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Needle-less injector of miniature type

The invention concerns a needle-less injector in the form of a hand-held unit, preferably of miniature type, with which a liquid is intracutaneously injected for example into human or animal tissue. The invention aims to expand the area of use of an injector of that kind.

Liquids in the sense of the present invention are preferably solutions, suspensions or dispersions which contain an active substance. Active substances can be pharmacologically active substances for treatment of the human or animal body or they may be substances for diagnostic or cosmetic uses.

Active substances for non-pharmaceutical uses can be for example in the area of plant protection insecticides, fungicides, growth-promoting or growth-inhibiting agents or fertilisers. The needle-less injector according to the invention permits the environmentally friendly application of agents with a systemic action, as the active substance is applied directly to the plant.

EP 0 063 341 and EP 0 063 342 disclose a needle-less injector which includes a piston pump for expelling the liquid to be injected, which is driven by a motor by means of a pressure agent. The liquid container is mounted laterally to the piston pump. The amount of liquid required for an injection is sucked into the pump chamber by way of an inlet passage and a flap check valve when the piston is retracted. As soon as the piston is moved in the direction of the nozzle body the liquid is urged through the outlet passage to the nozzle and expelled. The piston of the piston pump is a solid round piston.

EP 0 133 471 describes a needle-less vaccination unit which is operated with carbon dioxide under pressure, from a siphon cartridge by way of a special valve.

EP 0 347 190 discloses a vacuum compressed gas injector in which the depth of penetration of the injected drug can be adjusted by means of the gas pressure and the volume of the drug can be adjusted by way of the piston stroke.

EP 0 427 457 discloses a needle-less hypodermic syringe which is operated by means of compressed gas by way of a two-stage valve. The injection agent is disposed

in an ampoule which is fitted into a protective casing which is secured to the injector housing. The ampoule is fitted on to the end of the piston rod. Disposed at the other end of the ampoule is the nozzle whose diameter decreases towards the end of the ampoule.

WO 89/08469 discloses a needle-less injector for one-off use. WO 92/08508 sets forth a needle-less injector which is designed for three injections. The ampoule containing the drug is screwed into one end of the drive unit, with the piston rod being fitted into the open end of the ampoule. At its one end, the ampoule contains the nozzle through which the drug is expelled. A displaceable closure plug is provided approximately at the centre of the length of the ampoule. The dose to be injected can be adjusted by way of the screwing-in depth of the ampoule. The piston rod which projects from the drive unit after actuation of the injector is pushed back by hand. Both units are operated with compressed gas.

WO 93/03779 discloses a needle-less injector with a two-part housing and a liquid container which is fitted laterally to the unit. The drive spring for the piston is stressed by means of a drive motor. The spring is released as soon as the two parts of the housing are displaced relative to each other by pressing the nozzle against the injection location. Respective valves are provided in the intake passage for the liquid and in the outlet of the metering chamber.

WO 95/03844 discloses a further needle-less injector. It includes a liquid-filled cartridge which at one end includes a nozzle through which the liquid is expelled. At the other end the cartridge is closed by a cap-type piston which can be pushed into the cartridge. A piston which is loaded by a prestressed spring, after release of the spring, displaces the cap-type piston into the cartridge by a predetermined distance, with the amount of liquid to be injected being expelled in that case. The spring is triggered as soon as the nozzle is pressed sufficiently firmly against the injection location. This injector is intended for one-off or repeated use. The cartridge is arranged in front of the spring-loaded piston and is a fixed component of the injector. The position of the piston of the injector which is intended for a plurality of uses is displaced after each use by a distance in a direction towards the nozzle. The piston and the drive spring cannot be reset. The prestressing of the spring is initially sufficiently great to expel the entire amount of liquid in the cartridge all at once. The spring can only be stressed again if the

injector is dismantled and the drive portion of the injector assembled with a fresh, completely filled cartridge.

In some known design configurations of the needle-less injector the supply container for the liquid to be injected is arranged laterally beside the drive unit. The amount of liquid to be injected is sucked into the pump chamber when the solid piston of the piston pump is retracted. The inlet passage includes an inlet valve and the outlet passage includes an outlet valve. Both valves operate with an auxiliary force.

In other design configurations of the needle-less injector the supply container for the liquid to be injected serves directly as a pump chamber and is subjected to the sudden application of force which occurs upon expulsion of the amount of liquid to be injected.

In the case of the needle-less injectors which are operated with compressed gas, a part of the compressed gas escapes after each injection. The compressed gas container is possibly replaceable but it cannot be directly filled with compressed gas again. With such injectors, the drive unit has to be replaced as soon as the compressed gas container is empty.

Accordingly the object is that of providing a multi-use needle-less injector of a simple design, which is preferably suited for repeated expulsion of a predetermined amount of liquid. The amount of liquid which is expelled overall after many uses should preferably be greater than the amount of liquid contained in a supply container. It should be possible for either a plurality of partial amounts of the liquid to be successively dispensed from the supply container or for the amount of liquid contained in a supply container to be taken as a whole and expelled all at once. The supply container should be able to be replaced in a simple manner. A sufficiently great mechanical thrust force (impulse) is to be imparted to the predetermined amount of liquid so that the predetermined amount of liquid penetrates a membrane, a foil or biological tissue.

In accordance with the invention that object is attained by a needle-less injector for a liquid, which is arranged in the form of a hand-held unit in a cylindrical housing and which includes a supply container for the liquid. The housing substantially comprises two portions. The two portions are releasably or non-releasably connected together and are arranged rotatably relative to each other. The needle-less injector

includes a locking stressing mechanism for a spring-actuated drive, which is stressed prior to the expulsion of a predetermined amount of the liquid and which is provided with a triggering device. Fixed in the sprung portion of the locking stressing mechanism is a hollow plunger which is driven by the locking stressing mechanism. The hollow plunger is arranged slidably within a cylinder. It projects with its one end out of the cylinder. Preferably at its other end there is mounted a valve body which is the single valve body of the needle-less injector. A nozzle with at least one opening is disposed at the end of the cylinder. The space between the nozzle and the end of the hollow plunger is the pump chamber. A supply container for the liquid is provided within the housing. The supply container is in the form of a container which is separate from the needle-less injector and which - preferably by means of a press fit - is releasably connected to the end of the hollow plunger which projects out of the cylinder. The predetermined amount of the liquid which has been conveyed into the pump chamber upon retraction movement of the sprung portion and the hollow plunger connected thereto, through the hollow plunger, is determined by the stroke movement and the cross-section of the hollow plunger.

The locking stressing mechanism comprises a spring-loaded drive flange as the sprung portion, a drive for stressing the spring, a locking member, two abutments for the drive flange, between which the drive flange can move with a reciprocating movement, and a device for triggering the locking member. The travel of the drive portion is limited precisely by the two abutments. A force-transmitting transmission arrangement is disposed between the energy-storing spring and the drive for stressing the spring. The locking member is annular and has interengaging locking surfaces. A preferably cylindrical coil spring or a disk spring or a leaf spring, which acts as a tension spring or as a compression spring, can be used as the energy storage means.

The energy-storing spring can be stressed by means of a direct drive. For that purpose the drive flange is displaced by an axially acting external force. When a high level of spring force is involved, a force-stepup transmission arrangement is advantageous, for example a worm-thrust transmission arrangement, by means of which the spring is stressed by an external torque. A transmission arrangement of that kind is a single-speed or multi-speed transmission arrangement which is disposed between the spring and the drive for stressing the spring.

The drive flange can be of a cup-shaped configuration. The collar of the drive flange may include for example two sawtooth-shaped openings, against which two sawteeth in the upper part of the housing slide.

The average spring force can be between 10 N and 150 N. Between the two positions of the sprung portion of the locking stressing mechanism the spring force changes approximately by ±10% of the average spring force.

The locking member can be a ring which in itself is radially elastically deformable or a rigid ring with displacement projections or a rigid ring with leaf springs formed thereon or a ring which is subjected to prestressing by one or more metal springs. The ring can be closed or open; it can comprise a plurality of portions. The locking member is arranged displaceably in a plane perpendicular to the axis of the housing, or it is deformable in that plane.

Further details relating to the locking stressing mechanism for a spring-actuated drive are described in DE 195 45 226.

Fixed in the sprung portion of the locking stressing mechanism is a hollow plunger which is driven by the locking stressing mechanism. The hollow plunger engages into the cylinder and projects with a part of its length out of the cylinder; it is arranged slidably within the cylinder.

A nozzle is fitted to the end of the cylinder. The nozzle opening can have a hydraulic diameter of 10 μm to 500 μm, preferably 50 μm to 150 μm. The nozzle opening can have a length of 50 μm to 500 μm, preferably 100 μm to 300 μm.

When the nozzle has a plurality of openings, the longitudinal axes of the nozzle openings can run parallel to one another, or they can be inclined divergently with respect to one another. When the nozzle has a plurality of openings, the hydraulic diameters thereof can be different.

The nozzle can comprise a parallelepiped which is composed of two silicon plates and which for example is 1.1 mm wide, 1.5 mm long and 2.0 mm high. In the contact surface between the plates the parallelepiped can have a shallow triangular opening which is about 400 μm thick and which terminates in a single nozzle opening which is 50 μm wide, 50 μm thick and 200 μm long. It may be desirable for the nozzle to be surrounded over its entire periphery with an accurately fitting elastomer shaped portion. The internal contour of the elastomer shaped portion is matched to the external

contour of the nozzle and the external contour of the elastomer shaped portion is matched to the internal contour of a nozzle holder which preferably comprises metal. A 'floating mounting' of that kind means that the nozzle which is of brittle material is insensitive to loadings which act in a shock-like fashion and which occur in regular use of the needle-less injector.

A valve body which preferably consists of one piece is mounted preferably to the end of the hollow plunger which is disposed within the cylinder, which valve body is guided by the hollow plunger and is arranged axially displaceably with respect to the hollow plunger. The valve body moves substantially with the hollow body. The valve body is preferably of a shape which is rotationally symmetrical about a single axis, such as for example a circular cylinder or a truncated cone. Its diameter can be smaller than the diameter of the space in which the valve body is displaceably arranged. The valve body can rotate about its axis. The axis of the valve body always remains parallel to the axis of the hollow plunger. That therefore affords a defined sealing surface on the inlet side of the valve body. The distance over which the valve body can be displaced relative to the hollow plunger is limited by an abutment. The valve is closed in the position in which the valve body bears against the defined sealing surface.

The space between the nozzle and the valve body mounted to the hollow plunger is the pump chamber. It is possible to arrange a filter which is preferably in the form of a depth filter in front of the nozzle end of the pump chamber, that is to say in the expulsion passage for the liquid. If the liquid to be injected contains suspended particles, the pore width of the filter has to be matched to the size of the particles.

Further details relating to the hollow plunger and the valve body are set forth in DE 195 36 902.

The locking stressing mechanism and the energy-storing spring are preferably stressed relative to each other by rotation of the two housing portions, preferably by way of a worm-thrust transmission arrangement. The torque can be produced by hand or by means of a motor.

The cylinder diameter is preferably practically identical over its entire length to the outside diameter of the hollow plunger. The cylinder can be fixedly mounted in the one portion of the housing. In addition the cylinder can be axially displaceably mounted

in the one portion of the housing. The displaceable cylinder is held in its rest position by a return spring.

The two abutments for the sprung portion can be fixedly positioned in the housing. Furthermore the position of one of those abutments can be variable in the axial direction. In that way it is possible to alter the volume of the pump chamber while the outside diameter of the hollow plunger is constant. In an otherwise unaltered design configuration of the needle-less injector the amount of expelled liquid can be altered by varying the position of an abutment.

The position of the travel movement of the sprung portion and thus the stroke movement of the hollow plunger within the needle-less injector is delimited by the two abutments. With a given position for the abutments the position of the travel movement of the sprung portion and therewith the stroke travel of the hollow plunger is constant for each injection.

The locking member is displaced parallel to the plane of the ring or is radially deformed in the plane of the ring, by means of a triggering device. When the cylinder is fixedly mounted in the housing the triggering device is actuated by means of a triggering button which can be depressed with a finger and the locking member is released. When the cylinder is mounted slidably in the housing the triggering device is actuated when the cylinder is pressed in against the force of the return spring and the locking member is disengaged.

A supply container for the liquid is provided within the housing. That supply container is in the form of a container which is separate from the needle-less injector; it is connected to the end of the hollow plunger which is in opposite relationship to the pump chamber. The end of the hollow plunger is covered by the liquid which is disposed in the supply container.

The supply container which is connected to the hollow plunger can additionally be connected to the sprung portion. That connection can be a releasable or non-releasable push-in connection in which the sprung portion is provided with a plurality of snap hooks which engage into a peripherally extending groove in the supply container after the supply container has been pushed into the needle-less injector.

The predetermined amount of the liquid to be expelled is determined by the stroke movement and the cross-section of the hollow plunger. The stroke movement of the hollow plunger is delimited by the two abutments for the drive flange.

It is desirable to provide in front of the nozzle a removable closure cap for protecting the nozzle opening during storage of the needle-less injector prior to and during the period of use thereof from contamination and evaporation of the liquid.

The two portions of the housing, the locking stressing mechanism, the cylinder and the supply container preferably comprise plastics material, for example polybutyleneterephthalate. The hollow plunger preferably comprises metal, for example high-quality steel.

The valve body can comprise metal, ceramic, glass, precious stone, plastics material or elastomer.

The nozzle can comprise metal, plastics material, glass, silicon or precious stone such as sapphire, ruby or corundum.

The filter preferably comprises sintered metal or sintered plastics material.

The needle-less injector is preferably produced in the form of a hand-held unit. It can be held and operated with one hand in the injection procedure. The cylinder, the hollow plunger, the valve body, the nozzle and possibly the filter are miniaturised components.

The mode of operation of the needle-less injector is described hereinafter.

During storage of the needle-less injector which has not been used or which has already been put to use and between two injections, the needle-less injector is in the rest condition. The energy-storing spring is in a prestressed condition. The sprung portion bears against the abutment which limits the travel of the sprung portion in the rest condition. The hollow plunger engages deeply into the cylinder. There is only a small spacing between the end of the hollow plunger and the inside of the nozzle. The locking member is in the disengaged position.

The locking stressing mechanism is stressed when the two housing portions are rotated relative to each other. The sprung portion is displaced in the axial direction away from the cylinder, in which case the stressing of the energy-storing spring is increased. At the same time the hollow plunger is pulled a distance out of the cylinder and the pump chamber is increased in size. The hollow plunger still projects with a part

of its length into the cylinder. At the same time a part of the liquid contained in the storage container is conveyed through the hollow plunger and past the valve body into the pump chamber and the pump chamber is filled with liquid. The amount of liquid in the pump chamber is practically the same as the amount of liquid expelled upon an injection being administered. The sprung portion is displaced until the locking member jumps into its engaged position. In the case of a needle-less injector with a triggering button that button protrudes somewhat out of the housing.

The nozzle end of the needle-less injector is applied to and pressed against the injection location. In the case of a needle-less injector with triggering button the triggering button is actuated with a finger and pressed into the housing. In that way the locking member is pushed into the disengaged position and the injection is triggered. In the case of a needle-less injector with slidably arranged cylinder the injector is pressed with its nozzle end by hand with increasing force against the force of the return spring, against the injection location. In that situation the cylinder is pushed into the housing, the locking member is pushed into its disengaged position and the injection is triggered. When the needle-less injector is lifted off the injection location the return spring urges the cylinder back into its rest position.

As soon as the locking member has assumed the disengaged position the force K of the stressed energy-storing spring acts by way of the sprung portion, the hollow plunger and the closed valve at the end of the hollow plunger, during the period of time Δt, on the liquid in the pump chamber, whereby the mass of liquid m has imparted thereto the speed Δv and thus a mechanical impulse $K \cdot \Delta t = m \cdot \Delta v$, and it issues from the nozzle at high speed and intracutaneously penetrates into the tissue. The needle-less injector is in the rest condition again after the injection.

The needle-less injector according to the invention can serve in human medicine and in veterinary medicine for intracutaneous injection of an active substance in liquid form, for example, a medicinal preparation, into human or animal tissue. Examples of suitable pharmaceutical preparations are inter alia analgesics, vaccines, anti-diabetic agents, hormones, contraceptives, vitamins, antibiotics, sedatives, antimicrobial substances, amino acids and coronary agents.

The preparation of the drug can be in the form of a solution, a suspension or an emulsion. In the case of suspensions the mean particle size should not exceed 15 μm, preferably 10 μm.

Suitable agents for dissolving, suspending or emulsifying active substances and possibly required additives are for example water, alcohols, alcohol-water mixtures and emulsions of oil in water or water in oil. They include purified, sterilised water, ethanol, propane diol, benzyl alcohols, ethanol-water mixtures, oils (such as coconut oil, peanut oil, soya oil, castor oil, sunflower oil), fatty acid esters (such as isopropyl myristate, isopropyl palmitate and ethyloleate), triglycerides, triacetin, solketal, and propylene glycol. The formulations may also contain additives such as for example preserving agents as well as acids or bases for adjusting the pH-value.

The predetermined amount of a liquid can be injected by means of the needle-less injector into a leaf or the stalk of a plant through a membrane into the space behind the membrane.

The needle-less injector according to the invention enjoys the following advantages:

- It is of an easily manageable shape. The supply container for the liquid is disposed in the injector housing.
- It can be used for many - up to several hundred - injections which can be taken from one or more supply containers.
- Besides the valve at the end of the hollow plunger it does not have any further valves.
- The locking stressing mechanism can be easily handled, even when high spring forces are involved, even by unskilled persons, and can be stressed with the application of a relatively small amount of force by way of a worm-thrust transmission arrangement.
- The locking stressing mechanism is triggered by hand by pressing the trigger button with a finger or when the needle-less injector is pressed against the injection location.
- The drive unit is not replaced but only the supply container for the liquid.
- The valve mounted at the end of the hollow plunger operates without ancillary force and closes very quickly.

- The volume of the pump chamber can be varied by varying the position of one of the two abutments.
- The mechanical impulse of the amount of liquid to be injected can be adapted to the desired depth of penetration into the tissue or to the thickness of the membrane to be penetrated.
- The supply container for the liquid is adapted to the conditions involved upon storage of the container - possibly for years - and to the connection thereof to the injector. Its design configuration is independent of the demands which are made on the pump chamber in front of the nozzle.
- The supply container for the liquid is not exposed to the thrust force upon injection.
- The supply container for the liquid can be replaced in a simple manner.
- The amount of liquid to be delivered that is necessary for a given application can be injected in a simple manner consecutively in several partial amounts in different places in the area of injection.
- Needle-less injection affects the place injected considerably less than injection by means of a hypodermic syringe.

The invention will now be described in greater detail with reference to the Figures. Figure 1 is a view in longitudinal section through a needle-less injector with triggering button in the rest condition, in which the cylinder is fixedly arranged in the one housing portion. Figure 2 is a view in longitudinal section through a needle-less injector without triggering button in the stressed condition of the energy-storing spring, in which the cylinder is arranged displaceably in the one housing portion.

Referring to Figure 1 shown therein are the two housing portions (1) and (2) which are releasably connected together and which are arranged rotatably relative to each other. Of the locking stressing arrangement which is in the rest condition, the Figure shows the sprung portion (3), the locking member (4) in the disengaged condition, the triggering button (5) which acts on the locking member, and the energy-storing coil spring (6) in the form of a compression spring. Fixed in the sprung portion (3) is the hollow plunger (7) which engages into the cylinder (8). Mounted to the end of the cylinder is the nozzle (9) with the nozzle opening (10). The filter (11) is disposed in front of the nozzle. The nozzle end of the hollow plunger is provided with the valve

body (12). The pump chamber (13) is disposed between the valve body and the filter. The supply container (14) is arranged in the otherwise free space within the coil spring; it is fitted in the flange (15) on to the hollow plunger and is held on the hollow plunger by the press fit (19). The cage (16) which surrounds the coil spring is connected in positively locking relationship to the housing portion (1). The sprung portion (3) bears against the abutment (17). The nozzle is protected by the removable closure cap (18).

Referring to Figure 2, shown therein are the two housing portions (31) and (32) which are releasably connected together and which are arranged rotatably relative to each other. Of the locking stressing mechanism in the stressed condition, the Figure shows the sprung portion (33), the locking member (34) in the engaged condition and the energy-storing coil spring (36) in the stressed condition. Fixed in the sprung portion (33) is the hollow plunger (37) which engages into the cylinder (38). Mounted at the end of the cylinder is the nozzle (39) having the nozzle opening (40). The nozzle end of the hollow plunger is provided with the valve body (42). The pump chamber (43) is disposed between the valve body and the nozzle. The supply container (44) is arranged in the otherwise free space within the coil spring; it is fitted in the flange (45) on to the hollow plunger and is held on the hollow plunger by the press fit 49. The cage (46) which surrounds the coil spring is connected in positively locking relationship to the housing portion (31). The sprung portion (33) bears against the abutment (47) on the engaged locking member (34). The cylinder (38) is arranged axially slidably in the housing portion (31); it is held in its rest position by the helical return spring (48) which acts as a compression spring. The cylinder (38) is provided with a triggering device (not shown) which disengages the locking member (34) as soon as the cylinder (38) is pushed into the housing portion (31) against the force of the return spring when the needle-less injector is pressed against the injection location. Reference (a) denotes the travel of the drive portion between the two abutments. The stroke movement of the hollow plunger is identical to that travel.

Figure 2 shows the needle-less injector used for injection. The nozzle (39) is pressed against the schematically shown tightly stretched skin (35); with further pressure on the point of injection, the needle-less injector is triggered and the liquid is injected from the pump chamber (43) into the skin (39).

Figures 3 and 4 show one end of the supply container and the sprung portion in a further embodiment. In Figure 3 the hollow plunger has been introduced into the supply container but not yet connected to the hollow plunger.

Figure 3 is a view in longitudinal section of part of the (triple-shell) supply container (54). The outer shell of the supply container is a stiff casing (55) which is provided with a peripherally extending groove (52). The supply container is closed by the plug (56) which goes into the immersion connection portion (58) with a press fit (59). A part of the sprung portion (53) with the hollow plunger (57) fixed therein is shown in longitudinal section. On its side towards the supply container the sprung portion is provided with a plurality of snap hooks (51).

In Figure 4 the supply container is connected to the hollow plunger and the sprung portion, more specifically to the hollow plunger by the press fit (59) and to the sprung portion by way of the snap hooks (51) which engage into the peripherally extending groove (52) in the supply container.

The connection between the supply container and the sprung portion, which is shown in Figures 3 and 4, comprises snap hooks (51) with round shoulders and a peripherally extending groove (52) of semicircular cross-section. That connection is a releasable plug-in connection.

To provide a non-releasable plug-in connection, it is possible to adopt snap hooks with sawtooth-shaped shoulders and a peripherally extending groove of triangular cross-section.

Example 1: Structure of a needle-less injector according to the invention

A needle-less injector for intracutaneous injection into biological tissue has the following features:

The housing is of an outside diameter of about 20 mm and a length of about 70 mm. Both portions of the housing, the locking stressing mechanism and the spring cage, are made from polybutyleneterephthalate. The cylinder also comprises polybutyleneterephthalate; it is of an outside diameter of 5 mm and an inside diameter of 1.60 mm. The nozzle comprises quartz. The nozzle opening is of a diameter of 140 μm and a length of 220 μm. The hollow plunger of high-quality steel is of an outside diameter of 1.59 mm and an inside diameter of 0.35 mm. The piston stroke travel is 12 mm. The valve body comprises elastomer; it is in the form of a 2 mm thick disc with

an outside diameter of 1.60 mm. The disc is provided on its peripheral surface with axial openings through which the liquid can flow past the valve body into the pump chamber. The end of the hollow plunger is provided with a groove into which the valve body engages. The amount of liquid expelled is about 23 mm^3. The interchangeable supply container is of a volume of about 11 cm^3.

Example 2: Intracutaneous application of a liquid

An injection solution comprising 20g of dextran fluorescein (UW 3000) per litre of distilled water was injected through the skin of two dogs under anaesthetic using the needle-less injector according to the invention. For that purpose 4.5 ml of the dextran fluorescein solution was introduced into the supply container of the needle-less injector and the supply container was connected to the hollow plunger of the injector. The injector was actuated by stressing and triggering the locking stressing mechanism a plurality of times in order to expel the air from the hollow plunger, the pump chamber and the nozzle. The needle-less injector was then applied to a previously shaved part of the skin in the region of the stomach of the dogs and triggered. That procedure was repeated a plurality of times.

Blood samples were taken from the dogs at regular intervals and the content of dextran fluorescein in the blood plasma was determined. The results demonstrate the operability of the needle-less injector according to the invention.

Example 3: In-vitro examination of a viral suspension

In laboratory experiments using the needle-less injector, it was determined whether the viability of suspended live viruses was decreased when the suspension was expelled through the valve of the needle-less injector.

From the viral suspension obtained after expulsion from the needle-less injector, a yield of only approximately 1 $\log_{10}$ PFU (plaque forming units) in the case of relatively large DNA viruses (test virus: vaccinia virus) and less (approximately 0.5 $\log_{10}$ PFU) with small RNA viruses (test virus: bovine viral diarrhoea virus) was determined.

Example 4: In-vivo application of a vaccine with modified live viruses

In an animal experiment, the applicability of the needle-less injector for delivering a vaccine suspension with modified live viruses was tested. In this

experiment, both the safety and the tolerability of vaccination by means of the needle-less injector, as well as the effectiveness of this method of delivery were determined.

Six healthy dogs of the same age were assigned to two groups. Group 1 comprised two dogs, group 2 comprised four dogs. The animals in both groups were each vaccinated three times, in each case at an interval of three weeks, with a modified live vaccine for canine adenovirus.

In group 1, in each case 1 millilitre of the canine adenovirus vaccine (CAV-1) (Galaxy DA2ppvL+Cv, SNo 610041; Solvay Animal Health Inc.) was delivered intramuscularly in accordance with the manufacturer's recommendations by means of a hypodermic syringe. In group 2, an experimental canine adenovirus was delivered by means of the needle-less injector.

The experimental vaccine (CAV-2) used for vaccinating the animals in group 2 was manufactured from a weakened strain of the canine adenovirus. The titre was 7.2 $\log_{10}$ $TCID_{50}$ per 60 microlitres (TCID = tissue culture infective dose). At each injection site, six individual shots were administered (six times 10 microlitres = 60 microlitres for each vaccination). The injection area on the back of the dogs was shaved and the respective six injection sites were marked with a ball-point pen.

The effectiveness of the vaccination was established by determining the number of virus neutralising antibodies in the serum of the dogs, in each case three weeks after each vaccination.

Tolerability was determined by observation of the injection sites six seconds after the vaccination and subsequently daily until the end of the animal experiment. The injection sites were photographed and the results after palpating the injection sites were noted.

This experiment showed:

In the animals in group 2 a very slight reddening of the injection sites was evident during the first 2 to 3 days. A temporary swelling lasting 1 to 2 days could be determined only by palpation. This slight and entirely tolerable local reaction is very probably connected with the local amplification of the depleted modified live virus, and is therefore viewed as necessary for the proper effectiveness of the vaccine. This explanation is supported by the fact that after the injection of physiological common

salt solution, using the needle-less injector, absolutely no colouration and also not even a slight, temporary swelling was to be noted.

Effectiveness is determined by the virus neutralisation test. The results are shown in Table 1. The largest titres are still capable of neutralising canine adenoviruses.

In the serum of all the animals from the two groups, virus neutralising antibodies were evident three weeks after the first vaccination. After the second and third vaccination, a small intensification effect was shown.

The vaccination with the experimental canine adenovirus vaccine by means of the needle-less injector is exactly as effective as intramuscular vaccination with the conventional vaccination by means of a hypodermic syringe.

Table 1: Canine adenovirus neutralisation titres of canine serum

Dog		VN titre of canine serum		
Test number	Reference	21days after first vaccination	21 days after second vaccination	21 days after third vaccination
CAV-1 conventional vaccine intramuscular by means of hypodermic syringe				
1496	------	1024	1024	4096
1498	------	1024	1024	512
CAV-2 experimental vaccine Subcutaneous by means of needle-less injector				
1494	TTK9	4096	4096	8192
1495	USK9	4096	4096	8192
1497	UVL9	4096	8192	4096
1499	TVL9	2048	2048	2048

CLAIMS

1. A needle-less injector for a liquid, which is in the form of a hand-held unit, comprising a housing and a supply container for the liquid, wherein
   - the housing includes two portions (1; 2), (31; 32) which are connected together and which are arranged rotatably relative to each other, and
   - the needle-less injector includes a locking stressing mechanism with a sprung portion (3; 33; 53) which is displaceable between two abutments (17; 47) and which is provided with a triggering device, and a hollow plunger (7; 37; 57) which is fixed in the sprung portion (3; 33; 53) and which is driven by the locking stressing mechanism, wherein the hollow plunger is arranged slidably within a cylinder (8; 38) and includes a single valve body (12; 42) and disposed at the end of the cylinder is a nozzle (9; 39) having at least one opening (10; 40) and the space between the nozzle and the valve body forms a pump chamber (13; 43), and
   - the supply container (14; 44; 54) for the liquid is arranged within the housing and is in the form of a container separate from the needle-less injector and is connected by means of a press fit (19; 49; 59) to the end of the hollow plunger, which projects out of the cylinder, and
   - the amount of liquid which when the hollow plunger (7) is pulled out of the cylinder (8) has been conveyed through the hollow plunger into the pump chamber (43) is determined by the stroke travel (a) and the cross-section of the hollow plunger, and
   - the position of the hollow plunger stroke travel (a) within the needle-less injector is determined by the position of the two abutments (17; 47).

2. A needle-less injector according to claim 1 wherein
   - the two portions (1; 2), (31; 32) of the housing are releasably connected together.

3. A needle-less injector according to claims 1 and 2 wherein
   - the nozzle (9; 39) includes only one opening (10; 40) of a hydraulic diameter of from 10 µm to 500 µm, preferably from 50 µm to 150 µm, and
   - the nozzle opening (10; 40) is of a length of from 50 µm to 500 µm, preferably from 100 µm to 300 µm.

4. A needle-less injector according to claims 1 to 3 wherein
   - the nozzle (9; 39) includes a plurality of nozzle openings whose hydraulic diameter is possibly different.

5. A needle-less injector according to claims 1 to 4, wherein
   - the nozzle (9; 39) includes a plurality of nozzle openings, the longitudinal axes of which are parallel to one another or are inclined divergently with respect to one another.

6. A needle-less injector according to claims 1 to 5 wherein
   - the position of an abutment and therewith the hollow piston stroke travel (a) is variable.

7. A needle-less injector according to claims 1 to 6, wherein
   - the locking stressing mechanism can be stressed by rotating the two housing portions (1;2), (31; 32) manually with respect to one another.

8. A needle-less injector according to claims 1 to 7 wherein
   - the locking stressing mechanism can be stressed by way of a worm-thrust transmission arrangement by rotation of the two housing portions (1; 2), (31; 32) relative to each other.

9. A needle-less injector according to claims 1 to 8 wherein
   - the locking stressing mechanism includes a coil spring (6; 36), a disk spring or a leaf spring as the energy storage means.

10. A needle-less injector according to claims 1 to 8 wherein
    - the nozzle (9; 39) comprises metal, plastics material, glass, silicon or precious stone such as sapphire, ruby or corundum.

11. A needle-less injector according to claims 1 to 10 wherein
    - the separate supply container (14; 44; 54) for the liquid is in the form of a replaceable supply container and the sprung portion (53) is adapted to receive the separate supply container.

12. A needle-less injector according to claims 1 to 11 wherein
    - the separate supply container (14; 44; 54) for the liquid is releasably connected to the hollow plunger (7; 37; 57) and is displaceable with the stroke movement of the hollow plunger within the housing.

13. A needle-less injector according to claims 1 to 12 wherein
    - the separate supply container (54) for the liquid is releasably connected to the hollow plunger (57) and the sprung portion (53), and
    - the sprung portion (53) is provided with snap hooks (51) which engage into a peripherally extending groove (52) in the supply container.

14. A needle-less injector according to claims 1 to 13 wherein
    - the nozzle end of the needle-less injector is provided with a closure cap (18).

15. A needle-less injector according to claims 1 to 14 wherein
    - a filter (11) is disposed in front of the side of the nozzle, which is towards the pump chamber.

16. A needle-less injector according to claims 1 to 15 wherein
    - the separate supply container (14; 44; 54) for the liquid is filled with a liquid medicament, preferably from the group of analgesics, vaccines,

anti-diabetic agents, hormones, contraceptives, vitamins, antibiotics, sedatives, antimicrobial substances, amino acids and coronary agents.

17. A needle-less injector according to claims 1 to 16 for a liquid, which is in the form of a hand-held unit, comprising a housing and a supply container for the liquid, wherein

- the housing includes two portions (1; 2), (31; 32) which are releasably connected together and which are arranged rotatably relative to each other, and
- the needle-less injector includes a locking stressing mechanism with a sprung portion (3; 33; 53) displaceable between two abutments (17; 47) and a coil spring (6; 36), and the locking stressing mechanism can be stressed by way of a worm-thrust transmission arrangement by rotation of the two housing portions (1; 2), (31; 32) relative to each other, and the locking stressing mechanism is provided with a triggering device, and
- the needle-less injector includes a hollow plunger (7; 37; 57) which is fixed in the sprung portion (3; 33; 53) and which is driven by the locking stressing mechanism, wherein the hollow plunger is arranged displaceably within a cylinder (8; 38) and includes a single valve body (12; 42), and
- disposed at the end of the cylinder is a nozzle (9; 39) with a single opening (10; 40) and the space between the nozzle and the valve body forms a pump chamber (13; 43), and
- the supply container (14; 44; 54) for the liquid is arranged within the housing and is in the form of a supply container which is separate from the needle-less injector and which is connected by means of a press fit (59) to the end of the hollow plunger projecting out of the cylinder, and which is connected to the sprung portion (53) by means of snap hooks (51) which engage into a peripherally extending groove (52) in the supply container, and
- the position of the hollow plunger stroke travel (a) within the needle-less injector is determined by the position of the two abutments (17; 47), and

- the separate supply container (14; 44; 54) is filled with a liquid medicament.

18. Use of the needle-less injector according to claims 1 to 17 for injecting a liquid containing an active substance into a biological tissue.

19. Use of the needle-less injector according to claims 1 to 17 for injecting a liquid containing an active substance into a plant tissue.

20. Use of a needle-less injector according to claims 1 to 17 for injecting liquids containing an active substance into an animal tissue.

21. Use of the needle-less injector according to claims 1 to 17 for intracutaneous injection of vaccines into an animal.

22. Use of the needle-less injector according to claims 1 to 17 for subcutaneous injection of vaccines into an animal.

23. Use of the needle-less injector according to claims 1 to 17 for intracutaneous injecting of vaccines into a human.

24. Use of a needle-less injector according to claims 1 to 17 for subcutaneous injecting of vaccines into a human.

25. Use of the needle-less injector according to claims 1 to 17 for injecting a liquid through a membrane into the space behind said membrane.