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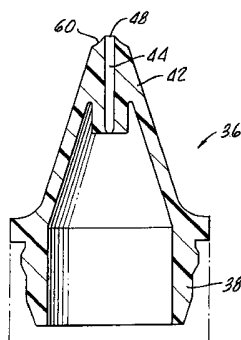
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(54) Title: CONTROLLED DROP DISPENSING TIP



(57) Abstract: A controlled drop dispensing tip (36) includes a body (38) suitable for attachment to a dispensing bottle and a nozzle (42) having a lumen (44) therethrough for flow of liquid formulation. An orifice (48) is provided in the nozzle which is in fluid communication with the lumen therethrough for formulation of droplets. The nozzle is formed from a material enabling uniform droplet dispensment of the liquid formulation independent of downward angular orientation of the tip.

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CONTROLLED DROP DISPENSING TIP

The present invention is generally related to a control
5 drop dispensing system and is more particularly directed to
such a system including a dispensing tip enabling uniform
droplet dispensment.

Applicators or systems for the delivery or instillation
10 of the liquid formulations into an eye by a user have long
been known.

Generally, bottles or vials, which contain eye drop
formulations, are flexible and have walls sufficiently thin to
15 enable squeezing of the bottle through a nozzle and dispensing
orifice.

In use, the user suspends the bottle over an eye to be
treated in an inverted or semi-inverted position in order to
20 direct the nozzle toward the eye. The formulation is expelled
as the user manually squeezes the wall of the bottle body or a
bottom of the bottle. This pressure differential within the
bottle drives out a quantity of formulation which exits the
vial or bottle via the nozzle orifice as a droplet and
25 descends through gravity into the eye positioned below the
nozzle.

While this procedure appears to be straightforward, it
often cannot be performed satisfactorily with small volume

bottles in order to dispense uniform drops. In addition to handling problems associated with over squeezing or unintentional squeezing of the bottle, the angle of the bottle and nozzle with regard to the eye is significant in
5 determining the droplet size produced.

The droplet size is important in that the dose prescribed to the patient must often be accurately adhered to. If the quantity which is effectively delivered is insufficient, the
10 treatment may not be efficient. On the other hand, if the quantity delivered is too large the surplus in certain cases may cause side effects.

Accordingly, it is important to be able to administer an
15 exact dose of the formulation required and the present invention provides for a controlled drop dispensing tip and system enabling uniform droplet dispensment of the liquid formulation independent of downward angular orientation of the tip.

20

SUMMARY OF THE INVENTION

A controlled drop dispensing tip in accordance with the present invention generally includes a body suitable for
25 attachment to a dispensing bottle and a nozzle having a lumen therethrough for flow of liquid formulation and an orifice in fluid communication with the lumen for the formation of droplets.

A nozzle is formed from a material which enables uniform droplet dispensement of the liquid formulation which is independent of downward angular orientation of the tip.

5 A system in accordance with the present invention includes a bottle and a liquid formulation disposed in the bottle in combination with the hereinabove described dispensing tip.

10 More particularly, the tip in accordance with the present invention may be a nanocomposite including a polymer and a nanofiller. The polymer may be low-density polyethylene and the nanofiller may be present in an amount of between about 9% and about 11% by weight, preferably about 10% by weight.

15 Thus, the present invention provides for a nozzle which is formed from a material comprising a nanocomposite in an amount enabling uniform droplet size dispensement of liquid formulation which is independent of the downward angular
20 orientation of the tip. Preferably, a liquid formulation is Alphagan® or Refresh Liquigel®.

Accordingly, a method for controlling dispensed droplet size includes providing a squeezable bottle, disposing a
25 liquid formulation within the bottle and attaching a dispensing tip to the bottle, the tip being formed from a material enabling uniform droplet dispersement of said liquid formulation independent of downward angular orientation of the

tip. Subsequently, the bottle is squeezed with the tip oriented in any downward direction.

BRIEF DESCRIPTION OF THE DRAWINGS

5

The present invention may be more clearly understood with reference to the following detailed description in conjunction with the appended drawings, of which:

10

Figure 1 is an illustration of a prior art bottle system indicating a variance in droplet formation which is dependent upon the downward angular orientation of the tip;

15

Figure 2 is an illustration of a tip and bottle system in accordance with the present invention similar to the illustration shown in Figure 1 indicating uniform drop dispensement despite angular downward orientation of the tip; and

20

Figure 3 is a cross-section of a nozzle tip suitable for use in the present invention.

DETAILED DESCRIPTION

25

With reference to Figure 1, there is shown a conventional prior art bottle 10 having a nozzle 12 for the dispensement of droplets 14, 16.

As illustrated, the droplet size is dependent upon the angular orientation indicated by the letter A of the nozzle 12 to an ordnance 20, as hereinafter described. This variance in droplet size may vary up to 50% or more. For example, a
5 prior art bottle may dispense a droplet size of about 12 microliters at 90°, whereas at an angle A of 45° the same prior art bottle may dispense a droplet size of about 26 microliters.

10 This variation in droplet size is also dependent upon the droplet size. For example, droplet sizes between 40 and 50 microliters are not as dependent upon orientation of delivery as are droplets of smaller size.

15 The present invention overcomes this effect through the utilization of nanocomposites.

With reference to Figure 2 there is shown a system 30 in accordance with the present invention which includes a bottle
20 32, a liquid formulation 34 disposed within the bottle 32 and a tip 36 having a body 38 suitable for attachment to the bottle 32 in a conventional manner, see also Figure 3.

The tip 36 includes a nozzle 42 having a lumen 44 and an
25 orifice 48 in fluid communication with the formulation 34 for the dispensement of droplets 50 of uniform size independent of a downward angular orientation A of the tip 36.

Preferably, the bottle 34 is formed from a low-density polyethylene and droplet size is unexpectedly found to be uniform despite a downward angular orientation of the tip 36 through the use of nanofillers in the low-density polyethylene (LDPE), preferably Dupont resin 206064. Such nanofilled LDPE material may be produced in a conventional manner such as, for example, set forth in U.S. 6,602,966. This patent is to be incorporated herewith in its entirety for the purpose of illustrating the manufacture of a nanocomposite filled polymer useful in the present invention.

A variety of nanofillers for use in nanocomposites are suitable for use in the present invention. Such nanofillers include natural clays (mined, refined and treated); synthetic clays; nanostructured silicas; nanoceramics; and nanotubes (carbon based) as set forth in an article entitled "Enhancing Medical Device Performance With Nanocomposite Polymers in Medical Device and Diagnostic Industry" pp. 114-123 (May 2002). This article is to be incorporated herewith in its entirety for the purpose of describing suitable nanofillers for formation of the nanocomposite in accordance with the present invention for the use within the nozzle 42.

Unexpectedly, it has been found that utilization of a nanofiller such as a montmorillonite clay (Merck Index [1318-93-0]) available from Aldrich Chemical Company, Milwaukee, Wisconsin in an amount of between about 9% and 10% by weight, preferably about 10% enable a uniform droplet formation independent of downward angular orientation A of the tip 36,

as shown in Table 1. Table 1 reports droplet size in microliters as a function of downward angular orientation between 45° and 90° for a nanocomposite of LDPE and nanofiller between 5% and 10% compared with a conventional Teflon material.

As shown for the formulations Alphagan® and Refresh Liquigel® droplet sizes are uniform compared to droplet sizes at 45° and 90° for Teflon and lower percentages of nanofiller. This effect is not as strong with formulations such as Lumigan.

These droplets were formed utilizing the nozzle 36 shown in Figure 3 which further includes an arcuate surface of revolution 60 surrounding the orifice 48 and depending from the orifice 48. It should be appreciated that the nozzle 36 is shown for illustrative purposes and that other nozzles may be utilized when formed from a material having interfacial tension with the liquid formulation 34 enabling uniform droplet dispensement of liquid formulation independent of downward orientation of the tip 36.

TABLE 1

Nozzle Material	Alphagan			Lumigan			Refresh Liquigel		
	45 Degrees	90 Degrees	Overall	45 Degrees	90 Degrees	Overall	45 Degrees	90 Degrees	Overall
10% Nanocomposite	15.8	17.9	16.9	26.4	14.7	20.6	15.4	17.9	16.7
8% Nanocomposite	35.1	18.7	26.9	23.9	12.8	18.4	33.2	18.2	25.7
5% Nanocomposite	34.5	18.8	26.7	26.5	12.1	19.3	33.7	21.4	27.6
Teflon Blend	33.0	25.9	29.5	33.3	20.6	27.0	26.3	12.0	19.2

As hereinabove summarized a method in accordance with the present invention includes disposing a liquid formulation such as, for example, Alphagan® or Refresh Liquigel® into a squeezable bottle and attaching a dispensing tip to the bottle, the tip being molded, shaped or otherwise formed with a material enabling uniform droplet dispersement of said liquid formulation independent of downward angular orientation of the tip, the material comprises nanocomposites such as hereinbefore discussed.

Uniform droplet dispersement is effected through squeezing the bottle with the tip orientation in a downward direction, such as, for example, between 45° and 90° as illustrated by the angle A in Figure 2.

Although there has been hereinabove described a specific controlled drop dispensing tip in accordance with the present invention for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. That is, the present invention may suitably comprise, consist of, or consist essentially of the recited elements. Further, the invention illustratively disclosed herein suitably may be practiced in the absence of any element which is not specifically disclosed herein. Accordingly, any and all modifications, variations or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A controlled drop dispensing tip comprising:
a body suitable for attachment to a dispensing
5 bottle; and
a nozzle having a lumen therethrough for flow of a
liquid formulation and an orifice in fluid communication with
said lumen for the formation of droplets, said nozzle being
formed from a material enabling uniform droplet dispense-
10 ment of said liquid formulation independent of downward angular
orientation of said tip.
2. The tip according to claim 1 wherein said material
is a polymer.
15
3. The tip according to claim 2 wherein said polymer
comprises a nanocomposite.
4. The tip according to claim 3 wherein said polymer
20 comprises low-density polyethylene.
5. The tip according to claim 4 wherein said
nanocomposite includes a nanofiller present in an amount of
between about 9 and about 11% by weight.
25
6. The tip according to claim 4 wherein said
nanocomposite includes a nanofiller present in an amount of
about 10% by weight.

7. A controlled drop dispensing system comprising:
a bottle;
a liquid formulation disposed in said bottle;
a tip having a body suitable for attachment to said
5 bottle and a nozzle formed from a material enabling uniform
droplet dispensement of said liquid formulation independent of
downward angular orientation of said tip.

8. The system according to claim 7 wherein said
10 material is a polymer.

9. The system according to claim 8 wherein said polymer
comprises a nanocomposite.

15 10. The system according to claim 9 wherein said polymer
comprises low-density polyethylene.

11. The system according to claim 10 wherein said
nanocomposite includes a nanofiller present in an amount of
20 between about 9 and about 11% by weight.

12. The system according to claim 10 wherein said
nanocomposite is present in an amount of about 10% by weight.

25 13. The system according to claim 12 wherein said liquid
formulation comprises Alphagan®.

14. The system according to claim 12 wherein said liquid
formulation comprises Refresh Liquigel®.

15. A controlled drop dispensing tip comprising:

a body suitable for attachment to a dispensing bottle; and

5 a nozzle having a lumen therethrough for flow of a liquid formulation and an orifice in fluid communication with said lumen for the formation of droplets, said nozzle being formed from a material enabling uniform droplet size dispense-ment of said liquid formulation independent of
10 downward angular orientation of said tip.

16. The tip according to claim 15 wherein said material is a polymer.

15 17. The tip according to claim 16 wherein said polymer comprises a nanocomposite.

18. The tip according to claim 17 wherein said polymer comprises low-density polyethylene.
20

19. The tip according to claim 18 wherein said nanocomposite includes a nanofiller present in an amount of between about 9 and about 11% by weight.

25 20. The tip according to claim 18 wherein said nanocomposite includes a nanofiller present in an amount of about 10% by weight.

21. A method for controlling dispensed droplet size, said method comprising:

providing a squeezable bottle;

disposing a liquid formulation in the bottle;

5 attaching a dispensing tip to the bottle, the tip being formed from a material enabling uniform droplet dispensement of said liquid formulation independent of downward angular orientation of the tip; and

10 squeezing the bottle with the tip oriented in a downward direction to produce the uniform droplets of said liquid formulation.

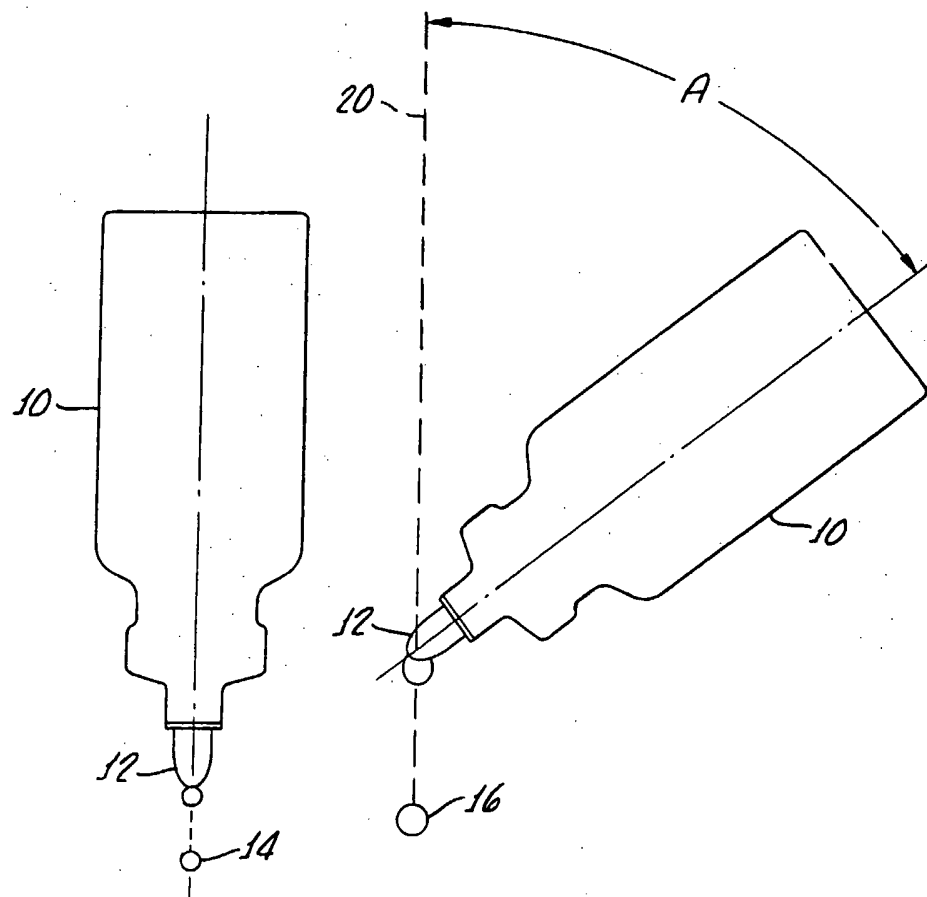


FIG. 1. (PRIOR ART)

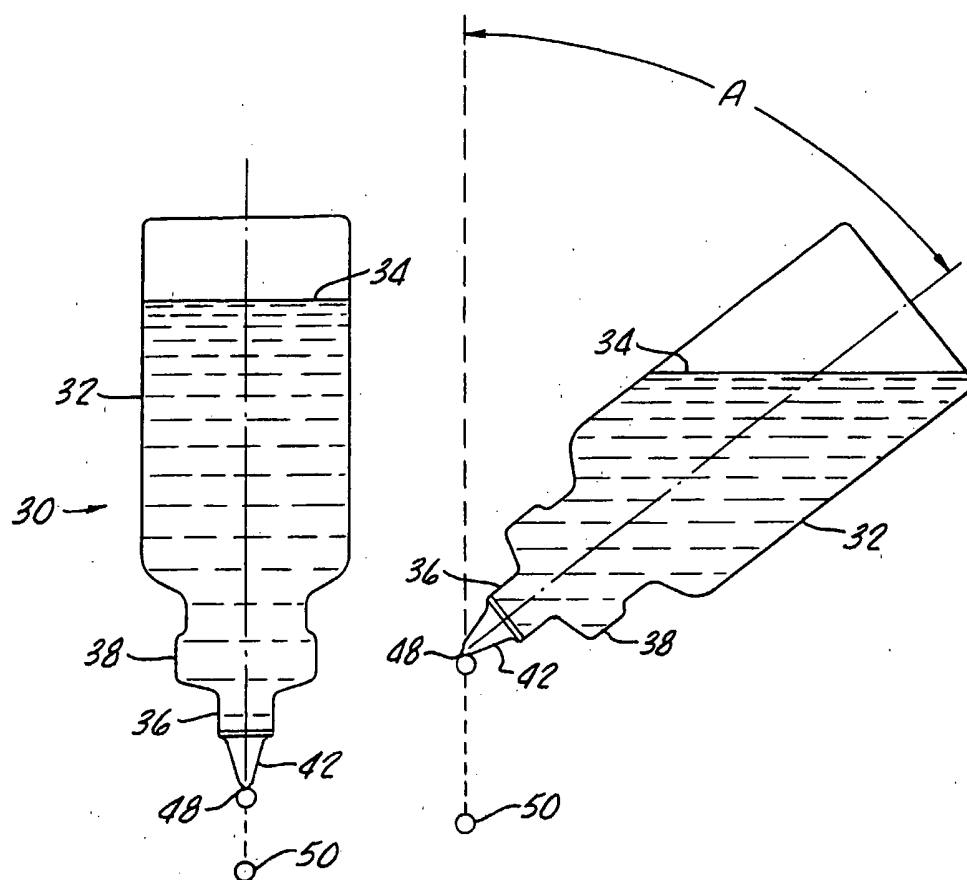


FIG. 2.

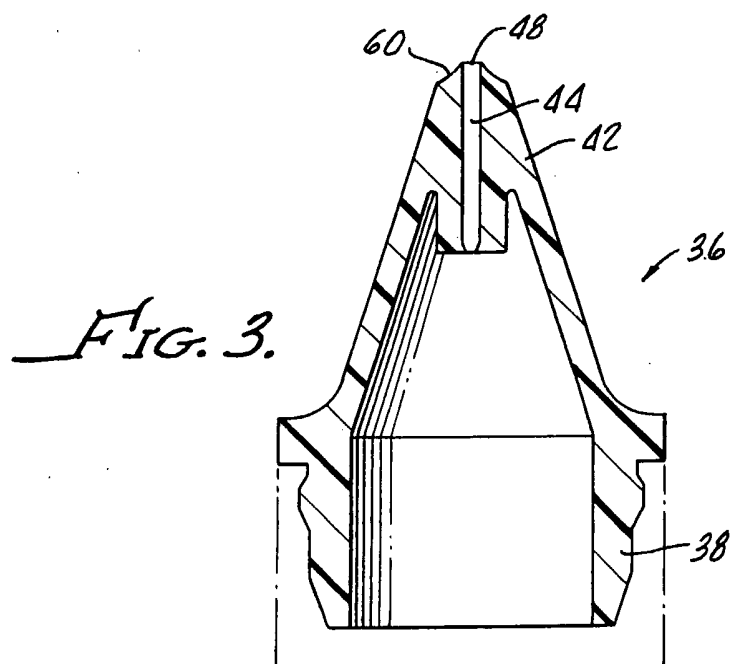


FIG. 3.

INTERNATIONAL SEARCH REPORT

In tional Application No
PC I/US2005/017166

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B65D47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B65D A61F B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 431 885 A (LABORATOIRES MERCK, SHARP & DOHME-CHIBRET) 12 June 1991 (1991-06-12)	1,2,7,8, 15,16,21
Y	page 3, line 26 - line 28	3-6, 9-14, 17-20
	page 5, line 43 - line 50; figure 8	
Y	WO 98/26001 A (DUPONT DOW ELASTOMERS L.L.C) 18 June 1998 (1998-06-18)	3-6, 9-14, 17-20
	page 13, line 1 - line 30	
X	US 2004/079766 A1 (KOKUBO SHIGEHICO) 29 April 2004 (2004-04-29)	1,2,7,8, 15,16
	paragraphs '0010!', '0030!' - '0032!'; figure 1	
	----- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

7 September 2005

Date of mailing of the international search report

22/09/2005

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/017166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 447 860 B1 (MUELLER CHAD ET AL) 10 September 2002 (2002-09-10) column 3, line 18 - line 28 -----	3-6, 9-14, 17-21
A	EP 0 590 293 A (HANSEN, BERND, DIPL.-ING) 6 April 1994 (1994-04-06) column 1, line 44 - line 54 column 2, line 55 - column 3, line 56 -----	1,2,7,8, 15,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No
PCT/US2005/017166

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0431885	A	12-06-1991	FR 2655623 A1	14-06-1991
			CA 2031632 A1	09-06-1991
			EP 0431885 A1	12-06-1991
			JP 3251249 A	08-11-1991
WO 9826001	A	18-06-1998	AU 743999 B2	14-02-2002
			AU 5430398 A	03-07-1998
			CA 2274667 A1	18-06-1998
			CN 1246135 A ,C	01-03-2000
			DE 69721042 D1	22-05-2003
			DE 69721042 T2	05-02-2004
			EP 0944670 A1	29-09-1999
			JP 2002514244 T	14-05-2002
			KR 2000057549 A	25-09-2000
			WO 9826001 A1	18-06-1998
			BR 9713708 A	09-05-2000
US 2004079766	A1	29-04-2004	JP 2004196417 A	15-07-2004
US 6447860	B1	10-09-2002	AU 5972401 A	26-11-2001
			BR 0111152 A	08-04-2003
			CA 2408740 A1	22-11-2001
			CN 1441721 A	10-09-2003
			CZ 20023742 A3	17-09-2003
			EP 1286831 A1	05-03-2003
			JP 2003533408 T	11-11-2003
			PL 365180 A1	27-12-2004
			WO 0187596 A1	22-11-2001
			US 2003008089 A1	09-01-2003
EP 0590293	A	06-04-1994	DE 4232305 C1	31-03-1994
			CA 2105031 A1	27-03-1994
			DE 59303848 D1	24-10-1996
			EP 0590293 A1	06-04-1994
			ES 2091529 T3	01-11-1996
			JP 7052964 A	28-02-1995
			MX 9305892 A1	31-03-1994
			US 5427275 A	27-06-1995