

Technical Field

Background Art

[0003] Also, although it is not the syringe-based squirt, an airless spray container (e.g., rhinal spray container) has also been proposed to apply a viscous pharmaceutical formulation to a rhinal mucosal membrane. For example, Patent Document 2 (JP 5185109 B) discloses an upside back-

pressure airless spray container being operable to control a spray angle and a spray distribution in a desired range thereof when spraying a gel base material comprising carboxy vinyl polymer which was treated by applying an
5 exogenous shear force.

Summary of Invention

Problems to be solved by Invention

[0004] The airless spray container being capable of delivering a multiple metered-dose formulation has an
10 advantage in containing and storing a plurality of formulation doses therein. However in case where the pharmaceutical formulation is used as a prophylaxis or a therapeutic medication for an infectious disease, most of patients or vaccine recipients feel less comfortable and
15 less sanitary to share the airless spray container with the nozzle inserted within their nasal cavities, which may also cause any other infectious diseases (in-hospital infections).

[0005] The present inventors have considered to use the
20 metered-dose syringe squirt of the aforementioned Patent Document 1 for spraying the formulation containing the gel base material comprising carboxy vinyl polymer treated by applying an exogenous shear force. However because the metered-dose syringe squirt has a basic structure different
25 from that of the upside back-pressure airless spray

container (especially the spray nozzle thereof) disclosed in the aforementioned Patent Document 2, a particular spray characteristics such as a particle size distribution of formulation, an uniform spray geometry, and a spray angle which is required for a targeted pharmaceutical benefits of the formulation has not been achieved so far.

[0006] To address the aforementioned drawbacks, the present inventors has finally made the present invention after finding an optimized shape and configuration of the nozzle of the metered-dose syringe-based squirt for spraying the viscous formulation having pre-described features to the rhinal mucosal membrane.

Means to Solve the Problems

[0007] One of aspects of the present invention is to provide a rhinal spray nozzle used for a medical syringe having a tip opening in fluid communication with a syringe barrel for storing a formulation, the rhinal spray nozzle comprises a hollow nozzle body having a tip portion defining a nozzle orifice thereon, a solid packing rod arranged within the nozzle body, and a nozzle chamber defined between the packing rod and the nozzle body to allow a fluid communication between the tip opening and the nozzle orifice, wherein the formulation comprises the gel material containing viscosity modification agent and carboxy vinyl polymer of which viscosity is modified by

applying an exogenous shear force, and wherein the nozzle orifice has a diameter in a range between 0.25 mm and 0.30 mm.

5 **[0008]** Preferably, the formulation comprises the gel material containing the viscosity modification agent such as sodium chloride or potassium chloride), a pH buffer solution such as dibasic sodium phosphate hydrate and sodium dihydrogenphosphate, and a neutralizing agent such as L-Arginine and sodium hydroxide, of which viscosity is
10 modified by applying an exogenous shear force.

[0009] Also preferably the nozzle orifice includes substantially no curved portion, and the tip portion has thickness along an injection direction of the formulation which is in a range between 0.20 mm and 0.30 mm.

15 **[0010]** Also preferably the nozzle body includes an inner wall having at least a portion formed in a cylindrical shape and the packing rod includes an outer wall at least a portion formed in a cylindrical shape having a plurality of circumferentially spaced grooves, the nozzle chamber is
20 defined between the at least portion of the inner wall of the nozzle body and the at least portion of the outer wall of the packing rod, and the packing rod includes a vortex-flow generation member opposed to the tip portion of the nozzle body. The vortex-flow generation member formed so
25 that a flow direction of the formulation from the grooves

of the packing rod may be offset to a central axis, thereby to generate a vortex flow of the formulation. Also preferably, the at least portion of the inner wall of the nozzle body is formed to have a cross section perpendicular to the injection direction continuously or step-wisely reducing towards the injection direction.

[0011] The gel material preferably has a viscosity of 2500 mPas or more, and more preferably 1000 mPas or more. Preferably a spray angle of the formulation sprayed from the nozzle orifice is in a range 45 degrees and 60 degrees, an average particle size of formulation droplets sprayed from the nozzle orifice is in a range 50 microns and 80 microns. Also preferably, counts of formulation droplets sprayed from the nozzle orifice having the particle size in a range between 10 to 100 microns are 70% or more of the total counts of the particle.

Advantages of Invention

[0012] According to the present invention, it is advantageous to achieve the given spray characteristics (a particle size distribution, an uniform spray geometry, and a spray angle) required to obtain a pharmaceutical benefits of the formulation comprising the gel material containing viscosity modification agent and carboxy vinyl polymer of which viscosity is modified by applying an exogenous shear force.

Brief Description of Drawings

[0013] Fig. 1 is a partially-fragmented side view of a general structure of a medical syringe comprising a rhinal spray nozzle of one embodiment according to the present invention.

[0014] Figs. 2A and 2B are partially-fragmented perspective views of the general structure of the rhinal spray nozzle of one embodiment of the present invention, showing configurations before and after the packing rod are inserted within the nozzle body, respectively.

[0015] Fig. 3A is a vertical cross-sectional view of the rhinal spray nozzle of Fig. 2B, and Figs. 3B, 3C and 3D are horizontal cross-sectional views of the rhinal spray nozzle taken along B-B line, C-C line and D-D line of Fig. 3A, respectively.

[0016] Figs. 4A and 4B are enlarged cross-sectional views of the tip portion of the nozzle body, in which the tip portion is provided with the curved portion in Fig. 4A but not in Fig. 4B.

[0017] Fig 5 shows spray patterns of the formulation sprayed from the nozzle orifice of Example 1.

[0018] Fig 6 shows a spray angle of the formulation sprayed from the nozzle orifice of Example 1.

[0019] Fig 7 shows a particle size distribution of the formulation sprayed from the nozzle orifice of Example 1.

[0020] Fig 8 shows the spray patterns of the formulation comprising the base materials A in the metered-dose syringe-based squirt provided with various rhinal spray nozzles, and also indicate whether the combination of the
5 base material and the rhinal spray nozzles is acceptable or not.

[0021] Fig 9 shows the spray patterns of the formulation comprising the base materials B1 in the metered-dose syringe-based squirt provided with various rhinal spray
10 nozzles.

[0022] Fig 10 shows the spray patterns of the formulation comprising the base materials C1 in the metered-dose syringe-based squirt provided with various rhinal spray nozzles.

15 [0023] Fig 11 shows the spray patterns of the formulation comprising the base materials C2 in the metered-dose syringe-based squirt provided with various rhinal spray nozzles.

[0024] Fig 12 shows the spray patterns of the
20 formulation comprising the base materials D in the metered-dose syringe-based squirt provided with various rhinal spray nozzles.

[0025] Fig 13 shows the spray patterns of the formulation comprising the base materials E1 in the
25 metered-dose syringe-based squirt provided with various

rhinal spray nozzles.

[0026] Fig 14 shows the spray patterns of the formulation comprising the base materials E2 in the metered-dose syringe-based squirt provided with various
5 rhinal spray nozzles.

[0027] Fig 15 shows the spray patterns of the formulation comprising the base materials E4 in the metered-dose syringe-based squirt provided with various rhinal spray nozzles.

10 **Description of Embodiments**

[0028] With reference to attached drawings, embodiments of a rhinal spray nozzle used for a medical syringe according to the present invention will be described hereinafter. In the following description, directional
15 terms such as "front", "rear", "proximal" and "distal" are conveniently used for better understandings, however those terms are not intended to limit the scope of the present invention. Also, like components are denoted by like reference signs throughout the attached drawings.

20 **[0029] [Medical Syringe]**

Fig. 1 is a partially-fragmented side view of a medical syringe 1 comprising a rhinal spray nozzle 10 of an embodiment according to the present invention. As illustrated in Fig. 1, the medical syringe 1 generally
25 comprises a syringe body 4 made of synthetic resin or glass

having a syringe barrel 3 capable of storing a pharmaceutical formulation therein, and a plunger rod 5 inserted within the syringe barrel 3 of the syringe body 4. The medical syringe 1 also comprises a piston 7 having a fixing member 5a provided at the distal end of the plunger rod 5 and sliding within the syringe barrel 3 so as to pump the formulation in the syringe barrel 3 out of a distal tip opening 6 of the syringe body 4, a finger flange 8 provided around a proximal end of the syringe body 4, and a plunger end member 9 transmitting the force applied by a practitioner such as a medical doctor to the plunger rod 5. The medical syringe 1 may be similar to the metered-dose syringe-based squirt of the aforementioned Patent Document 1.

[0030] It should be noted that the rhinal spray nozzle 10 of the present invention may be applicable to any type of the medical syringes 1 which pump the formulation in the syringe barrel 3 by pushing the plunger rod 5 (and the piston 7), and thus, the present invention will not be limited to the known configurations of the medical syringe. Therefore, the present disclosure will eliminate further description for the detailed structure of the medical syringe (or the metered-dose syringe-based squirt) 1, and discuss in more detail about the structure and the function of the rhinal spray nozzle 10 used for the medical syringe.

It should be noted that the disclosure of the aforementioned Patent Document 1 is incorporated herein by reference into the present application.

[0031] [Rhinal Spray Nozzle]

5 As shown in Fig. 1, the medical syringes 1 further comprises the rhinal spray nozzle 10 opposed to the tip opening 6 of the syringe body 4, and a protection cap 50 for protecting a sterilized tip portion 22 of the rhinal spray nozzle 10 from contaminant and mechanical impact.

10 Figs. 2A and 2B are partially-fragmented perspective views, showing the general structure of the rhinal spray nozzle 10 of an embodiment of the present invention. As shown, the rhinal spray nozzle 10 generally comprises a hollow nozzle body 20 having the tip portion 22 with a nozzle orifice 21 and a solid packing rod (packing bar) 30 provided within
15 the nozzle body 20. Figs. 2A and 2B show the rhinal spray nozzle 10 before and after the packing rod 30 is arranged or inserted within the nozzle body 20, respectively. The tip portion 22 of the nozzle body 20 has a circular shape
20 and is provided with the nozzle orifice 21 at the center thereof.

[0032] Fig. 3A is a vertical cross-sectional view of the rhinal spray nozzle 10 of Fig. 2B. Figs. 3B, 3C and 3D are horizontal cross-sectional views of the rhinal spray nozzle
25 10 taken along B-B line, C-C line and D-D line of Fig. 3A,

respectively. The hollow nozzle body 20 defines an internal space 24 of a substantially cylindrical shape. As shown in Figs. 3C and 3D, the internal space 24 includes a nozzle small-diameter portion 25 closer to the nozzle orifice 21 of the hollow nozzle body 20, a nozzle large-diameter portion 26 opposing to the tip opening 6 of the syringe body 4, and a nozzle shoulder 27 which is designed to have a diameter continuously or step-wisely reducing from the nozzle large-diameter portion 26 towards the nozzle small-diameter portion 25.

[0033] On the other hand, the solid packing rod 30 to be inserted within the nozzle body 20 has an outer wall 33 having a configuration substantially complementary with an inner wall 23 of the nozzle body 20 (internal space 24). As shown in Figs. 2A, 3C and 3D, a rod small-diameter portion 35 and a rod large-diameter portion 36 include shoulder 37 which is designed to have a diameter continuously or step-wisely reducing from a rod large-diameter portion 36 towards a rod small-diameter portion 35.

[0034] Preferably, as illustrated in Fig. 3A, the inner wall 23 of the nozzle body 20 is provided with a protrusion 23a, while the outer wall 33 of the packing rod 30 is provided with a recess 33a for receiving the protrusion 23a. When the packing rod 30 is fully inserted within the internal space 24 of the nozzle body 20, the protrusion 23a

may be closely fit in the recess 33a to ensure connection between the packing rod 30 and the nozzle body 20.

[0035] Also as illustrated in Figs. 2A-2B and 3A-3D, the packing rod 30 includes a plurality of grooves 38, 39
5 circumferentially spaced from one another both on the rod small-diameter portion 35 and the rod large-diameter portion 36. Also, the packing rod 30 is inserted within the nozzle body 20 so as to define a gap 40 between the nozzle shoulder 27 and the rod shoulder 37 (Fig. 3A). Thus,
10 the rhinal spray nozzle 10 assembled as illustrated in Fig. 2B has a nozzle chamber 42 defined by the grooves 38, 39 and the gap 40 which allows fluid communication of the formulation 2 delivered from the tip opening 6 of the syringe body 4 through the nozzle chamber 42 to the tip
15 portion 22 of the rhinal spray nozzle 10.

[0036] Furthermore, as shown in Fig. 3B, the packing rod 30 includes a vortex-flow generation member 44 opposed to the tip portion 22 of the rhinal spray nozzle 10. The vortex-flow generation member 44 is configured to generate
20 a vortex flow of the formulation 2 that is delivered from each of the grooves 38 of the rod small-diameter portion 35 before being injected from the nozzle orifice 21 of the nozzle body 20. More particularly, the end portions of the rod small-diameter portion 35 which define the vortex-flow
25 generation member 44 are formed so as to extend offset the

vertical central axis of the nozzle orifice 21. Thanks to generation of the vortex flow of the formulation 2 before being injected from the nozzle orifice 21, the spray angle of the formulation 2 can be expanded to spray it in a more uniform manner.

5 [0037] As illustrated in Figs. 3C-3D, it is preferable to design the grooves 38 of the rod small-diameter portion 35 to be less than the grooves 39 of the rod large-diameter portion 36 so as to increase the pressure of the formulation 2 in the vortex-flow generation member 44 before being injected from the nozzle orifice 21. Also, thanks to the diameters of the rod large-diameter portion 36 and the rod small-diameter portion 35 which are designed to continuously or step-wisely be reduced from the former to the latter, it is easier to insert the rhinal spray nozzle 10 deeply into the nasal cavity and to spray the formulation towards the inferior nasal concha and even deeper portions of the patient. Thus preferably, the diameter of the rod small-diameter portion 35 is smaller enough than the nasal cavity opening of the patient without minimizing fear of the patient.

15 [0038] [Optimal Spray of Formulation into Nasal Cavity]

In general, when a fluid such as a phosphate buffered saline (PBS) having substantially no viscosity is sprayed towards the inferior nasal concha by means of the medical

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syringe 1 through the rhinal spray nozzle 10 of the above embodiment, the fluid immediately comes out from the nasal cavity or runs out from the uvula pharyngeal portion through the inferior nasal meatus of the patient, because of lack of retention characteristic of the fluid. Thus, in order to keep the sprayed formulation retained on the inferior nasal concha of the patient, the formulation is required to have a predetermined viscosity. Also in general, the viscosity of the formulation is likely reduced during passing through the spray nozzle, and therefore, in order to maintain the desired spray retention characteristic of the formulation, it is necessary to maintain the viscosity thereof not only before being sprayed but also immediately after being sprayed.

[0039] Also, besides the spray retention characteristic, appropriate characteristics for an uniform spray geometry, a spray angle, and a particle size distribution (i.e., an average particle size) of the formulation are required when it is applied by the medical syringe 1 using the rhinal spray nozzle 10. In particular, the uniform spray geometry of the formulation is referred to as a characteristic where the sprayed formulation is distributed in a substantially uniform concentration, and is evaluated with a sprayed pattern on a plane arranged perpendicularly to the spraying direction of the formulation injected from the nozzle

orifice 21. Thus, the present disclosure evaluates the sprayed pattern as being acceptable (abbreviated as "OK") with the formulation for the rhinal spray nozzle 10 of the present invention when having substantially a circular or full-cone shape as illustrated in Fig. 5, and as being unacceptable (abbreviated as "NG") when having an oblong or hollow-cone shape.

[0040] The spray angle is referred to as the maximum dispersing angle of the sprayed formulation droplet (which may be referred to as a "formulation particle"), and the present disclosure evaluates the spray angle as being acceptable (abbreviated as "OK") with the formulation for the rhinal spray nozzle 10 of the present invention when the formulation falls within a range between 40 to 60 degrees.

[0041] Furthermore in general, the formulation particles cannot be delivered to the inferior nasal concha of the patient when being too big, meanwhile they are likely inhaled to the bronchi and/or the lung of the patient upon breathing when being too fine. In either case, the expected therapeutic benefits of the formulation cannot be achieved. Therefore, the present disclosure evaluates the average particle size as being acceptable (abbreviated as "OK") with the formulation for the rhinal spray nozzle 10 of the present invention when the average particle size

falls within a range between 50 to 80 microns and the counts of the particles having the particle size in a range between 10 to 100 microns are 70% or more of the total counts of the particles.

5 **[0042]** [Examples]

As will be described in detail, several rhinal spray nozzles 10 having different sizes and/or shapes which is used for the medical syringe 1 were prepared to evaluate whether the rhinal spray nozzles 10 are acceptable or not
10 (OK or NG) when spraying various formulations containing the gel base materials, by checking the viscosity and/or viscosity retention rate (or the spray retention characteristic), the spray uniformity (or the spray pattern), the spray angle, and the average particle size of
15 the formulations.

[0043] [Preparation of Rhinal Spray Nozzles]

Several rhinal spray nozzles 10a-10k capable of being connected to the medical syringe 1 of the aforementioned embodiment were produced, by modifying the diameter (ϕ) of
20 the nozzle orifice 21 and the thickness (d) of the tip portion 22 along the injection direction of the formulation, and by providing a curved portion or not on the tip portion 22 (yes or no).

[0044] [Table 1]

	Nozzle a	Nozzle b	Nozzle c	Nozzle d	Nozzle e	Nozzle f	Nozzle g	Nozzle h	Nozzle i	Nozzle j	Nozzle k
orifice diameter ϕ	0.25	0.25	0.26	0.3	0.3	0.3	0.3	0.4	0.4	0.45	0.55
thickness d	0.15	0.25	0.25	0.13	0.2	0.3	0.25	0.25	0.25	0.25	0.25
curved portion	no	no	yes	no	no	no	yes	no	yes	no	no
(unit : mm)											

[0045] Figs. 4A and 4B are enlarged cross-sectional views of the tip portion 22 of the nozzle body 20, in which the tip portion 22 is provided with the curved portion 46 in Fig. 4A (yes) but not in Fig. 4B (no). Each of the rhinal spray nozzles 10a-10k includes the nozzle orifices 21 having the diameters (ϕ) in the range between 0.25 mm to 0.55 mm, and the tip portion 22 having the thickness (d) in the range between 0.13 mm to 0.30 mm along the injection direction of the formulation. The rhinal spray nozzles 10c, 10g, 10i each have the curved portion 46 with the tip portion 22 as illustrated in Fig. 4A.

[0046] [Preparation of Various Formulations Containing Base Material]

Next, various formulations to be sprayed by means of the medical syringe 1 with the aforementioned rhinal spray nozzles 10 were prepared in following prescriptions.

[Base Material A]:

a phosphate buffered saline (Reference example),

[Base Material B]:

a base material obtained by modifying an amount of carboxy vinyl polymer to have a given viscosity,

[Base Material C]:

5 a base material obtained by adding a viscosity modification agent (sodium chloride) to have a given viscosity,

[Base Material D]:

a base material obtained by applying an exogenous shear force to have a given viscosity, and

10 [Base Material E]:

a base material obtained adding a viscosity modification agent (sodium chloride) and by applying an exogenous shear force to have a given viscosity.

[0047] With respect to the base materials D and E, the
15 exogenous shear force may be applied in any process, and although not limited thereto, it may be applied by preparing, mixing components of the base material, blending them to be homogeneous, and rotating it at a relatively high speed by means of an intermittent jet stream
20 generation type high-speed emulsification device. Also the base materials so processed may further be heat-treated and sterilized in an atmosphere of high-pressure steam.

[0048] [Table 2]

Base Material A (Reference Example)	
Phosphate Buffered Saline	
Viscosity	1 mPas
Viscosity Retention Rate	(N/A)

[0049] [Table 3]

Base Material B1		Base Material B2	
Carboxy Vinyl Polymer	0.07425 wt%	Carboxy Vinyl Polymer	0.0557 wt%
L-Arginine	0.08505 wt%	L-Arginine	0.0942 wt%
Purified Water	99.8407 wt%	Purified Water	99.8501 wt%
Viscosity	2500 mPas	Viscosity	1000 mPas
Viscosity Retention Rate	28.4 %	Viscosity Retention Rate	17.5 %
prepared by modifying an amount of carboxy vinyl polymer to have viscosity of 2500 mPs		prepared by modifying an amount of carboxy vinyl polymer to have viscosity of 1000 mPs	

5 [0050] [Table 4]

Base Material C1		Base Material C2	
Carboxy Vinyl Polymer	0.5 wt%	Carboxy Vinyl Polymer	0.5 wt%
L-Arginine	1.0 wt%	L-Arginine	1.0 wt%
Sodium Chloride	0.5 wt%	Sodium Chloride	0.5 wt%
Purified Water	98.0 wt%	Ethanol	0.5 wt%
		Purified Water	97.5 wt%
Viscosity	2400 mPas	Viscosity	2400 mPas
Viscosity Retention Rate	82.6 %	Viscosity Retention Rate	81.6 %
prepared by adding a viscosity modification agent (Sodium Chloride) to have viscosity of 2400 mPa		prepared by adding a viscosity modification agent (Sodium Chloride) to have viscosity of 2400 mPa and by adding an ethanol for improving spray pattern	
Base Material C3			
Carboxy Vinyl Polymer	0.375 wt%		
L-Arginine	0.7 wt%		
Sodium Chloride	0.25 wt%		
Purified Water	98.675 wt%		
Viscosity	1000 mPas		
Viscosity Retention Rate	76.5 %		
prepared by adding a viscosity modification agent (Sodium Chloride) to have viscosity of 1000 mPa			

[0051] [Table 5]

Base Material D	
Carboxy Vinyl Polymer	0.5 wt%
L-Arginine	1.0 wt%
Purified Water	98.5 wt%
Viscosity	2500 mPas
Viscosity Retention Rate	99.5 %
prepared by applying an exogenous shear force to have a viscosity of 2500 mPa	

[0052] [Table 6]

Base Material E1		Base Material E2	
Carboxy Vinyl Polymer	0.5 wt%	Carboxy Vinyl Polymer	0.5 wt%
L-Arginine	1.0 wt%	L-Arginine	1.0 wt%
Sodium Chloride	0.25 wt%	Sodium Chloride	0.25 wt%
Purified Water	98.25 wt%	Ethanol	0.5 wt%
Viscosity	2500 mPas	Purified Water	97.75 wt%
Viscosity Retention Rate	99.8 %	Viscosity	2400 mPas
prepared by adding a viscosity modification agent (Sodium Chloride) and by applying an exogenous shear force to have viscosity of 2500 mPa		Viscosity Retention Rate	98.6 %
prepared by adding a viscosity modification agent (Sodium Chloride) and by applying an exogenous shear force to have viscosity of 2500 mPa		prepared by adding a viscosity modification agent (Sodium Chloride) and by applying an exogenous shear force to have viscosity of 2500 mPa and by adding an ethanol for improving spray pattern	
Base Material E3		Base Material E4	
Carboxy Vinyl Polymer	0.375 wt%	Carboxy Vinyl Polymer	0.55 wt%
L-Arginine	0.7 wt%	L-Arginine	1.20 wt%
Sodium Chloride	0.125 wt%	Concentrated Glycerin	1.00 wt%
Purified Water	98.8 wt%	Dibasic Sodium Phosphate Hydrate	0.1765 wt%
Viscosity	1000 mPas	Sodium Dihydrogenphosphate	0.0270 wt%
Viscosity Retention Rate	100 %	Sodium Chloride	0.4250 wt%
prepared by adding a viscosity modification agent (Sodium Chloride) and by applying an exogenous shear force to have viscosity of 1000 mPa		Purified Water	69.6215 wt%
prepared by adding a viscosity modification agent (Sodium Chloride) and by applying an exogenous shear force to have viscosity of 1000 mPa		Viscosity	1000 mPas
		Viscosity Retention Rate	100 %
		prepared by adding a viscosity modification agent (Sodium Chloride) and by applying an exogenous shear force to have viscosity of 1000 mPa	

5 [0053] Example 1

An influenza vaccine composition (the formulation comprising the gel base material E4 containing an

inactivated whole-virus antigen influenza vaccine) was prepared by mixing a gel base material and a stock solution of an influenza vaccine as follows.

[Table 7]

Influenza Vaccine Composition	
Inactivated Whole-Virus Antigen Influenza Vaccines	
A/California/7/2009 (H1N1)	30 µgHA
A/Victoria/210/2009 (H3N2)	30 µgHA
B/Brisbane/60/2008	60 µgHA
Carboxy Vinyl Polymer	5.50 mg
L-Arginine	12.00 mg
oncentrated Glycerin	10.00 mg
Dibasic Sodium Phosphate Hydrate	1.765 mg
Sodium Dihydrogenphosphate	0.270 mg
Sodium Chloride	4.25 mg
Purified Water	proper quantity
Total	1.0 mL

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[0054] [Evaluation Process]

a) Viscosity/Viscosity Retention Rate

The viscosity of the base material A-E according to the present embodiment is measured by a C-type viscosimeter at 20 degrees C. The viscosity retention rate is referred to the remaining rate of the viscosity of the base material A-E immediately after being sprayed.

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[0055]

b) Spray Uniformity (Spray Pattern)

After filling each of the base materials A-E in the medical syringe 1 (metered-dose syringe-based squirt) provided with various rhinal spray nozzles 10a-10k, each of the base materials A-E was sprayed from the respective rhinal spray

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nozzles 10a-10k towards a paper arranged vertically and spaced away from the nozzle orifice 21 by a predetermined distance. For example, Fig 5 shows the spray patterns being acceptable in a particular combination of the base material and the rhinal spray nozzle 10, both of which have circular shapes (rather than oval shapes) and show uniform full-cone spraying (rather than hollow-cone spraying).

[0056]

c) Spray Angle

After filling each of the base materials A-E in the medical syringe 1 provided with various rhinal spray nozzles 10a-10k, each of the base materials A-E was sprayed. A high-speed microscope commercially available from Keyence Corporation® (model No. VW-9000) was used to measure the spray angle of the formulation sprayed from the nozzle orifice 21 of each of the rhinal spray nozzles 10a-10k. For example, Fig 6 shows the spray angle being acceptable in a particular combination of the base material and the rhinal spray nozzle 10, since the spray angle was 50.51 degrees while the desired or acceptable range according to the present disclosure is set between 40-60 degrees.

[0057]

d) Average Particle Size and Particle size Distribution

Also after filling each of the base materials A-E in the medical syringe 1 (metered-dose syringe-based squirt)

provided with various rhinal spray nozzles 10a-10k, each of the base materials A-E was sprayed by pushing the plunger rod 5 at a predetermined speed (e.g., 80 mm/s). A laser-diffraction particle size distribution measuring apparatus was used for measuring the particle size of the formulation sprayed from the nozzle orifice 21 of the rhinal spray nozzles 10a-10k so as to determine the average particle size and the rate or percentage of counts of the particles having the particle size in a range between 10 to 100 microns over the total counts thereof. For example, Fig 7 shows the average particle size of the sprayed formulation is 56.60 microns and the percentage of counts of the particles having the particle size in a range between 10 to 100 microns over the total counts thereof is 86.90%, which is acceptable in a particular combination of the base material and the rhinal spray nozzle 10.

[0058] After filling the base materials A, B1-B2, C1-C3, D, E1-E4 in the medical syringe 1 (metered-dose syringe-based squirt) provided with various rhinal spray nozzles 10a-10k, the test results were obtained as illustrated in Tables 8-10 for:

- a) Viscosity (V) and Viscosity Retention Rate (VRR),
- b) Spray Pattern (SP),
- c) Spray Angle (SA), and
- d) Average Particle Size (APS), Particle Size Distribution

(PSD), and Percentage of Counts of the particles between 10 to 100 microns (PC).

[0059] Similarly, Figs. 8-15 show the spray patterns of the formulation comprising the base materials A, B1, C1-C2, D, E4 (eight types) in the medical syringe 1 (metered-dose syringe-based squirt) provided with various rhinal spray nozzles 10a-10k, and also indicate whether the combination of each of the base materials and the rhinal spray nozzles 10 is acceptable or not (abbreviated herein as "OK" and "NG").

Base Material A (PBS)	Nozzle a	Nozzle b	Nozzle c	Nozzle d	Nozzle e	Nozzle f	Nozzle g	Nozzle h	Nozzle i	Nozzle j	Nozzle k
	orifice diameter	0.25	0.25	0.26	0.3	0.3	0.3	0.4	0.4	0.45	0.55
	thickness d	0.15	0.25	0.25	0.13	0.2	0.3	0.25	0.25	0.25	0.25
	curved portion	no	no	yes	no	no	no	yes	no	yes	no
	V = 1mPs	OK	OK	NG	NG	OK	OK	NG	NG	NG	NG
	VRR (N/A)	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular
	SP	full cone	full cone	semi-hollow cone	full cone	full cone	full cone	hollow cone	full cone	hollow cone	hollow cone
	SA	60 degrees	55 degrees	75 degrees	73 degrees	58 degrees	55 degrees	75 degrees	58 degrees	76 degrees	80 degrees
	APS	57 μm	64 μm	71 μm	55 μm	59 μm	66 μm	72 μm	69 μm	77 μm	74 μm
	PSD	90% or more	90% or more	80% or more	90% or more	90% or more	90% or more	80% or more	90% or more	80% or more	80% or more
Base Material B1	PC	-94.20%	-92.00%	-88.60%	-96.30%	-92.40%	-90.20%	-86.70%	-91.40%	-83.30%	-81.60%
	V=2500mPs	OK	OK	NG	NG	OK	OK	NG	NG	NG	NG
	VRR=28.4%	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular
	SP	full cone	full cone	hollow cone	full cone	full cone	full cone	hollow cone	full cone	semi-hollow cone	semi-hollow cone
	SA	50 degrees	45 degrees	75 degrees	62 degrees	58 degrees	55 degrees	82 degrees	58 degrees	77 degrees	72 degrees
	APS	69 μm	77 μm	79 μm	68 μm	58 μm	55 μm	76 μm	70 μm	80 μm	84 μm
	PSD	90% or more	80% or more	80% or more	90% or more	90% or more	90% or more	80% or more	90% or more	70% or more	70% or more
	PC	-92.10%	-88.40%	-83.90%	-91.10%	-96.20%	-94.90%	-83.80%	-92.80%	-84.40%	-78.90%
	V=1000mPs	OK	OK	NG	NG	OK	OK	NG	NG	NG	NG
	VRR=17.5%	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular
Base Material B2	SP	full cone	full cone	hollow cone	full cone	full cone	full cone	hollow cone	full cone	semi-hollow cone	semi-hollow cone
	SA	56 degrees	53 degrees	78 degrees	71 degrees	60 degrees	63 degrees	85 degrees	65 degrees	74 degrees	75 degrees
	APS	63 μm	70 μm	76 μm	55 μm	61 μm	59 μm	67 μm	66 μm	72 μm	84 μm
	PSD	90% or more	80% or more	80% or more	90% or more	90% or more	90% or more	80% or more	90% or more	80% or more	80% or more
	PC	-94.90%	-88.90%	-88.40%	-93.30%	-93.80%	-95.50%	-86.80%	-94.80%	-85.90%	-82.80%
	V=2400mPs	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
	VRR=82.6%	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular
	SP	semi-hollow cone	semi-hollow cone	semi-hollow cone	hollow cone	semi-hollow cone	semi-hollow cone	hollow cone	semi-hollow cone	hollow cone	hollow cone
	SA	76 degrees	72 degrees	62 degrees	79 degrees	61 degrees	50 degrees	84 degrees	60 degrees	70 degrees	72 degrees
	APS	66 μm	68 μm	72 μm	64 μm	69 μm	63 μm	64 μm	63 μm	67 μm	65 μm
Base Material C1	PSD	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	70% or more	72 degrees
	PC	-84.10%	-82.70%	-83.50%	-81.60%	-82.80%	-83.30%	-82.80%	-93.70%	-80.60%	-79.40%
	V=2500mPs	OK	OK	NG	NG	OK	OK	NG	NG	NG	NG
	VRR=28.4%	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular
	SP	full cone	full cone	hollow cone	full cone	full cone	full cone	hollow cone	full cone	hollow cone	hollow cone
	SA	60 degrees	55 degrees	75 degrees	73 degrees	58 degrees	55 degrees	75 degrees	58 degrees	76 degrees	80 degrees
	APS	57 μm	64 μm	71 μm	55 μm	59 μm	66 μm	72 μm	69 μm	77 μm	74 μm
	PSD	90% or more	90% or more	80% or more	90% or more	90% or more	90% or more	80% or more	90% or more	80% or more	80% or more
	PC	-94.20%	-92.00%	-88.60%	-96.30%	-92.40%	-90.20%	-86.70%	-91.40%	-83.30%	-81.60%
	V=2500mPs	OK	OK	NG	NG	OK	OK	NG	NG	NG	NG

	Nozzle a	Nozzle b	Nozzle c	Nozzle d	Nozzle e	Nozzle f	Nozzle g	Nozzle h	Nozzle i	Nozzle j	Nozzle k
orifice diameter	0.25	0.25	0.26	0.3	0.3	0.3	0.3	0.4	0.4	0.45	0.55
thickness d	0.15	0.25	0.25	0.13	0.2	0.3	0.25	0.25	0.25	0.25	0.25
curved portion	no	no	yes	no	no	no	yes	no	yes	no	no
V=2400mps VRR=81.6%	NG	NG	NG	OK	OK	NG	NG	NG	NG	NG	NG
SP	circular	oval	circular	circular	circular	circular	circular	oval	circular	circular	circular
	semi-hollow cone	semi-hollow cone	semi-hollow cone	full cone	full cone	full cone	hollow cone	full cone	hollow cone	semi-hollow cone	hollow cone
SA	65 degrees	58 degrees	70 degrees	53 degrees	43 degrees	36 degrees	84 degrees	59 degrees	68 degrees	70 degrees	70 degrees
APS	64 μm	65 μm	68 μm	62 μm	66 μm	65 μm	62 μm	60 μm	61 μm	67 μm	61 μm
PSD	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more
PC	-86.80%	-87.90%	-86.80%	-87.40%	-88.3	-83.00%	-85.80%	-88.70%	-87.20%	-82.20%	-83.70%
V=1000mps VRR=76.5%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
SP	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular
	semi-hollow cone	semi-hollow cone	semi-hollow cone	hollow cone	semi-hollow cone	semi-hollow cone	hollow cone	semi-hollow cone	hollow cone	hollow cone	hollow cone
SA	81 degrees	78 degrees	74 degrees	83	68 degrees	66 degrees	82 degrees	70 degrees	77 degrees	76 degrees	77 degrees
APS	65 μm	66 μm	69 μm	64 μm	67 μm	64 μm	62 μm	61 μm	65 μm	71 μm	64 μm
PSD	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more	80% or more
EC	-86.80%	-88.60%	-84.60%	-87.20%	-86.00%	-87.30%	-83.80%	-87.10%	-85.50%	-86.80%	-87.50%
V=2500mps VRR=99.5%	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
SP	oval	oval	oval	circular	circular	circular	oval	oval	circular	circular	circular
	full cone	full cone	semi-hollow cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	semi-hollow cone
SA	58 degrees	58 degrees	58 degrees	47 degrees	38 degrees	39 degrees	50 degrees	42 degrees	40 degrees	38 degrees	55 degrees
APS	70 μm	72 μm	76 μm	86 μm	89 μm	91 μm	78 μm	88 μm	88 μm	86 μm	77 μm
PSD	80% or more	80% or more	80% or more	80% or more	70% or more	70% or more	80% or more	70% or more	70% or more	70% or more	70% or more
PC	-84.40%	-82.80%	-83.50%	-80.70%	-77.80%	-73.30%	-83.50%	-75.10%	-70.40%	-72.60%	-77.20%

orifice diameter thickness d curved portion	Nozzle														Nozzle k	
	a	b	c	d	e	f	g	h	i	j						
Base Material E1 V=2500mps VRR=99.8%	0.25	0.25	0.26	0.3	0.3	0.3	0.3	0.4	0.4	0.45						0.55
	0.15	0.25	0.25	0.13	0.2	0.3	0.25	0.25	0.25	0.25						0.25
	no	no	yes	no	no	no	yes	no	yes	no						no
	OK	NG	OK	OK	OK	OK	NG	OK	OK	OK						OK
	circular	oval	circular	circular	circular	circular	circular	circular	circular	circular	circular					
Base Material E2 V=2400mps VRR=98.6%	full cone	semi-hollow cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone						full cone
	42 degrees	60 degrees	65 degrees	68 degrees	52 degrees	52 degrees	78 degrees	55 degrees	42 degrees	65 degrees						60 degrees
	66 μm	68 μm	72 μm	58 μm	57 μm	63 μm	64 μm	63 μm	67 μm	70 μm						65 μm
	80% or more	80% or more	90% or more	90% or more	90% or more	80% or more	90% or more	80% or more	80% or more	80% or more						80% or more
	-87.30%	-87.10%	-91.60%	-90.50%	-91.80%	-85.40%	-91.70%	-88.50%	-86.90%	(83.4.2%)						-82.80%
Base Material E3 V=1000mps VRR=100%	OK	OK	OK	OK	OK	NG	NG	OK	OK	OK						OK
	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular						circular
	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone						full cone
	55 degrees	48 degrees	68 degrees	58 degrees	47 degrees	35 degrees	78 degrees	47 degrees	48 degrees	47 degrees						47 degrees
	68 μm	71 μm	58 μm	56 μm	58 μm	75 μm	66 μm	77 μm	75 μm	76 μm						73 μm
Base Material E4 V=1000mps VRR=100%	80% or more	80% or more	90% or more	90% or more	90% or more	80% or more	90% or more	80% or more	80% or more	80% or more						80% or more
	-86.80%	-89.20%	-90.40%	-91.20%	-92.80%	-88.40%	-90.70%	-89.40%	-87.50%	(87.4.2%)						-88.80%
	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK						OK
	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular						circular
	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone						full cone
Base Material E5 V=1000mps VRR=100%	58 degrees	56 degrees	69 degrees	62 degrees	52 degrees	41 degrees	68 degrees	53 degrees	54 degrees	52 degrees						52 degrees
	55 μm	63 μm	64 μm	54 μm	52 μm	59 μm	60 μm	68 μm	65 μm	63 μm						61 μm
	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	80% or more						80% or more
	-90.40%	-91.30%	-92.00%	-90.80%	-91.50%	-92.60%	-91.00%	-91.00%	-90.30%	-87.50%						-88.20%
	OK	OK	NG	OK	OK	OK	NG	OK	OK	OK						NG
Base Material E6 V=1000mps VRR=100%	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular						circular
	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone						full cone
	69 degrees	55 degrees	75 degrees	65 degrees	52 degrees	42 degrees	72 degrees	55 degrees	58 degrees	58 degrees						78 degrees
	57 μm	63 μm	64 μm	62 μm	55 μm	59 μm	58 μm	58 μm	58 μm	61 μm						63 μm
	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	80% or more						80% or more
Base Material E7 V=1000mps VRR=100%	-90.40%	-91.30%	-92.00%	-90.80%	-92.50%	-91.60%	-91.10%	-91.00%	-90.30%	-88.70%						-86.90%
	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK						OK
	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular						circular
	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone	full cone						full cone
	69 degrees	55 degrees	75 degrees	65 degrees	52 degrees	42 degrees	72 degrees	55 degrees	58 degrees	58 degrees						78 degrees
Base Material E8 V=1000mps VRR=100%	57 μm	63 μm	64 μm	62 μm	55 μm	59 μm	58 μm	58 μm	58 μm	61 μm						63 μm
	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	90% or more	80% or more						80% or more
	-90.40%	-91.30%	-92.00%	-90.80%	-92.50%	-91.60%	-91.10%	-91.00%	-90.30%	-88.70%						-86.90%
	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK						OK
	circular	circular	circular	circular	circular	circular	circular	circular	circular	circular						circular

[0063] [Evaluations]

If all of the aforementioned parameters including a) Viscosity (V) and Viscosity Retention Rate (VRR), b) Spray Pattern (SP), c) Spray Angle (SA), and d) Average Particle Size (APS), Particle Size Distribution (PSD) and Percentage of Counts of the particles between 10 to 100 microns (PC) are within the desired range, then the combination of the base material and the rhinal spray nozzle 10 is determined as acceptable (OK) and even one of the parameters is out of the desired range, the combination is determined as unacceptable (NG).

[0064] The base material A having very low viscosity as shown in Table 2 and the base materials B1-B2 having low viscosity retention rates as shown in Table 3 are not suitable for the rhinal spray formulation.

[0065] The base material C was prepared by adding a viscosity modification agent (sodium chloride) to have a predetermined viscosity (e.g., 2400 mPa or 1000 mPa) as shown in Table 4 so that the viscosity retention rate is high and the formulation is likely retained in the nasal cavity. Also, the base material D was prepared by applying an exogenous shear force to have a predetermined viscosity (e.g., 2500 mPa) as shown in Table 5 so that the viscosity retention rate is high and the formulation is likely retained in the nasal cavity. However, the spray pattern

of the formulation containing the base materials C and D filled in the medical syringe provided with the rhinal spray nozzles 10a-10k are acceptable only for the rhinal spray nozzles 10d and 10e. Thus, the rhinal spray nozzles 10 achieve the desired spray characteristics only when it is used with the base materials C2 and has the diameter of the nozzle orifice of 0.30 mm and the thickness between 0.13 mm through 0.20 mm.

[0066] The base material E was prepared by applying an exogenous shear force to have a predetermined viscosity (e.g., 2400 mPa or 1000 mPa) as shown in Table 6 so that the viscosity retention rate is high and the formulation is likely retained in the nasal cavity. However, the rhinal spray nozzles 10c, 10g having the curved portion on the nozzle orifice 21 of the tip portion 22 failed to achieve the desired spray nozzle, thus several of the base materials E were determined as unacceptable due to failure to achieve the desired spray characteristics. When focusing on the base materials E3 and E4, all of the rhinal spray nozzles 10 achieved the desired spray characteristics when the diameter of the nozzle orifice 21 was 0.3 mm and the thickness d of the tip portion 22 was in a range between 0.13 mm and 0.20 mm.

Industrial Applicability

[0067] As described above, the rhinal spray nozzle used

for a medical syringe according to the present invention substantially improves the spray uniformity (spray pattern), the spray angle, particle size distribution (an average particle size) in spraying the pharmaceutical formulation such as an endermatic influenza vaccine comprising the gel material containing viscosity modification agent and carboxy vinyl polymer of which viscosity is modified by applying an exogenous shear force so as to improve the retention of the formulation in the nasal cavity of the patient, thereby to achieve higher pharmaceutical benefits of the formulation.

Denotation of Reference Numerals

1: medical syringe, 2: pharmaceutical formulation, 3: syringe barrel, 4: syringe body, 5: plunger rod, 5a: fixing member, 6: opening, 7: piston, 8: finger flange, 9: plunger end member, 10: rhinal spray nozzle, 20: nozzle body, 21: nozzle orifice, 22: tip portion, 23: inner wall, 23a: protrusion, 24: internal space, 25: nozzle small-diameter portion, 26: nozzle large-diameter portion, 27: nozzle shoulder, 30: packing rod, 33: outer wall, 33a: recess, 35: rod small-diameter portion, 36: rod large-diameter portion, 37: rod shoulder, 38, 39: groove, 40: gap, 42: nozzle chamber, 44: vortex-flow generation member, 46: curved portion, 50: protection cap.

CLAIMS

We claim:

1. A rhinal spray nozzle used for a medical syringe having a tip opening in fluid communication with a syringe barrel for storing a formulation, the rhinal spray nozzle comprising:

a hollow nozzle body having a tip portion defining a nozzle orifice thereon;

a solid packing rod arranged within the nozzle body;

10 and

a nozzle chamber defined between the packing rod and the nozzle body to allow a fluid communication between the tip opening and the nozzle orifice;

wherein the formulation comprises the gel material containing viscosity modification agent and carboxy vinyl polymer of which viscosity is modified by applying an exogenous shear force, and

wherein the nozzle orifice has a diameter in a range between 0.25 mm and 0.30 mm.

20

2. The rhinal spray nozzle according to claim 1, wherein the formulation comprises the gel material containing an electrolyte as the viscosity modification agent which is selected from a group consisting of sodium chloride, potassium chloride, dibasic sodium phosphate hydrate, and

25

sodium dihydrogenphosphate, of which viscosity is modified by applying an exogenous shear force.

3. The rhinal spray nozzle according to claim 1 or 2,
5 wherein the nozzle orifice includes substantially no curved portion.

4. The rhinal spray nozzle according to any one of preceding claims, wherein the tip portion has thickness
10 along an injection direction of the formulation which is in a range between 0.20 mm and 0.30 mm.

5. The rhinal spray nozzle according to any one of preceding claims,

15 wherein the nozzle body includes an inner wall having at least a portion formed in a cylindrical shape and the packing rod includes an outer wall at least a portion formed in a cylindrical shape having a plurality of circumferentially spaced grooves,

20 wherein the nozzle chamber is defined between the at least portion of the inner wall of the nozzle body and the at least portion of the outer wall of the packing rod, and

wherein the packing rod includes a vortex-flow generation member opposed to the tip portion of the nozzle
25 body.

6. The rhinal spray nozzle according to claim 5, wherein the vortex-flow generation member is formed so that a flow direction of the formulation from the grooves of the packing rod is offset to a central axis, thereby to generate a vortex flow of the formulation.

7. The rhinal spray nozzle according to claim 5 or 6, wherein the at least portion of the inner wall of the nozzle body is formed to have a cross section substantially perpendicular to the injection direction which is continuously or step-wisely reduced towards the injection direction.

8. The rhinal spray nozzle according to any one of preceding claims, wherein the gel material has a viscosity of 2500 mPas or more.

9. The rhinal spray nozzle according to claim 8, wherein the gel material has a viscosity of 1000 mPas or more.

10. The rhinal spray nozzle according to any one of preceding claims, wherein a spray angle of the formulation sprayed from the nozzle orifice is in a range 45 degrees and 60 degrees.

11. The rhinal spray nozzle according to any one of preceding claims, wherein an average particle size of formulation droplets sprayed from the nozzle orifice is in
5 a range 50 microns and 80 microns.

12. The rhinal spray nozzle according to any one of preceding claims, wherein counts of formulation droplets sprayed from the nozzle orifice having the particle size in
10 a range between 10 to 100 microns are 70% or more of the total counts of the particle.