an axial gap 34 is formed between the piston 18 and a distal end face of the adjusting member 112,

by actuating of a release mechanism, the adjustment sleeve 114 together with the adjusting member 112 starts to rotate, as illustrated in Fig. 24. If the axial gap 34 is eliminated and the adjusting member 112 with its distal end face gets in contact with the piston's 18 proximal end face, rotation of the adjusting member 12 will stop because of the mechanical and hence frictional contact.

Even though an abutment position as illustrated in Fig. 24 has been reached, the adjustment sleeve 14 may further rotate under the effect of the torsion spring 126 as illustrated in Fig. 25. In effect, the adjustment sleeve 114 further enters the adjusting member's 112 receptacle 128.

Preferably, the threaded engagement of adjustment sleeve 114, adjusting member 112 and piston rod 116 is of self-locking type, so that any distally directed axial movement of the piston rod 116 is directly and unalteredly transferred to the adjusting member 112 and to the adjacent piston 18 during repeated dose-dispensing steps.

To summarize, all embodiments according to Figs. 8 through 25 provide a reconfigurable or detachable clearance-elimination, which is particularly suitable for drug delivery devices designed for replaceable cartridges.

List of Reference Numerals

10	drive mechanism
12	housing component
13	receptacle
14	housing component
15	neck portion
16	cartridge
18	piston
20	thrust piece/receptacle
22	coupling element
24	lock rod
26	piston rod
28	slanted plane
30	slanted plane
32	mount
34	clearance
40	drive mechanism
42	housing component
44	through opening
46	thrust piece/receptacle
48	piston rod
49	distal portion
50	laser
52	piston rod
53	rib
54	receptacle/thrust piece
55	stepped down portion
56	socket
58	adhesive
60	drive mechanism
62	piston rod

64 thrust piece/receptacle
66 clamping member
67 receptacle
68 jaw
69 jaw
70 drive mechanism
72 housing component
74 housing component
76 piston rod
78 thrust piece/receptacle
80 blocking ring
82 lock rod
84 neck portion
85 socket
86 sidewall
90 adjusting member
92 piston rod
94 inner thread
96 outer thread
98 spring element
100 interlock member
112 adjusting member
114 adjustment sleeve
116 piston rod
118 outer thread
120 inner thread
122 inner thread
126 spring element
128 receptacle
130 receptacle

Claims

1. A drug delivery device for dispensing of a dose of a medicinal product, comprising:

   - a housing,

   - a cartridge comprising the medicinal product, the cartridge further comprising a piston slidably arranged therein in an axial direction,

   - a drive mechanism for a drug delivery device for dispensing of a dose of a medicinal product, the drive mechanism comprising:

     - a holder for the cartridge,

     - a piston rod to be operably engaged with the cartridge's piston for dispensing of a dose of the medicinal product, characterized by:

     - at least one adjusting member displaceably arranged in axial direction relative to the piston and/or relative to the piston rod for eliminating axial clearance between the piston and the piston rod, wherein the adjusting member is attached to a proximal end of the piston or is pre-assembled to a distal portion of the piston rod and further comprises a receptacle to receive a distal portion of the piston rod,

     - an interlock means adapted to interact with the adjusting member for locking the piston rod's distal portion in place at an arbitrary position inside the adjusting member's receptacle to establish a mechanical coupling rigid in compression of piston rod and piston irrespective of a relative distance between piston and piston rod.

2. The drug delivery device according to claim 1, wherein the interlock means is adapted to provide a retention force substantially larger than an axial force required to displace the adjusting member and/or the piston.

3. The drug delivery device according to any one of the preceding claims, wherein the interlock means is designed as positive, frictional or adhesive lock.

4. The drug delivery device according to any one of the preceding claims, wherein the adjusting member's receptacle and a distal portion of the piston rod are bonded or welded.

5. The drug delivery device according to any one of the preceding claims, wherein a deformable adhesive disposed in the adjusting member's receptacle is adapted to provide a clearance-eliminating axial displacement of piston rod and adjusting member, and wherein the adjusting member and the piston rod are to be mutually interlocked by curing of said adhesive.

6. The drug delivery device according to claim 4 or 5, wherein in a pre-assembly configuration, the adjusting member is pre-assembled to the distal portion of the piston rod by means of the deformable nun-cured adhesive.

7. The drug delivery device according to claim 5, wherein in a pre-assembly configuration, the adjusting member comprises a first adhesive component and the piston rod at its distal portion comprises a second adhesive component of a two-component adhesive.

8. The drug delivery device according to any one of the preceding claims, wherein the interlock means is adapted to radially clamp the adjusting member's receptacle and the piston rod's distal portion.

9. The drug delivery device according to any one of the preceding claims, wherein piston rod at its distal portion comprises at least one radially

movable jaw to interact with the adjusting member's receptacle, wherein the jaw has a slanted inner surface to engage with a correspondingly slanted surface of an axially movable lock rod.

10. The drug delivery device according to any one of the preceding claims 1 to 8, wherein the interlock means comprises an eccentrically supported clamping member to mutually clamp the adjusting member and the piston rod.

11. The drug delivery device according to any one of the preceding claims 1 to 8, wherein the interlock means comprises a blocking ring arranged on the outer circumference of the piston rod's distal portion to radially prop against an inside facing wall of the adjusting member's receptacle, wherein the blocking ring is further adapted to impede an axial movement of piston rod and adjusting member towards each other.

12. The drug delivery device according to any one of the preceding claims, wherein the piston rod comprises a hollow shaft adapted for axial insertion of a lock rod for activating a locked mode or for eliminating axial clearance.

13. The drug delivery device according to any one of the preceding claims, wherein the adjusting member and the piston rod are threadedly engaged and rotatably biased by a spring member.

14. The drug delivery device according to claim 13, wherein an interlock member movably arranged in radial direction at the piston rod radially engages with a corresponding recess at an inner surface of the adjusting member for selectively releasing and/or interlocking of a clearance-eliminating relative rotation between piston rod and adjusting member.

15. The drug delivery device according to claim 13, wherein the adjusting member and the distal portion of the piston rod comprise threaded receptacles facing towards each other, wherein the receptacles are threadedly engaged by means of a threaded adjustment sleeve, rotatably biased by the spring member relative to the piston rod or relative to the adjusting member.

16. The drug delivery device according to any one of the preceding claims 13 to 15, wherein the threaded engagement of adjusting member, adjusting sleeve and/or piston rod is of self-locking type.

17. The drug delivery device according to any one of the preceding claims, wherein the housing comprises a through opening or a transparent window to deliver an adhesive or an electromagnetic radiation for locking in position of piston and piston rod.

18. A method of eliminating clearance between a piston and a piston rod in a drive mechanism of a drug delivery device, wherein the drive mechanism comprises a holder for a product-containing cartridge having a piston slidably arranged therein in an axial direction, wherein the piston rod is to be operably engaged with the cartridge's piston for dispensing of a dose of the medicinal product, further comprising an adjusting member attached to a proximal end

of the piston or being pre-assembled to a distal portion of the piston rod, wherein the adjusting member comprises a receptacle to receive a distal portion of the piston rod, the method of eliminating said clearance during or after assembly of the drive mechanism is characterized by the steps of:

- axially moving of the piston rod relative to the adjusting member and/or axially moving the adjusting member relative to the piston for eliminating axial clearance between the piston and the piston rod,

- locking the piston rod's distal portion in place at an arbitrary position inside the adjusting member's receptacle by an interlock means adapted to interact with the adjusting member and

- establishing a mechanical coupling rigid in compression of piston rod and piston irrespective of a relative distance between piston and piston rod by means of the interlock means.