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(54) **SYRINGE**

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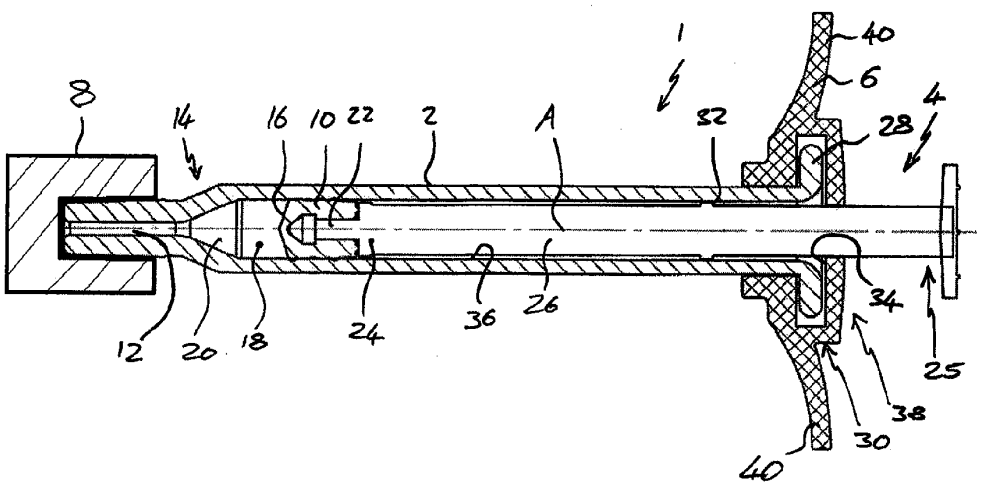
(57) **ABSTRACT**

The present invention relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.



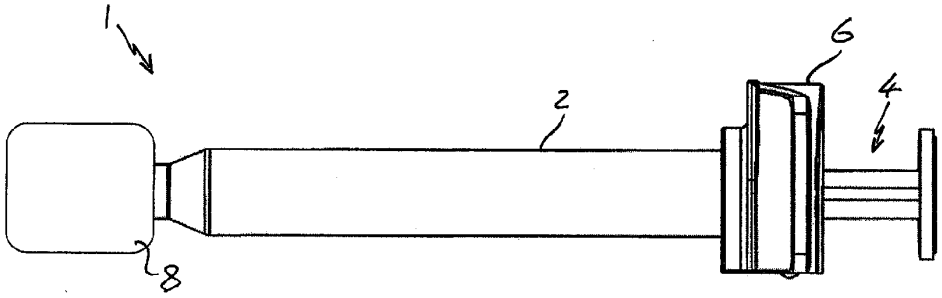


Fig 1

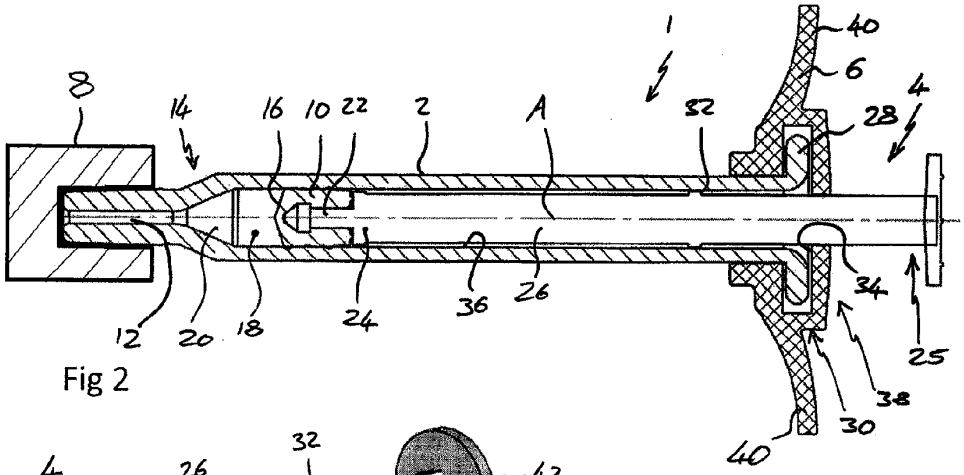


Fig 2

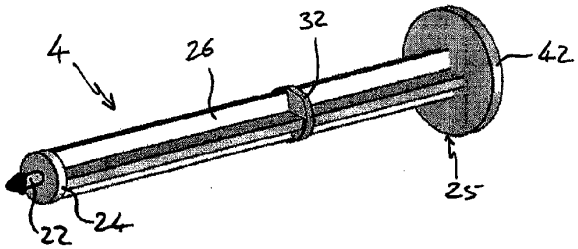


Fig 3

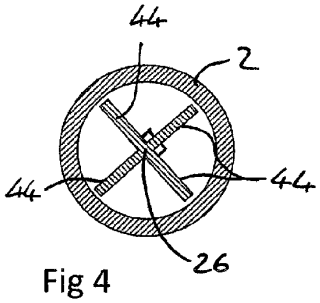


Fig 4

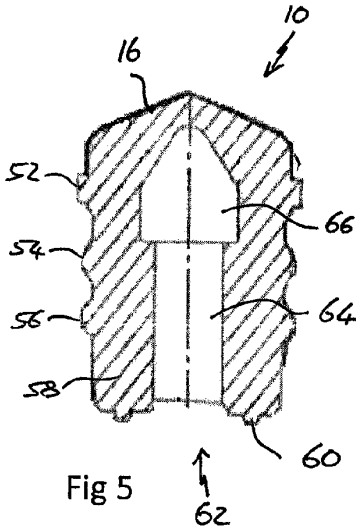


Fig 5

SYRINGE

TECHNICAL FIELD

[0001] The present invention relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.

BACKGROUND ART

[0002] Many medicaments are delivered to a patient in a syringe from which the user can dispense the medicament. If medicament is delivered to a patient in a syringe it is often to enable the patient, or a caregiver, to inject the medicament. It is important for patient safety and medicament integrity that the syringe and the contents of that syringe are sufficiently sterile to avoid infection, or other, risks for patients. Sterilisation can be achieved by terminal sterilisation in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas.

[0003] For small volume syringes, for example those for injections into the eye in which it is intended that about 0.1 ml or less of liquid is to be injected the sterilisation can pose difficulties that are not necessarily associated with larger syringes. Changes in pressure, internal or external to the syringe, can cause parts of the syringe to move unpredictably, which may alter sealing characteristics and potentially compromise sterility. Incorrect handling of the syringe can also pose risks to product sterility.

[0004] Furthermore, certain therapeutics such as biologic molecules are particularly sensitive to sterilisation, be it cold gas sterilisation, thermal sterilisation, or irradiation. Thus, a careful balancing act is required to ensure that while a suitable level of sterilisation is carried out, the syringe remains suitably sealed, such that the therapeutic is not compromised. Of course, the syringe must also remain easy to use, in that the force required to depress the plunger to administer the medicament must not be too high.

[0005] There is therefore a need for a new syringe construct which provides a robust seal for its content, but which maintains ease of use.

DISCLOSURE OF THE INVENTION

[0006] The present invention provides a pre-filled syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid comprises an ophthalmic solution. In one embodiment, the ophthalmic solution comprises a VEGF-antagonist.

[0007] In one embodiment, the syringe is suitable for ophthalmic injections, more particularly intravitreal injections, and as such has a suitably small volume. The syringe may also be silicone oil free, or substantially silicone oil free, or may comprise a low level of silicone oil as lubricant. In one embodiment, despite the low silicone oil level, the stopper break loose and slide force is less than 20N.

[0008] For ophthalmic injections, it is particularly important for the ophthalmic solution to have particularly low particle content. In one embodiment, the syringe meets US Pharmacopeia standard 789 (USP789).

Syringe

[0009] The body of the syringe may be a substantially cylindrical shell, or may include a substantially cylindrical bore with a non circular outer shape. The outlet end of the body includes an outlet through which a fluid housed within the variable volume chamber can be expelled as the volume of said chamber is reduced. The outlet may comprise a projection from the outlet end through which extends a channel having a smaller diameter than that of the variable volume chamber. The outlet may be adapted, for example via a luer lock type connection, for connection to a needle or other accessory such as a sealing device which is able to seal the variable volume chamber, but can be operated, or removed, to unseal the variable volume chamber and allow connection of the syringe to another accessory, such as a needle. Such a connection may be made directly between the syringe and accessory, or via the sealing device. The body extends along a first axis from the outlet end to a rear end.

[0010] The body may be made from a plastic material (e.g. a cyclic olefin polymer) or from glass and may include indicia on a surface thereof to act as an injection guide. In one embodiment the body may comprise a priming mark. This allows the physician to align a pre-determined part of the stopper (such as the tip of the front surface or one of the circumferential ribs, discussed later) or plunger with the mark, thus expelling excess ophthalmic solution and any air bubbles from the syringe. The priming process ensures that an exact, pre-determined dosage is administered to the patient.

[0011] The stopper may be made from rubber, silicone or other suitable resiliently deformable material. The stopper may be substantially cylindrical and the stopper may include one or more circumferential ribs around an outer surface of the stopper, the stopper and ribs being dimensioned such that the ribs form a substantially fluid tight seal with an internal surface of the syringe body. The front surface of the stopper may be any suitable shape, for example substantially planar, substantially conical or of a domed shape. The rear surface of the stopper may include a substantially central recess. Such a central recess could be used to connect a plunger to the stopper using a snap fit feature or thread connection in a known manner. The stopper may be substantially rotationally symmetric about an axis through the stopper.

[0012] The plunger comprises a plunger contact surface and extending from that a rod extends from the plunger contact surface to a rear portion. The rear portion may include a user contact portion adapted to be contacted by a user during an injection event. The user contact portion may comprise a substantially disc shaped portion, the radius of the disc extending substantially perpendicular to the axis along which the rod extends. The user contact portion could be any suitable shape. The axis along which the rod extends may be the first axis, or may be substantially parallel with the first axis.

[0013] The syringe may include a backstop arranged at a rear portion of the body. The backstop may be removable from the syringe. If the syringe body includes terminal flanges at the end opposite the outlet end the backstop may be configured to substantially sandwich terminal flanges of the body as this prevent movement of the backstop in a direction parallel to the first axis.

[0014] The rod may comprise at least one rod shoulder directed away from the outlet end and the backstop may include a backstop shoulder directed towards the outlet end to cooperate with the rod shoulder to substantially prevent movement of the rod away from the outlet end when the backstop shoulder and rod shoulder are in contact. Restriction of the movement of the rod away from the outlet end can help to maintain sterility during terminal sterilisation operations, or other operations in which the pressure within the variable volume chamber or outside the chamber may change. During such operations any gas trapped within the variable volume chamber, or bubbles that may form in a liquid therein, may change in volume and thereby cause the stopper to move. Movement of the stopper away from the outlet could result in the breaching of a sterility zone created by the stopper. This is particularly important for low volume syringes where there are much lower tolerances in the component sizes and less flexibility in the stopper. The term sterility zone as used herein is used to refer to the area within the syringe that is sealed by the stopper from access from either end of the syringe. This may be the area between a seal of the stopper, for example a circumferential rib, closest to the outlet and a seal of the stopper, for example a circumferential rib, furthest from the outlet. The distance between these two seals defines the sterility zone of the stopper since the stopper is installed into the syringe barrel in a sterile environment.

[0015] To further assist in maintaining sterility during the operations noted above the stopper may comprise at a front circumferential rib and a rear circumferential rib and those ribs may be separated in a direction along the first axis by at least 3 mm, by at least 3.5 mm, by at least 3.75 mm or by 4 mm or more. One or more additional ribs (for example 2, 3, 4 or 5 additional ribs, or between 1-10, 2-8, 3-6 or 4-5 additional ribs) may be arranged between the front and rear ribs. In one embodiment there are a total of three circumferential ribs.

[0016] A stopper with such an enhanced sterility zone can also provide protection for the injectable medicament during a terminal sterilisation process. More ribs on the stopper, or a greater distance between the front and rear ribs can reduce the potential exposure of the medicament to the sterilising agent. However, increasing the number of ribs can increase the friction between the stopper and syringe body, reducing ease of use. While this may be overcome by increasing the siliconisation of the syringe, such an increase in silicone oil levels is particularly undesirable for syringes for ophthalmic use.

[0017] The rod shoulder may be arranged within the external diameter of the rod, or may be arranged outside the external diameter of the rod. By providing a shoulder that extends beyond the external diameter of the rod, but still fits within the body, the shoulder can help to stabilise the movement of the rod within the body by reducing movement of the rod perpendicular to the first axis. The rod shoulder may comprise any suitable shoulder forming elements on the rod, but in one embodiment the rod shoulder comprises a substantially disc shaped portion on the rod.

[0018] In one embodiment of the syringe, when arranged with the plunger contact surface in contact with the stopper and the variable volume chamber is at its intended maximum volume there is a clearance of no more than about 2 mm between the rod shoulder and backstop shoulder. In some embodiments there is a clearance of less than about 1.5 mm and in some less than about 1 mm. This distance is selected to substantially limit or prevent excessive rearward (away from the outlet end) movement of the stopper.

[0019] In one embodiment the variable volume chamber has an internal diameter greater than 5 mm or 6 mm, or less than 3 mm or 4 mm. The internal diameter may be between 3 mm and 6 mm, or between 4 mm and 5 mm.

[0020] In another embodiment the syringe is dimensioned so as to have a nominal maximum fill volume of between about 0.1 ml and about 1.5 ml. In certain embodiments the nominal maximum fill volume is between about 0.5 ml and about 1 ml. In certain embodiments the nominal maximum fill volume is about 0.5 ml or about 1 ml, or about 1.5 ml.

[0021] The length of the body of the syringe may be less than 70 mm, less than 60 mm or less than 50 mm. In one embodiment the length of the syringe body is between 45 mm and 50 mm.

[0022] In one embodiment, the syringe is filled with between about 0.01 ml and about 1.5 ml (for example between about 0.05 ml and about 1 ml, between about 0.1 ml and about 0.5 ml, between about 0.15 ml and about 0.175 ml) of a VEGF antagonist solution. In one embodiment, the syringe is filled with 0.165 ml of a VEGF antagonist solution. Of course, typically a syringe is filled with more than the desired dose to be administered to the patient, to take into account wastage due to "dead space" within the syringe and needle. There may also be a certain amount of wastage when the syringe is primed by the physician, so that it is ready to inject the patient.

[0023] Thus, in one embodiment, the syringe is filled with a dosage volume (i.e. the volume of medicament intended for delivery to the patent) of between about 0.01 ml and about 1.5 ml (e.g. between about 0.05 ml and about 1 ml, between about 0.1 ml and about 0.5 ml) of a VEGF antagonist solution. In one embodiment, the dosage volume is between about 0.03 ml and about 0.05 ml. For example, for Lucentis, the dosage volume is 0.05 ml or 0.03 ml (0.5 mg or 0.3 mg) of a 10 mg/ml injectable medicament solution; for Eylea, the dosage volume is 0.05 ml of a 40 mg/ml injectable medicament solution. Although unapproved for ophthalmic indications, bevacizumab is used off-label in such ophthalmic indications at a concentration of 25 mg/ml; typically at a dosage volume of 0.05 ml (1.25 mg). In one embodiment, the extractable volume from the syringe (that is the amount of product obtainable from the syringe following filling, taking into account loss due to dead space in the syringe and needle) is about 0.09 ml.

[0024] In one embodiment the length of the syringe body is between about 45 mm and about 50 mm, the internal diameter is between about 4 mm and about 5 mm, the till volume is between about 0.12 and about 0.3 ml and the dosage volume is between about 0.03 ml and about 0.05 ml.

[0025] As the syringe contains a medicament solution, the outlet may be reversibly sealed to maintain sterility of the medicament. This sealing may be achieved through the use of a sealing device as is known in the art. For example the OVS™ system which is available from Vetter Pharma International GmbH.

[0026] It is typical to siliconise the syringe in order to allow ease of use, i.e. to apply silicone oil to the inside of the barrel, which decreases the force required to move the stopper. However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including

"floaters" and an increase in intra-ocular pressure. Furthermore, silicone oil can cause proteins to aggregate. A typical 1 ml syringe comprises 100-800 μg silicone oil in the barrel, though a survey of manufacturers reported that 500-1000 μg was typically used in pre-filled syringes (Badkar et al. 2011, AAPS PharmaSciTech, 12(2):564-572). Thus, in one embodiment, a syringe according to the invention comprises less than about 800 μg (i.e. about less than about 500 μg, less than about 300 μg, less than about 200 μg, less than about 100 μg, less than about 75 μg, less than about 50 μg, less than about 25 μg, less than about 15 μg, less than about 10 μg) silicone oil in the barrel. If the syringe comprises a low level of silicone oil, this may be more than about 1 μg, more than about 3 μg, more than about 5 μg, more than about 7 μg or more than about 10 μg silicone oil in the barrel. Thus, in one embodiment, the syringe may comprise about 1 μg-about 500 μg, about 3 μg-about 200 μg, about 5 μg-about 10 μg or about 10 μg-about 50 μg silicone oil in the barrel. Methods for measuring the amount of silicone oil in such a syringe barrel are known in the art and include, for example, differential weighing methods and quantitation by infrared-spectroscopy of the oil diluted in a suitable solvent. Various types of silicone oil are available, but typically either DC360 (Dow Corning®; with a viscosity of 1000 cP) or DC365 emulsion (Dow Corning®; DC360 oil with a viscosity of 350 cP) are used for syringe siliconisation. In one embodiment, the pre-filled syringe of the invention comprises DC365 emulsion.

[0027] During testing it was surprisingly found that, for syringes having small dimensions, such as those discussed above, and particularly those described in conjunction with the Figures below, the break loose and sliding forces for the stopper within the syringe are substantially unaffected by reducing the siliconisation levels far below the current standard to the levels discussed here. This is in contrast to conventional thinking that would suggest that if you decrease the silicone oil level, the forces required would increase (see e.g. Schoenknecht. AAPS National Biotechnology Conference 2007—Abstract no. NBC07-000488, which indicates that while 400 μg silicone oil is acceptable, usability improves when increased to 800 μg). Having too great a force required to move the stopper can cause problems during use for some users, for example accurate dose setting or smooth dose delivery may be made more difficult if significant strength is required to move, and/or keep in motion, the stopper. Smooth administration is particularly important in sensitive tissues such as the eye, where movement of the syringe during administration could cause local tissue damage. Break loose and slide forces for pre-filled syringes known in the art are typically in the region of less than 20N, but where the pre-filled syringes contain about 100 μg-about 800 μg silicone oil. In one embodiment the glide/slide force for the stopper within the pro-filled syringe is less than about 11N or less than 9N, less than 7N, less than 5N or between about 3N to 5N. In one embodiment, the break loose force is less than about 11N or less than 9N, less than 7N, less than 5N or between about 2N to 5N. Note that such measurements are for a filled syringe, rather than an empty syringe. The forces are typically measured at a stopper travelling speed of 190 mm/min. In one embodiment, the forces are measured with a 30G×0.5 inch needle attached to the syringe. In one embodiment, the syringe has a nominal maximal fill volume of between about 0.5 ml and 1 ml, contains less than about 100 μg silicone oil and has a break loose force between about 2N to 5N.

[0028] In one embodiment the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450 nm or less (i.e. 400 nm or less, 350 nm or less, 300 nm or less, 200 nm or less, 10 nm or less, 50 nm or less, 20 nm or less). Methods to measure the thickness of silicone oil in a syringe are known in the art and include the rap.ID Layer Explorer® Application, which can also be used to measure the mass of silicone oil inside a syringe barrel.

[0029] In one embodiment, the syringe is silicone oil free, or substantially silicone oil free. Such low silicone oil levels can be achieved by using uncoated syringe barrels and/or by avoiding the use of silicone oil as a lubricant for product contacting machine parts, or pumps in the syringe assembly and fill line. A further way to reduce silicone oil and inorganic silica levels in a pre-filled syringe is to avoid the use of silicone tubing in filling lines, for example between storage tanks and pumps.

[0030] The syringe according to the invention may also meet certain requirements for particulate content. In one embodiment, the ophthalmic solution comprises no more than 2 particles ≥50 μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 5 particles ≥25 μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 50 particles ≥10 μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 2 particles ≥50 μm in diameter per ml, no more than 5 particles ≥25 μm in diameter per ml and no more than 50 particles ≥10 μm in diameter per ml. In one embodiment, a syringe according to the invention meets USP789 (United States Pharmacopoeia: Particulate Matter in Ophthalmic Solutions). In one embodiment the syringe has low levels of silicone oil sufficient for the syringe to meet USP789.

VEGF Antagonists

Antibody VEGF Antagonists

[0031] VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and bevacizumab (Avastin®).

Non-Antibody VEGF Antagonist

[0032] In one aspect of the invention, the non-antibody VEGF antagonist is an immunoadhesin. One such immuoadhesin is aflibercept (Eylea®), which has recently been approved for human use and is also known as VEGF-trap (Holash et al. (2002) *PNAS USA* 99:11393-98; Riely & Miller (2007) *Clin Cancer Res* 13:4623-7s). Aflibercept is the preferred non-antibody VEGF antagonist for use with the invention. Aflibercept is a recombinant human soluble VEGF receptor fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. It is conveniently produced as a glycoprotein by expression in recombinant CHO K1 cells. Each monomer can have the following amino acid sequence (SEQ ID NO: 1):

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