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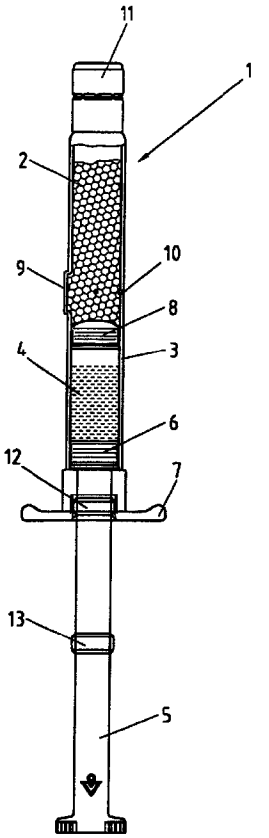
(54) Titre : PROCESSUS DE MELANGE D'UNE SUBSTANCE PHARMACEUTIQUE DIFFICILE A DISSOUDRE AVEC UN SOLVANT SE SERVANT D'UNE SERINGUE POUR EFFECTUER LEDIT PROCESSUS

(54) Title: PROCESS FOR BLENDING A DIFFICULTLY SOLUBLE PHARMACEUTICAL SUBSTANCE WITH A SOLVENT USING A SYRINGE FOR APPLYING THE PROCESS



(57) Abrégé/Abstract:
The process serves to blend a difficultly soluble pharmaceutical substance filled preferably in the front chamber (2) on the cannula side of the syringe barrel (3) of a dual-chamber syringe (1) with a solvent filled in the second chamber (4). Both chambers (2, 4) are

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(57) Abrégé(suite)/Abstract(continued):
separated from one another by a central stopper (8). By displacing the stopper (6) located at the plunger rod (5), first the central stopper (8) is displaced into the area of a by-pass (9) arranged in the wall of the syringe barrel (3) where it is stopped by lock stops (10). The solvent is then transferred via the by-pass (9) into the front chamber (2), which is sealed off by a closure system (11) arranged on the cannula side, thereby building up pressure in this chamber (2). Finally, the stopper (6) is pushed out by the built up pressure so that a portion of the solution together with a portion of the pharmaceutical substance flows back into the rear chamber (4) via the by-pass (9).

Abstract

The process serves to blend a difficultly soluble pharmaceutical substance filled preferably in the front chamber (2) on the cannula side of the syringe barrel (3) of a dual-chamber syringe (1) with a solvent filled in the second chamber (4). Both chambers (2, 4) are separated from one another by a central stopper (8). By displacing the stopper (6) located at the plunger rod (5), first the central stopper (8) is displaced into the area of a by-pass (9) arranged in the wall of the syringe barrel (3) where it is stopped by lock stops (10). The solvent is then transferred via the by-pass (9) into the front chamber (2), which is sealed off by a closure system (11) arranged on the cannula side, thereby building up pressure in this chamber (2). Finally, the stopper (6) is pushed out by the built up pressure so that a portion of the solution together with a portion of the pharmaceutical substance flows back into the rear chamber (4) via the by-pass (9).

PROCESS FOR BLENDING A DIFFICULTLY SOLUBLE PHARMACEUTICAL SUBSTANCE WITH A SOLVENT USING A SYRINGE FOR APPLYING THE PROCESS

The invention refers to a process for blending a difficultly soluble pharmaceutical substance filled preferably in the front chamber on the cannula side of the syringe barrel of a dual-chamber syringe with a solvent filled in the second chamber, both chambers being separated from one another by a central stopper. The invention further refers to a syringe for the application of this process.

Dual-chamber syringes (such as are known from DE 199 12 322, for instance) are used particularly where pharmaceutical substances in a dissolved form are unstable, i.e. they deterioriate relatively quickly. For this reason, these substances are filled into one chamber in a dry form, for instance freeze dried, and the solvent is filled separately into the second chamber. Prior to application, the solvent is transferred to the chamber containing the pharmaceutical substance, so that it returns to its dissolved state. If necessary, the blending can be assisted by shaking the syringe.

In the case of substances that return to their dissolved state only with difficulty, the blending achieved by this method is frequently insufficient. Therefore, the syringe must be shaken for a sufficient amount of time, which is not only time consuming but also risks damaging the syringe. On the other hand, it must be ensured that the pharmaceutical substance is completely dissolved prior to injecting it.

Based on this, the object of the invention is a process which achieves a faster and more reliable blending of the pharmaceutical substance with the solvent. In addition, a syringe is to be created which permits a simple application of this process.

According to one aspect of the invention, there is provided a process for blending a difficultly-soluble pharmaceutical substance contained in a front chamber, provided with a cannula, of a syringe barrel of a dual-chamber syringe, having a solvent contained in a rear chamber thereof, wherein both chambers are separated from one another by a central stopper, whereby, by displacement of a plunger located on a plunger rod, the central stopper is displaced into the area of a by-pass arranged in a wall of the syringe barrel, whereupon the solvent is transferred via the by-pass into the front chamber, which is sealed off by a closure

system arranged at an end of the cannula, characterized in that the central stopper is arrested by stop means in the region of the bypass and then pressure is built up in the front chamber, and finally the plunger is returned under said pressure and a portion of the solution together with a portion of the pharmaceutical substance flows back from the front chamber into the rear chamber via the by-pass .

According to another aspect of the invention, there is provided a syringe for medical purposes for the application of the process defined above, particularly for pharmaceutical substances of poor solubility, having a syringe barrel, at least one plunger arranged in said barrel, which can be displaced by means of a plunger rod, as well as a finger rest at one end of the syringe barrel provided with an opening for passage of the plunger rod, the syringe being in the form of a dual-chamber syringe in which, until the time of application, a pharmaceutical agent and a solvent therefor are kept separate from each other in a distal and a proximal chamber by means of a central stopper in the barrel, and which agent and solvent can be brought together via a by-pass arranged in a wall of the barrel, characterized in that the distal chamber has a cannula and a closure system on the cannula firmly attached in such a way that it is sealed against pressure building up in the interior of the syringe barrel, that within the area of the by-pass lock stops projecting radially inwardly of the barrel are provided for arresting the central stopper, and that the plunger rod is provided with two radially projecting limit-stop elements, a first, distal, limit-stop element being arranged near the stopper and a second, proximal, limit-stop element being arranged at such a distance from the distal limit-stop element that when this limit-stop element is placed against a contact surface of the finger rest, the plunger faces the central stopper with a gap or, at most, contacts it.

With regard to the process, the desired object is preferably achieved by first displacing the plunger located on the plunger rod so that the central stopper is displaced into the area of a by-pass arranged in the wall of the syringe barrel where it is stopped by lock stops, whereupon the solvent is transferred via the by-pass into the front chamber, which is sealed off by a closure system arranged on the cannula side, thus building up pressure in this chamber, and finally, the plunger is pushed out by the built up pressure and a portion of the solution together with a portion of the pharmaceutical substance flows back into the rear chamber via the by-pass.

The progress achieved by the invention is primarily due to the fact that the multiple flow of the solvent and the pharmaceutical substance through the by-pass creates a strong turbulence which achieves a high degree of blending. This can be achieved relatively simply by repeatedly pressing on the syringe rod in a kind of pumping action.

In a preferred embodiment of the invention, the pressure build-up is restricted by a disengageable limit stop on the plunger rod. This ensures that the central stopper is not displaced beyond the area of the by-pass.

In addition, within the scope of the invention, it is recommended that the transfer and reverse flow of the solution with the pharmaceutical substance be repeated as often as required by the degree of solubility. Particularly in order to ensure the complete dissolution of the substance, a specific number of plunger strokes may be prescribed, which can be followed by the user simply by counting.

In regard to the device, the invention is based on a syringe for medical purposes comprising a syringe barrel, at least one plunger arranged in it which can be displaced by means of a plunger rod, as well as a finger rest at one end of the syringe barrel with an opening for passage of the plunger rod, and more particularly in the form of a dual-chamber syringe in which, until the time of application, the pharmaceutical agent and the solvent are kept separate from each other in a distal and in a proximal chamber by means of an additional stopper in the middle and can be brought together via a by-pass, and more particularly for pharmaceutical substances of poor solubility.

The object of the invention is achieved in that the closure system on the cannula side is firmly attached in such a way that it is non-detachable and sealed against pressure build up in the interior of the syringe barrel, in that, within the area of the by-pass, lock stops projecting radially inward are provided for the central stopper, and in that the plunger rod is provided with two radially projecting limit-stop elements, the first, distal limit-stop element being arranged near the stopper and the second, proximal limit-stop element being arranged at such a distance from the distal limit-stop element that when this limit-stop element is placed against a contact surface of the finger rest, the stopper faces the central stopper with a gap or, at most, contacts it.

In order to ensure that the central stopper sits firmly in both flow directions of the solvent and the pharmaceutical substance, it is expedient that the lock stops immobilize the central stopper in both directions.

According to a first embodiment of the invention, the limit-stop elements may be formed by radially projecting threaded zones and the contact surface by an interior thread of the finger rest. For handling prior to using the syringe, it is also advantageous for the threaded zones and the interior thread to have only a few turns, since this provides a quick transition from the mixing process to the application.

According to a second embodiment of the invention, the limit-stop elements are formed by radially projecting pins and the contact surface by a shoulder of the finger rest projecting radially inward.

In this case, it is recommended that the shoulder be provided with recesses for passage of the pins.

The invention is explained in more detail below using an embodiment shown in the drawing, in which:

Fig. 1 shows a dual-chamber syringe in the initial position that allows the application of the process according to the invention.

Fig. 2 shows the syringe according to Figure 1 with the central stopper displaced into the area of the by-pass and the solvent almost completely transferred.

Fig. 3 shows the syringe according to Figure 2, but after the plunger rod has been returned to the initial position.

Fig. 4 shows a more or less similar illustration of Figure 2, but with a partially reconstituted substance.

Fig. 5 shows the syringe according to Figure 3, but with a completely reconstituted substance.

Fig. 6 shows the syringe in a ready-to-use state after screwing the plunger rod in through the second threaded zone.

Fig. 7 shows the syringe in an alternative embodiment.

Figures 8 - 13 show the syringe according to Fig. 7 in the function position according to Figures 1 - 6.

The dual-chamber syringe 1 shown in the drawing serves (initially in a known way) to initially keep the substance filled in the chamber 2 on the cannula side of the syringe barrel 3 in a freeze-dried or powder-like state separate from the solvent filled in the second chamber 4, and to mix them together only prior to use. To this end, the syringe 1 is assembled in the usual way and filled, the pharmaceutical substance being filled as a powder or lyophilized in the freeze-drier.

In detail, the syringe 1 comprises the syringe barrel 3, a plunger 6 arranged in it and which can be displaced by means of a plunger rod 5 as well as a finger rest 7 connected to one end of the syringe barrel 3. This finger rest 7 is provided with an opening for passage of the plunger rod, which has an interior thread.

The dual-chamber syringe is designed in such a way that the pharmaceutical agent is kept separate from the solvent in the other chamber 4 by means of a central stopper 8, the syringe barrel 3 being provided with a by-pass 9.

Preparing the syringe contents for application, the plunger 6 attached to it is displaced towards the end on the cannula side by means of the plunger rod 5, the overpressure in the solvent displacing the central stopper 8 towards the by-pass 9. As soon as the central stopper 8 has opened the way via the by-pass 9, the solvent flows into the chamber 2 on the cannula side, whereupon the pharmaceutical substance located there can dissolve in the solvent.

If the pharmaceutical substance is only slightly soluble, the syringe would subsequently have to be shaken until it was completely dissolved. However, this type of blending is comparably ineffective, so long preparation times might be necessary before the syringe can finally be applied.

Therefore, initially in the area of the by-pass 9, the syringe 1 has radially inward projecting lock stops 10 for the central stopper 8, so that it is held in the area of the by-pass (9), at least as long as the plunger 6 of the plunger rod (5) does not push it beyond the area of the by-pass 9. In addition, the syringe barrel 3 is sealed off by a closure system 11 on the cannula side which is firmly attached in such a way that it is nondetachable and sealed against pressure building up in the interior of the syringe barrel 3.

In a further example of an embodiment according to Figures 1 to 6, the plunger rod 5 is provided with two radially projecting limit-stop elements in the form of threaded zones 12, 13, the first, distal threaded zone 12 being arranged near the plunger 6, preventing the plunger rod 5 from being unintentionally pushed in. Thus, in order to prepare the syringe for the application, the threaded zone 12 must first be screwed through the interior thread of the finger rest 7. The second, proximal threaded zone 13 is arranged at such a distance from the distal threaded zone 12 that when this threaded zone 13 is placed against the interior thread of the finger rest 7, the plunger 6 faces the central stopper 8 at a distance or, at most, touches it. Thus, when the plunger rod 5 is pressed in it touches a limit stop which prevents the central stopper 8 from being pushed beyond the area of the by-pass 9.

If the plunger rod 5 is displaced towards the end on the cannula side, a steadily increasing counterpressure builds up in the front chamber 2. This counterpressure is greatest as soon as all the solvent is located in the front chamber 2 and the plunger 6 and stopper 8 are touching. If the force on the plunger rod 5 is reduced, it is pushed back by the pressure in the chamber 2, resulting in the solvent and the pharmaceutical substance flowing back into the second chamber 4. Following this, the plunger rod 5 can be activated once again, so that the solvent is again transferred to the chamber 2 on the cannula side. The essentials of this process are shown in Figures 3 and 4 of the drawing.

The flow through the by-pass 9, of which there may be several, results in a strong turbulence in the solvent and the pharmaceutical substance, thus achieving a particularly thorough blending and, therefore, an accelerated dissolution. The lock stops 10 ensure that the central stopper 8 is immobilized against pressure loads from both directions.

As a result, by multiple pressing and releasing of the plunger rod 5, the user can achieve a complete reconstitution of the pharmaceutical product.

The closure system 11 on the cannula side must be designed in such a way that it can stand up to the pressures that occur in the interior of the syringe barrel 3. This means that those closure systems with a safety seal come into particular consideration. This signifies that the closure system 11 is provided with a security ring, for instance, which must be removed before a tip cap can be pulled off the shoulder of the needle of the syringe barrel 3.

As soon as the blending or dissolution process of the pharmaceutical substance has been completed, the closure system 11 can be removed, whereupon the plunger rod 5 and its second, proximal threaded zone 13 is screwed into and through the interior thread of the finger rest 7, so that as soon as this second threaded zone 13 is located in the interior of the syringe barrel 3, the syringe 1 is ready for application.

Instead of the threaded zones, the additional embodiment according to Figures 7 to 13 has radially projecting pins that accordingly act as limit-stop elements on a shoulder of the finger rest projecting radially inward. This shoulder is provided with recesses which, after rotating the plunger rod accordingly, permit passage of the pins, as is shown in the sectional diagram in Fig. 7. Thus, handling this embodiment is basically the same as the embodiment with the threaded zones described previously.

Claims:

1. A process for blending a difficultly-soluble pharmaceutical substance contained in a front chamber, provided with a cannula, of a syringe barrel of a dual-chamber syringe, having a solvent contained in a rear chamber thereof, wherein both chambers are separated from one another by a central stopper, whereby, by displacement of a plunger located on a plunger rod, the central stopper is displaced into the area of a by-pass arranged in a wall of the syringe barrel, whereupon the solvent is transferred via the by-pass into the front chamber, which is sealed off by a closure system arranged at an end of the cannula, characterized in that the central stopper is arrested by stop means in the region of the bypass and then pressure is built up in the front chamber, and finally the plunger is returned under said pressure and a portion of the solution together with a portion of the pharmaceutical substance flows back from the front chamber into the rear chamber via the by-pass.

2. Process according to Claim 1, characterized in that the build-up of said pressure is restricted by a disengageable limit stop on the plunger rod.

3. Process according to Claims 1 and 2, characterized in that the transfer and reverse flow of the solution with the pharmaceutical substance is repeated as required by the degree of solubility of the pharmaceutical.

4. A syringe for medical purposes for the application of the process according to Claim 1, particularly for pharmaceutical substances of poor solubility, having a syringe barrel, at least one plunger arranged in said barrel, which can be displaced by means of a plunger rod, as well as a finger rest at one end of the syringe barrel provided with an opening for passage of the plunger rod, the syringe being in the form of a dual-chamber syringe in which, until the time of application, a pharmaceutical agent and a solvent therefor are kept separate from each other in a distal and a proximal chamber by means of a central stopper in the barrel, and which agent and solvent can be brought together via a by-pass arranged in a wall of the barrel, characterized in that the distal chamber has a cannula and a closure system on the cannula firmly attached in such a way that it is sealed against pressure building up in the interior of the syringe barrel, that within the area of the by-pass lock stops projecting radially inwardly of the barrel are provided for

arresting the central stopper, and that the plunger rod is provided with two radially projecting limit-stop elements, a first, distal, limit-stop element being arranged near the stopper and a second, proximal, limit-stop element being arranged at such a distance from the distal limit-stop element that when this limit-stop element is placed against a contact surface of the finger rest, the plunger faces the central stopper with a gap or, at most, contacts it.

5. Syringe according to Claim 4, characterized in that the lock stops immobilize the central stopper from movement in both directions.

6. Syringe according to Claim 4 or 5, characterized in that the limit-stop elements are formed by radially-projecting threaded zones and the contact surface by an interior thread of the finger rest.

7. Syringe according to Claim 4 or 5, characterized in that the limit-stop elements are formed by radially projecting pins and the contact surface by a shoulder of the finger rest projecting radially inwardly.

8. Syringe according to Claim 7, characterized in that the shoulder is provided with recesses for passage of the pins.

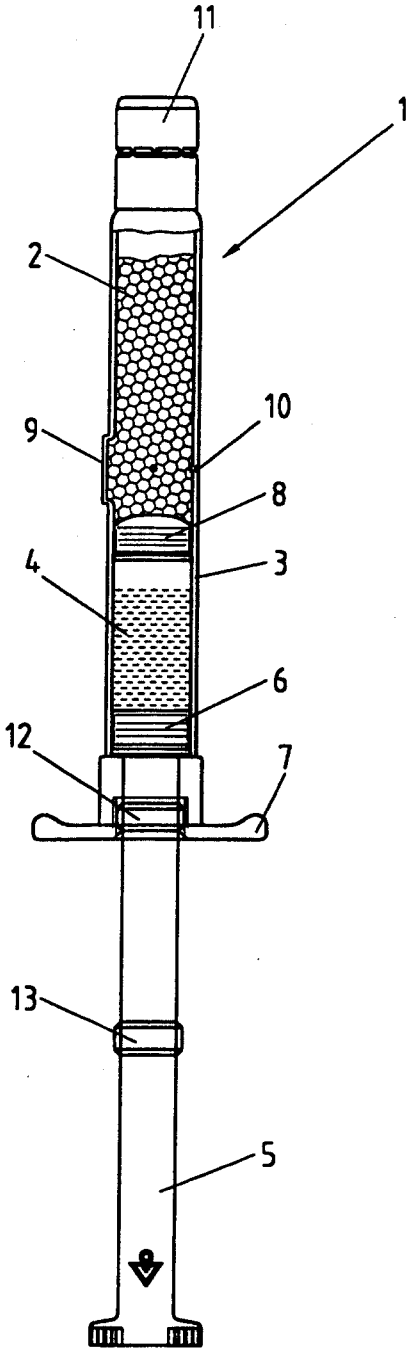


Fig. 1

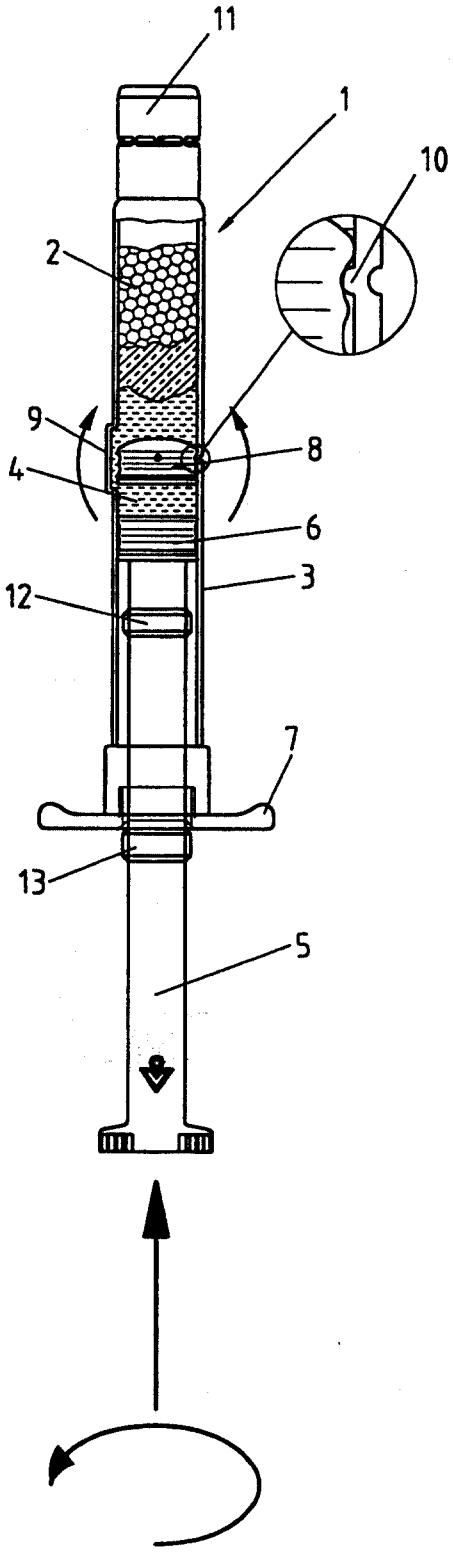


Fig. 2

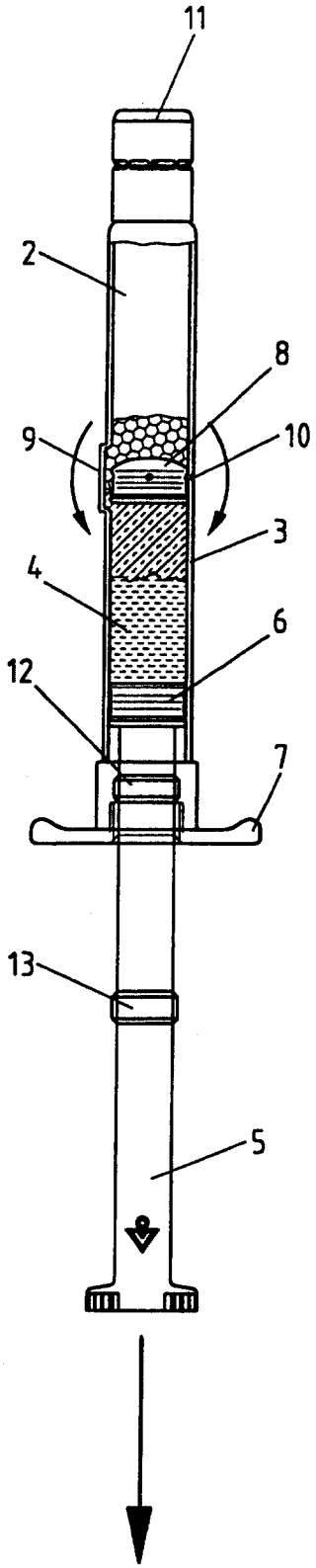


Fig. 3

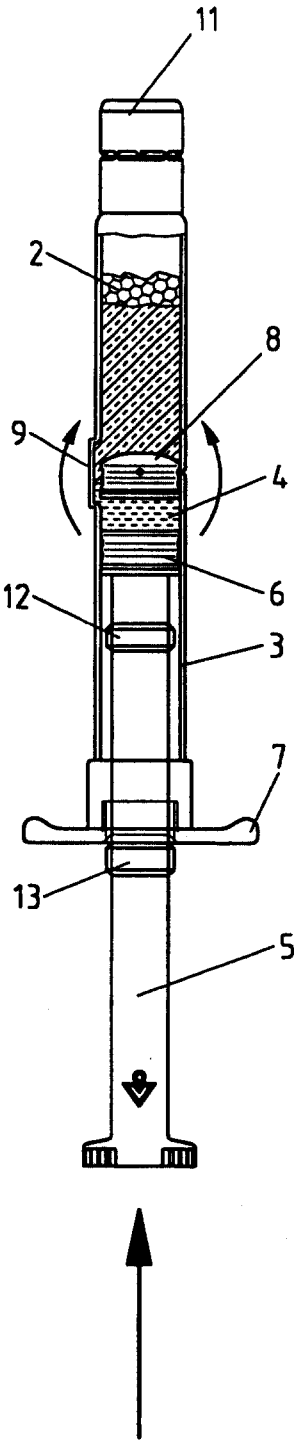


Fig. 4

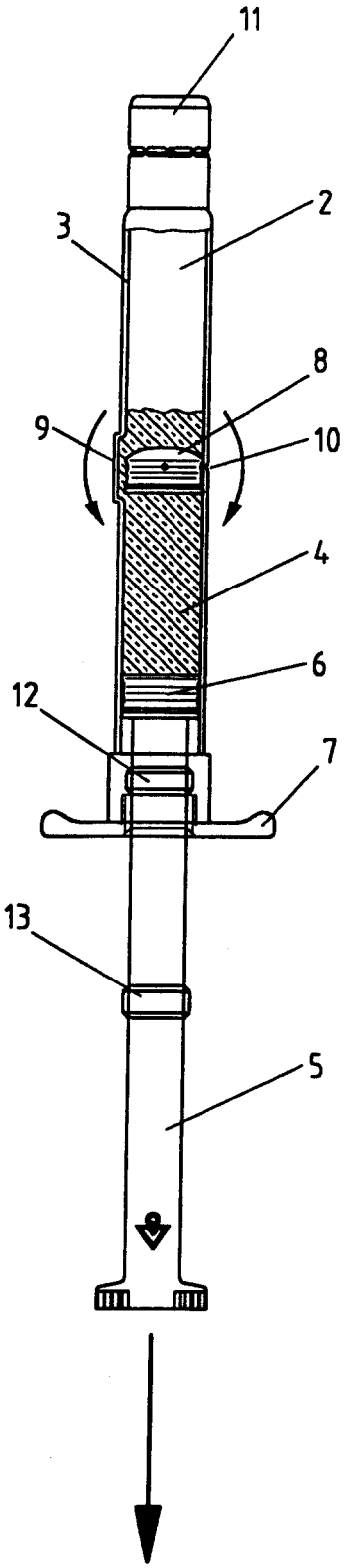


Fig. 5

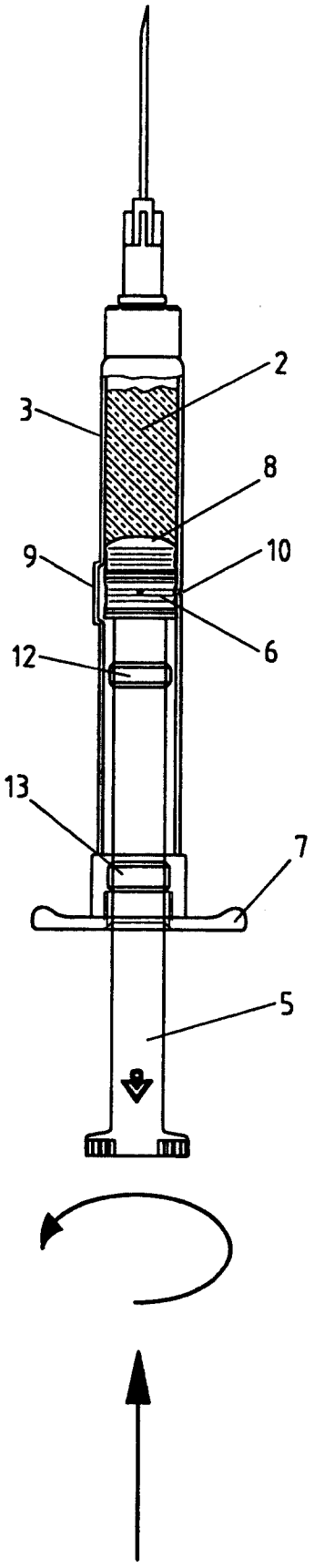


Fig. 6

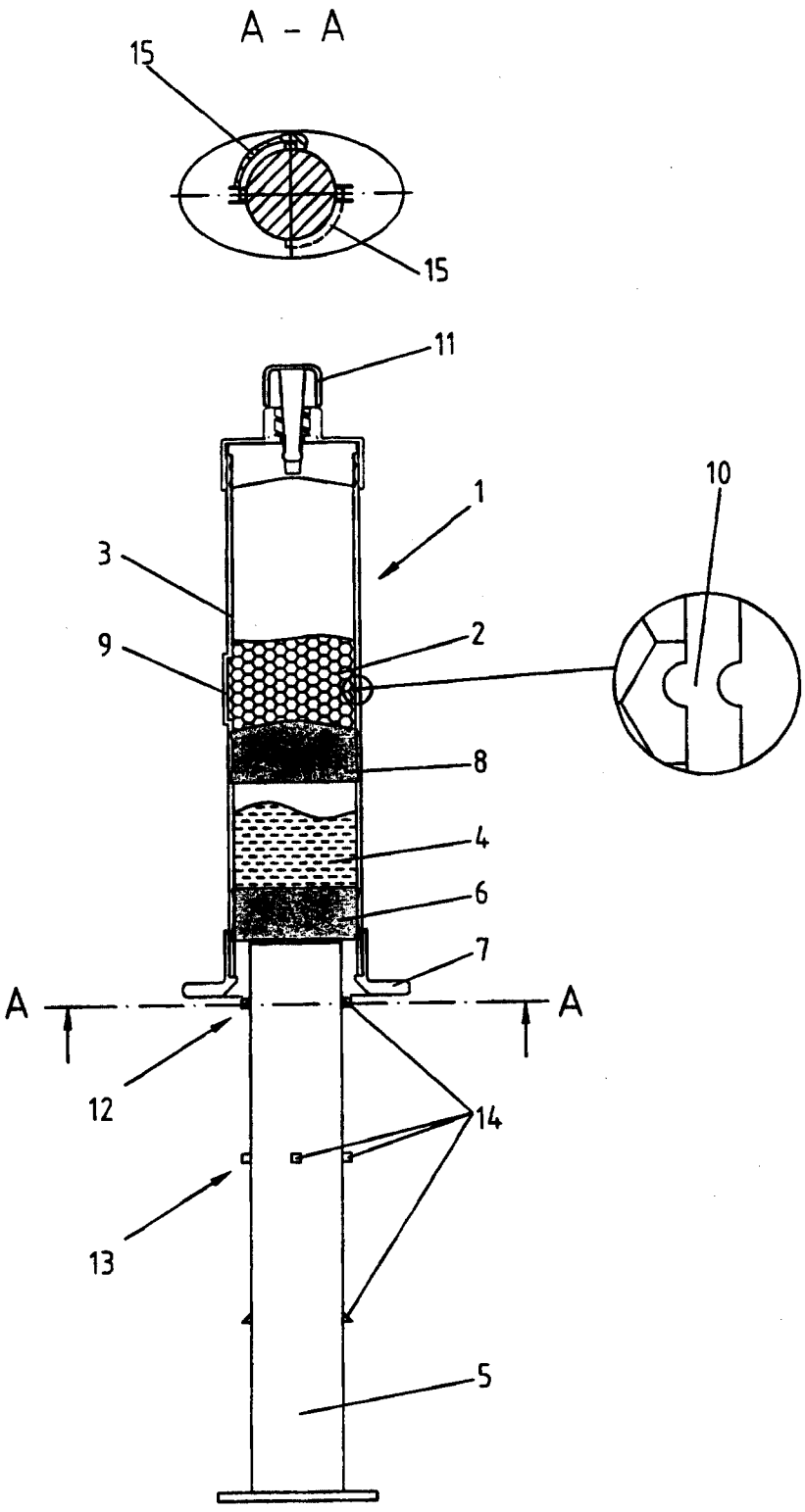


Fig. 7

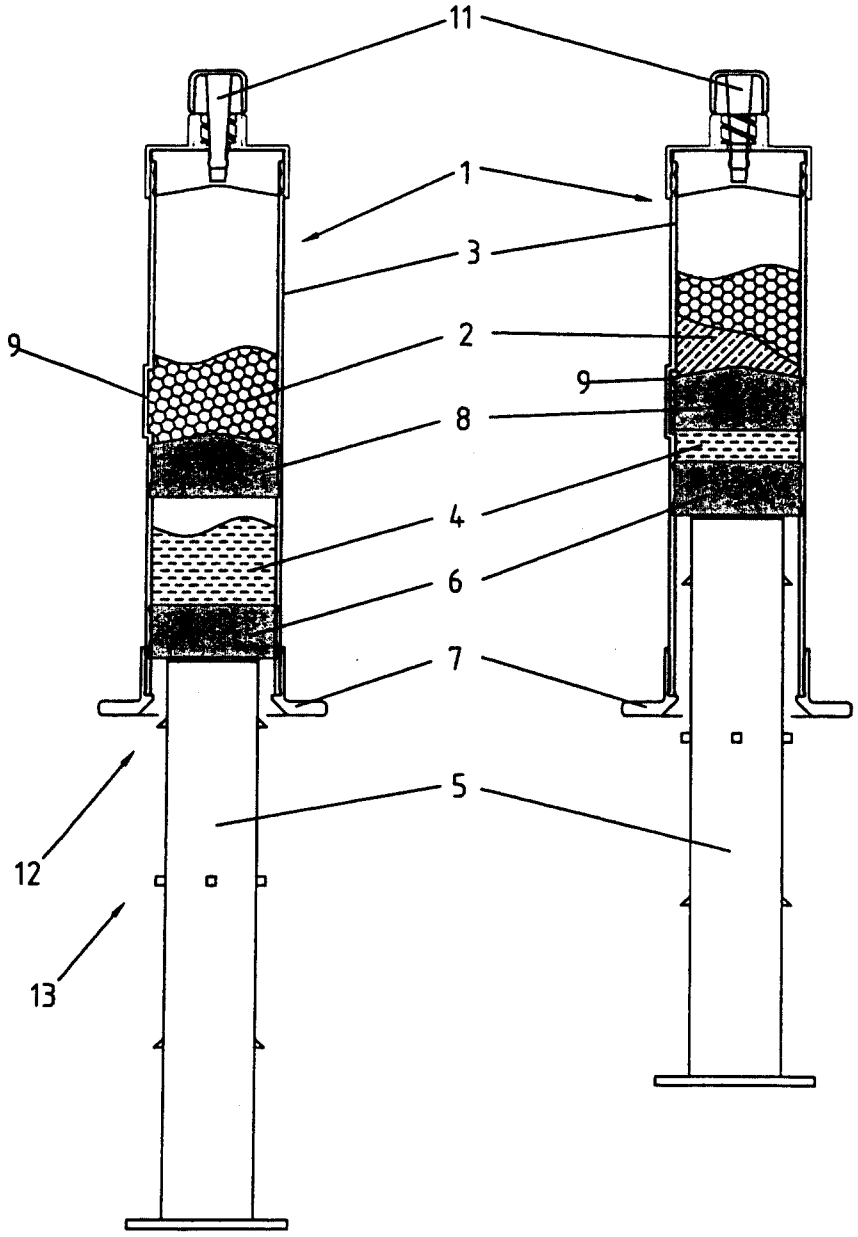


Fig. 8

Fig. 9

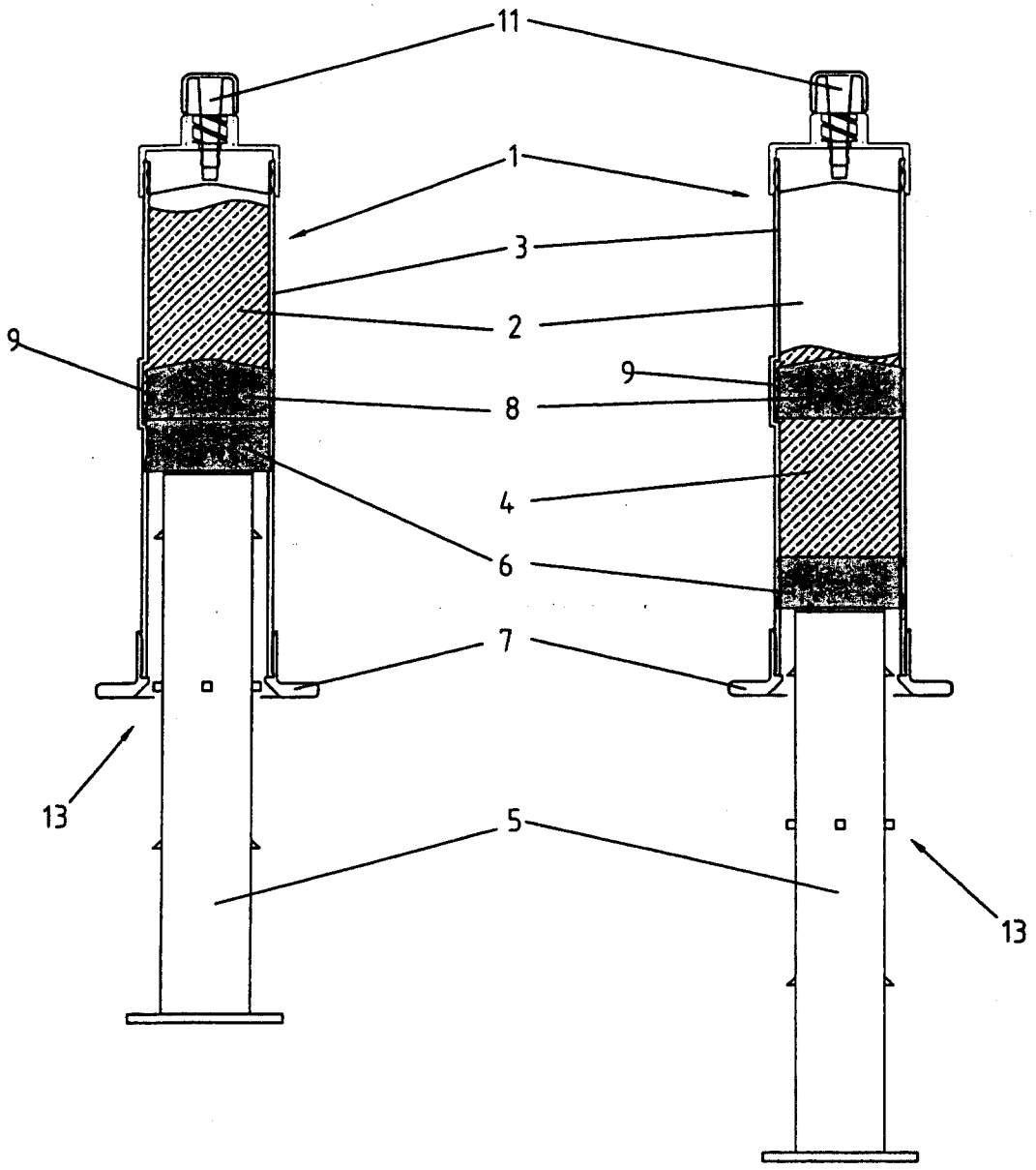


Fig. 10

Fig. 11

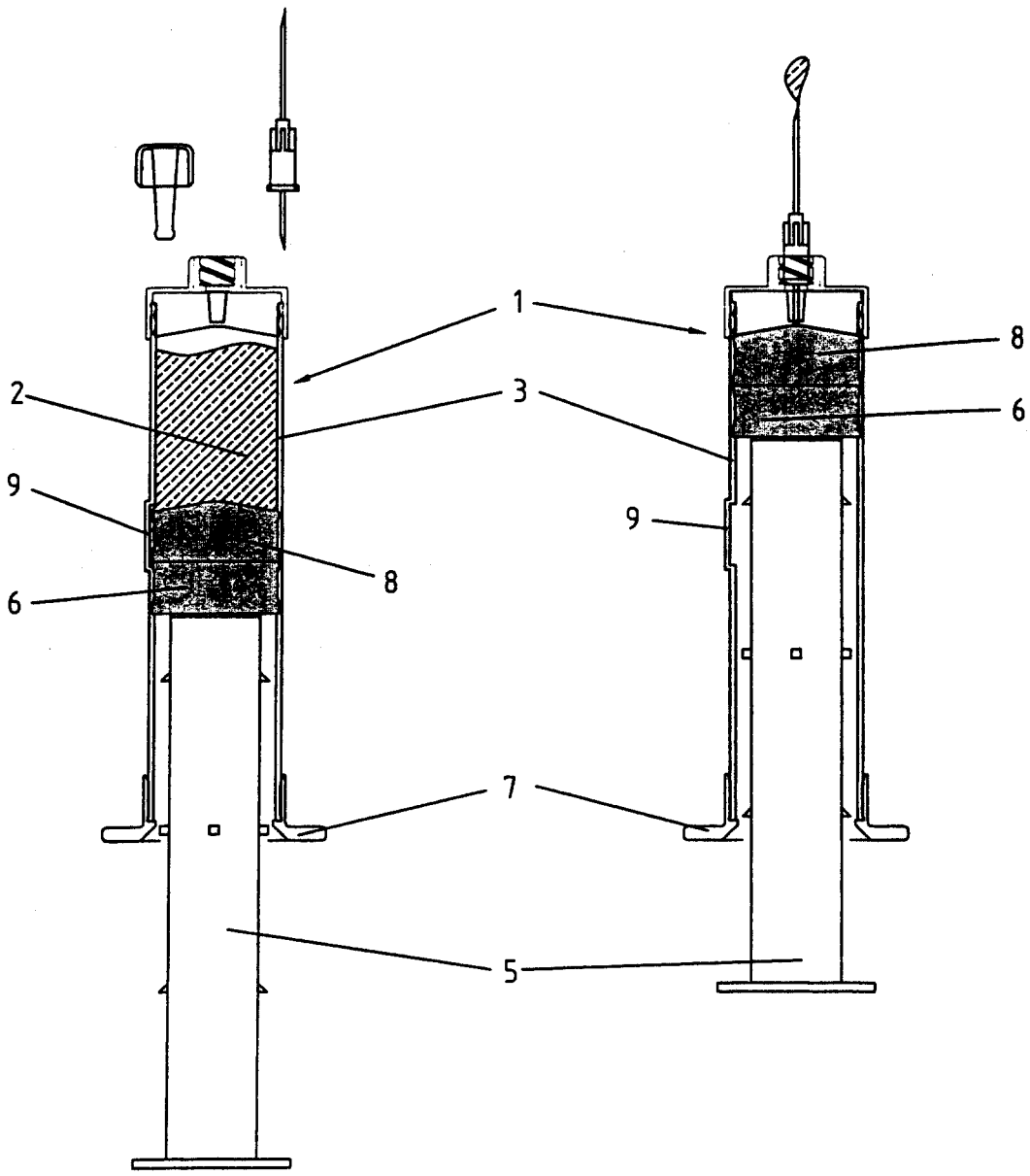
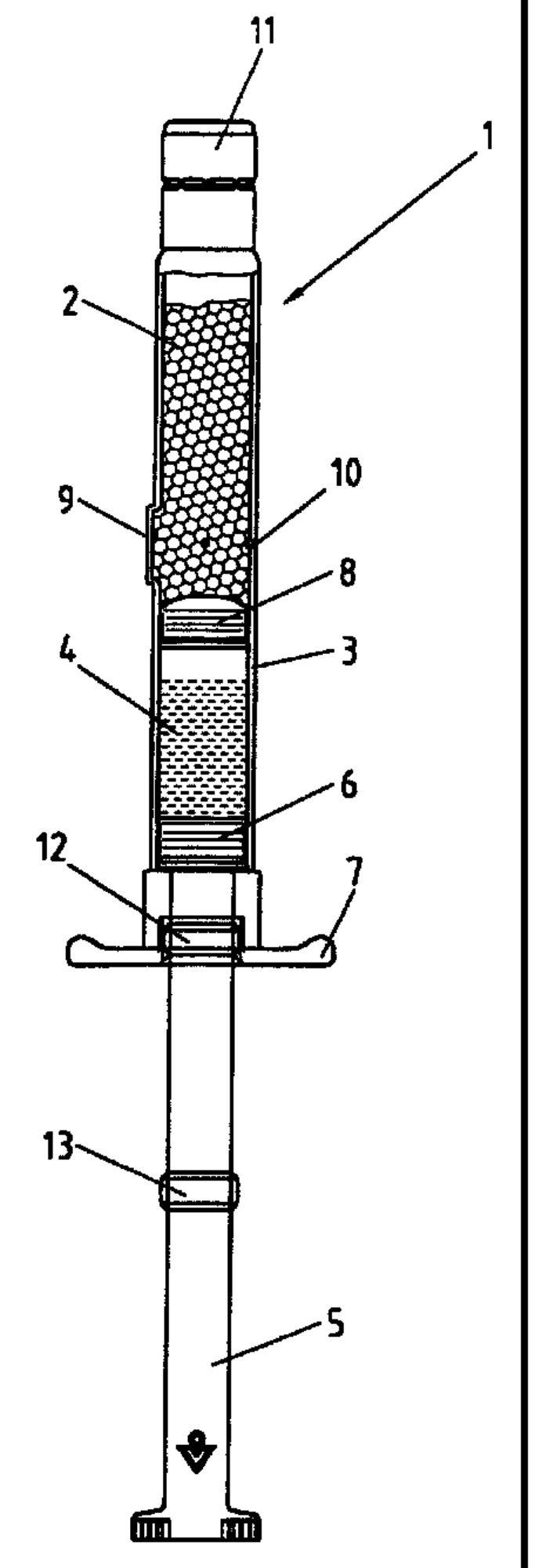


Fig. 12

Fig. 13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